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The 15-Country Collaborative Study of Cancer Risk among Radiation Workers in the Nuclear Industry: Estimates of Radiation-Related Cancer Risks

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A 15-Country collaborative cohort study was conducted to provide direct estimates of cancer risk following protracted low doses of ionizing radiation. Analyses included 407,391 nuclear industry workers monitored individually for external radiation and 5.2 million person-years of follow-up. A significant association was seen between radiation dose and all-cause mortality [excess relative risk (ERR) 0.42 per Sv, 90% CI 0.07, 0.79; 18,993 deaths]. This was mainly attributable to a dose-related increase in all cancer mortality (ERR/Sv 0.97, 90% CI 0.28, 1.77; 5233 deaths). Among 31 specific types of malignancies studied, a significant association was found for

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lung cancer (ERR/Sv 1.86, 90% CI 0.49, 3.63; 1457 deaths) and a borderline significant ($P = 0.06$) association for multiple myeloma (ERR/Sv 6.15, 90% CI <0, 20.6; 83 deaths) and ill-defined and secondary cancers (ERR/Sv 1.96, 90% CI −0.26, 5.90; 328 deaths). Stratification on duration of employment had a large effect on the ERR/Sv, reflecting a strong healthy worker survivor effect in these cohorts. This is the largest analytical epidemiological study of the effects of low-dose protracted exposures to ionizing radiation to date. Further studies will be important to better assess the role of tobacco and other occupational exposures in our risk estimates.

INTRODUCTION

Ionizing radiation is a well-established risk factor for human cancer (*1–3*). Radiation protection standards for environmental and occupational exposures to ionizing radiation are based mainly on cancer risk estimates derived from populations exposed primarily at moderate to high dose rates, in particular the Japanese atomic bomb survivors (*4*). Risk estimation therefore requires extrapolation from relatively high-dose-rate acute or fractionated exposures to the lower-dose, low-dose-rate protracted exposures of public health concern, as well as transportation of risk between populations with very different underlying cancer risks. These extrapolations are subject to substantial uncertainty.

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.[2] 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 monitored carefully over time through the use of personal dosimeters. Risk estimates have previously been derived in a number of studies of nuclear industry workers (*3*). However, the statistical power of individual studies is low, and in most cohorts the confidence intervals of the risk estimates were compatible with a wide range of possibilities, from reduced risks to risks that are an order of magnitude greater than those on which current radiation protection recommendations are based. Improved precision has come from studies that combined cohorts of nuclear industry workers from Canada, the United Kingdom and the United States (*5, 6*) and from analyses of the UK National Registry for Radiation Workers (NRRW) (*7*), which consists largely of workers in the nuclear industry.

Most studies to date showed 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 among employees of Oak Ridge National Laboratory (ORNL) in the U.S. (*8*) and of the Atomic Weapons Establishment (AWE) in the UK (*9*), as well as among radiation workers (and specifically nuclear workers) in the Canadian National Dose Registry (*10–12*). Analyses of specific types of cancer were also carried out in most studies; no consistent pattern of increase for any single cancer type has been observed across cohorts.

The 15-Country nuclear worker study was set up to improve the precision of direct estimates of radiation-induced cancer risk after exposure to protracted low doses of ionizing radiation and to strengthen the scientific basis for setting radiation protection standards. The 15-Country Study includes all of the cohorts from the UK NRRW study (*7*) and the previous 3-Country combined study (*5, 6*), except Rocky Flats (*13*) because of the large number of workers in that cohort with potential for internal contamination. Inclusion criteria in the 15-Country Study differed somewhat from those used in previous studies (*14*), and hence not all of the workers from these studies are included in the 15-Country Study. Results from some of the national components of the 15-Country Study have been published recently (*15–22*).

Risk estimates per unit radiation dose for the two main causes of death considered by radiation protection authorities—all cancers excluding leukemia and leukemia excluding chronic lymphocytic leukemia (CLL)—have been published elsewhere and compared with estimates derived from analysis of data on atomic bomb survivors (*23*). The current paper presents detailed results of the 15-Country Study, including risk estimates per unit radiation dose for cause-specific cancer mortality. The paper further assesses the influence of confounding factors, effect modifiers, and different analytical strategies. Results for non-cancer causes of death will be published in detail elsewhere.

METHODS

The 15-Country Study was designed as a multi-national retrospective cohort study. Methods are described in detail in the accompanying paper (*14*). Information was collected on nearly 600,000 workers in 15 countries. To be eligible for inclusion in the study, a cohort had to satisfy a number of quality criteria defined *a priori* (*24*), including non-selective mortality follow-up with a high level of completeness, availability of individual annual recorded dose estimates for all monitored workers, and availability of information on monitoring policies and practices over time.

Main Study Population

The main study population was defined as workers who had been employed in at least one of the study facilities for at least 1 year, who had been monitored for external radiation exposure, and whose doses resulted predominantly from exposure to higher-energy photon radiation (X and γ rays in the range 100–3000 keV) (*14*). Workers with potential for substantial doses from other radiation types were excluded from the main study population, since the measurement and recording of these doses was subject to considerable variability, particularly in earlier years (*25*). Workers with potential for high-dose-rate exposure were also excluded (*14*).

Dosimetry

For each worker monitored for external radiation exposure, a dosimetric history was reconstructed using recorded photon doses from in-

[2] Throughout this 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.

TABLE 1
Observed and Expected Numbers of Deaths by Cumulative Radiation Dose, Trend Test Statistics and ERRs per Sv for Specific Causes of Death

Cause of death	No.		Cumulative dose (mSv)[a]				
			<5	5−	10−	20−	50−
A. Main groupings of causes of death							
All causes	18,993	Observed	11,525	2083	1960	1768	855
		Expected	11,681.9	2009.6	1947.2	1752.2	831.8
Cancers	5,233	Observed	3129	566	526	494	258
		Expected	3190.4	540.8	536.2	494.9	245.2
All excluding leukemia	5,024	Observed	3010	537	500	476	249
		Expected	3062.1	519.1	513.6	475.4	236.2
All excluding leukemia, lung and pleura	3,528	Observed	2185	360	354	308	158
		Expected	2193.7	359.5	349.5	320.3	158.9
Solid cancers	4,770	Observed	2855	512	473	454	237
		Expected	2902.5	493.0	488.4	452.9	225.6
Smoking-related solid cancers	2,737	Observed	1569	289	282	275	169
		Expected	1597.3	287.9	294.9	276.6	143.4
Smoking-related solid cancers other than lung	1,280	Observed	773	131	134	102	78
		Expected	766.9	131.9	131.4	122.4	65.3
Nonsmoking-related solid cancers	2,033	Observed	1275	203	197	188	75
		Expected	1283.1	202.8	198.5	181.5	87.2
Non-cancer causes	13,315	Observed	8076	1465	1405	1248	587
		Expected	8164.7	1432.5	1378.6	1228.2	574.1
Unknown cause of death	445	Observed	320	52	29	26	10
		Expected	326.8	36.3	32.4	29.1	12.5
B. Specific types of cancer							
Buccal and pharynx	113	Observed	74	13	12	3	5
		Expected	71.9	11.5	9.8	8.7	5.5
Oesophagus	144	Observed	84	13	17	17	9
		Expected	81.3	16.1	16.0	15.3	8.1
Stomach	347	Observed	204	36	33	28	27
		Expected	203.5	34.2	35.5	35.4	20.1
Small intestine	12	Observed	10	0	0	0	2
		Expected	8.3	0.9	1.0	1.0	0.5
Colon	410	Observed	248	46	44	38	16
		Expected	254.1	41.0	41.8	37.5	17.1
Rectum	185	Observed	108	21	16	21	8
		Expected	114.0	18.3	17.9	16.5	9.2
Liver	62	Observed	44	5	4	4	1
		Expected	44.3	5.7	4.3	3.8	2.2
Biliary tract	43	Observed	27	7	5	3	0
		Expected	28.3	4.1	3.9	3.5	1.8
Pancreas	272	Observed	161	33	28	22	16
		Expected	163.8	29.0	28.9	26.2	13.0
Nasal cavity	9	Observed	8	0	0	1	0
		Expected	6.6	0.6	0.7	0.8	0.3
Larynx	46	Observed	28	5	3	6	3
		Expected	27.7	4.2	5.4	4.4	2.4
Lung	1457	Observed	799	158	147	171	92
		Expected	832.8	155.1	162.8	153.9	77.7
Pleura	39	Observed	20	4	4	5	3
		Expected	23.4	3.2	3.6	4.4	2.3
Bone	16	Observed	13	2	0	1	0
		Expected	13.2	0.9	0.7	0.6	0.3
Connective tissue	39	Observed	27	4	6	0	1
		Expected	28.0	3.5	3.1	2.5	1.2
Melanoma	87	Observed	59	10	6	5	3
		Expected	59.5	7.0	7.3	6.4	3.6
Female breast	103	Observed	89	5	5	2	1
		Expected	84.0	8.7	5.5	2.7	1.4
Cervix uteri	14	Observed	12	1	1	0	0
		Expected	12.0	1.4	0.5	0.1	0.0

TABLE 1
Extended

Cumulative dose (mSv)						Trend test			RR at
100−	150−	200−	300−	400−	500+	(*P* value)	ERR/Sv	90% CI	l00 mSv[b]
303	189	191	77	28	14	2.12	0.42	(0.07, 0.79)	1.04
308.6	168.1	177.6	80.6	22.1	13.2	(0.017)			
95	75	56	21	7	6	2.52	0.97	(0.28, 1.77)	1.10
89.3	48.2	51.9	24.8	7.0	4.2	(0.006)			
91	74	56	19	7	5	2.43	0.97	(0.27, 1.80)	1.10
86.5	46.8	49.9	23.7	6.7	4.1	(0.007)			
59	45	38	13	5	3	1.30	0.59	(−0.16, 1.51)	1.06
58.7	31.9	33.0	15.9	4.3	2.3	(0.097)			
85	73	52	19	6	4	2.12	0.87	(0.16, 1.71)	1.09
82.5	44.4	47.7	22.7	6.4	3.9	(0.017)			
55	36	43	9	7	3	1.86	0.91	(0.04, 1.98)	1.09
53.0	28.3	31.3	15.1	5.7	3.4	(0.032)			
22	12	20	4	4	0	0.06	0.21	(<0[c], 1.68)	1.02
24.2	13.4	13.9	6.7	2.6	1.3	(0.477)			
36	32	16	9	0	2	0.92	0.62	(−0.36, 1.92)	1.06
32.2	17.2	18.5	8.9	2.0	1.1	(0.180)			
204	114	133	55	20	8	0.87	0.20	−0.19, 0.63	1.02
215.4	118.2	124.2	55.1	14.9	9.0	(0.193)			
4	0	2	1	1	0	0.14	0.29	(<0, 4.04)	1.03
3.9	1.7	1.5	0.7	0.2	0.0	(0.443)			
2	1	2	0	1	0	0.18	0.40	(<0, 5.99)	1.04
2.3	1.2	1.3	0.5	0.1	0.1	(0.427)			
0	0	3	1	0	0	−0.78	<0	—	0.84[d]
2.5	1.4	1.7	1.0	0.3	0.3	(0.782)			(*0.57*, *1.15*)
6	7	4	1	1	0	0.41	0.49	(<0, 3.92)	1.05
7.5	4.2	4.2	1.6	0.5	0.3	(0.341)			
0	0	0	0	0	0	0.10	3.18	(<0, 28.3[e])	1.32
0.2	0.0	0.0	0.0	0.0	0.0	(0.460)			
5	5	3	5	0	0	0.14	0.21	(<0, 3.07)	1.02
6.4	4.6	4.5	2.0	0.5	0.4	(0.443)			
4	4	1	2	0	0	0.53	1.27	(<0, 7.62)	1.13
3.8	1.7	2.1	1.0	0.3	0.2	(0.298)			
1	2	1	0	0	0	1.29	6.47	(<0, 27.0)	1.65
0.9	0.3	0.3	0.2	0.0	0.0	(0.099)			
0	0	1	0	0	0	−0.67	<0	—	0.58[d]
0.7	0.3	0.3	0.1	0.0	0.0	(0.749)			(*0.13*, *1.57*)
3	2	3	2	2	0	1.44	2.10	(-0.59, 6.77)	1.21
4.5	2.3	2.6	1.4	0.3	0.1	(0.074)			
0	0	0	0	0	0	−0.70	<0	—	0.04[d]
0.0	0.0	0.0	0.0	0.0	0.0	(0.759)			(*0.00*, *4.05*)
0	0	1	0	0	0	−0.40	<0	—	0.83[d]
0.7	0.4	0.5	0.3	0.0	0.0	(0.655)			(*0.33*, *1.63*)
32	24	23	5	3	3	2.38	1.86	(0.49, 3.63)	1.19
28.8	14.9	17.3	8.4	3.1	2.1	(0.009)			
1	2	0	0	0	0	0.45	5.28	(<0, 39.9)	1.53
0.8	0.4	0.5	0.2	0.1	0.0	(0.325)			
0	0	0	0	0	0	−0.66	<0	—	0.16[d]
0.1	0.1	0.0	0.0	0.0	0.0	(0.746)			(*0.00*, *2.72*)
0	1	0	0	0	0	0.10	0.32	(<0, 11.5[e])	1.03
0.3	0.1	0.2	0.0	0.0	0.0	(0.462)			
2	1	1	0	0	0	−0.06	0.15	(<0, 5.44[e])	1.01
1.2	0.7	0.8	0.3	0.1	0.0	(0.524)			
1	0	0	0	0	0	−0.47	<0	—	0.61[d]
0.4	0.2	0.0	0.0	0.0	0.0	(0.682)			(*0.10*, *2.21*)
0	0	0	0	0	0	0.09	−0.11	(<0, 131[e])	0.99
0.0	0.0	0.0	0.0	0.0	0.0	(0.466)			

TABLE 1
Continued

Cause of death	No.		Cumulative dose (mSv) <5	5−	10−	20−	50−
Other uterus	13	Observed	10	1	1	1	0
		Expected	10.3	0.8	1.0	0.9	0.0
Ovary	35	Observed	27	3	4	1	0
		Expected	27.3	3.2	2.0	1.8	0.5
Prostate	301	Observed	159	34	36	35	15
		Expected	153.2	39.7	39.2	34.5	17.6
Testis	27	Observed	23	1	2	1	0
		Expected	23.9	1.2	0.9	0.7	0.1
Bladder	145	Observed	78	21	21	15	3
		Expected	79.9	18.9	16.4	15.2	6.9
Kidney	127	Observed	82	8	15	7	10
		Expected	83.5	11.8	11.9	10.6	5.0
Brain and CNS	235	Observed	153	19	25	25	5
		Expected	151.1	22.8	23.0	21.4	9.8
Thyroid	17	Observed	6	3	4	3	1
		Expected	9.6	1.8	2.1	2.4	0.7
Ill-defined and secondary	328	Observed	197	34	30	35	12
		Expected	195.5	33.8	34.4	34.4	16.0
Non-Hodgkin lymphoma	248	Observed	155	27	25	24	12
		Expected	163.7	23.8	22.2	20.2	9.6
Hodgkin's disease	44	Observed	36	2	2	1	1
		Expected	34.6	2.9	2.6	1.7	1.0
Multiple myeloma	83	Observed	64	4	4	3	4
		Expected	58.2	8.4	6.3	6.0	2.5
Other cancers	106	Observed	70	7	8	10	7
		Expected	70.1	9.4	8.7	8.9	4.3
Non malignant tumors	57	Observed	43	3	4	4	2
		Expected	39.8	4.9	5.3	4.8	1.6
C. Leukemia							
All leukemia	275	Observed	141	41	38	29	14
		Expected	152.8	32.0	34.2	30.6	14.0
Leukemia excluding CLL	196	Observed	105	30	23	19	9
		Expected	110.1	22.1	23.6	22.2	10.4
CLL	47	Observed	19	5	8	8	5
		Expected	21.8	6.6	7.1	5.7	2.8
CML	45	Observed	25	4	4	6	3
		Expected	24.7	5.5	6.0	5.1	2.2
Acute leukemia	137	Observed	74	23	15	13	5
		Expected	77.9	14.8	15.3	15.8	7.6
ALL	19	Observed	7	3	5	2	2
		Expected	10.3	2.1	2.1	2.3	1.2
AML	81	Observed	47	15	7	8	2
		Expected	48.7	8.5	8.2	8.5	4.0
D. Non-malignant respiratory diseases							
Respiratory diseases	792	Observed	381	107	118	103	46
		Expected	416.5	101.2	102.9	92.2	42.9
Emphysema	138	Observed	56	24	23	23	5
		Expected	62.3	20.4	21.1	17.4	8.2
Emphysema and chronic obstructive bronchitis	331	Observed	127	51	58	57	15
		Expected	141.7	48.8	49.2	49.3	20.8
Chronic obstructive pulmonary disease, NOS	144	Observed	63	18	15	26	15
		Expected	65.7	16.2	16.7	22.9	12.3

[a] Bone marrow dose used for leukemia, multiple myeloma and lymphomas, lung dose for lung, pleural and smoking related cancers, and for non-malignant respiratory diseases; colon doses for all other causes. Lag time of 2 years used for leukemia, 10 years for all other causes.

[b] Based on a linear excess relative risk model unless otherwise indicated.

[c] <0: Central risk estimate or lower confidence bound is on boundary of parameter space (−1/max dose).

[d] RR from a log-linear risk model (90% CI).

[e] Wald-based upper confidence bound.

TABLE 1
Extended (continued)

Cumulative dose (mSv)						Trend test			RR at
100−	150−	200−	300−	400−	500+	(*P* value)	ERR/Sv	90% CI	100 mSv[b]
0	0	0	0	0	0	0.25	0.16	(<0, 94.1[d])	1.02
0.0	0.0	0.0	0.0	0.0	0.0	(0.403)			
0	0	0	0	0	0	−0.93	<0	—	0.09[d]
0.1	0.0	0.0	0.0	0.0	0.0	(0.825)			(*0.00*, *2.58*)
7	10	4	1	0	0	0.37	0.77	(<0, 4.58)	1.08
6.4	3.7	4.2	2.0	0.4	0.2	(0.357)			
0	0	0	0	0	0	−0.01	<0	—	0.69[d]
0.0	0.0	0.0	0.0	0.0	0.0	(0.502)			(*0.00*, *4.90*)
2	2	3	0	0	0	−1.10	<0	—	0.78[d]
3.0	1.9	1.6	0.9	0.4	0.2	(0.865)			(*0.50*, *1.10*)
4	0	1	0	0	0	0.34	2.26	(<0, 14.9)	1.23
1.9	0.9	0.8	0.4	0.2	0.1	(0.367)			
5	3	0	0	0	0	−0.74	<0	—	0.82[d]
3.3	1.5	1.4	0.5	0.2	0.0	(0.769)			(*0.53*, *1.17*)
0	0	0	0	0	0	−0.06	<0	—	0.91[d]
0.3	0.1	0.1	0.0	0.0	0.0	(0.522)			(*0.12*, *2.84*)
9	5	4	0	0	2	1.59	1.96	(−0.26, 5.90)	1.20
5.8	2.7	3.1	1.8	0.3	0.2	(0.056)			
1	1	1	0	2	0	0.26	0.44	(<0, 4.78)	1.04
3.7	1.8	1.8	0.8	0.2	0.1	(0.397)			
1	1	0	0	0	0	0.01	−0.18	(<0, 7.25[e])	0.98
0.4	0.2	0.3	0.2	0.1	0.0	(0.496)			
1	2	1	0	0	0	1.57	6.15	(<0, 20.6)	1.61
0.7	0.5	0.3	0.1	0.0	0.0	(0.058)			
1	1	1	1	0	0	0.39	1.23	(<0, 9.78)	1.12
1.8	0.8	0.9	0.7	0.2	0.0	(0.349)			
1	0	0	0	0	0	−0.16	<0	—	0.83[d]
0.3	0.2	0.2	0.0	0.0	0.0	(0.562)			(*0.19*, *2.15*)
5	2	3	1	0	1	0.62	0.70	(<0, 4.52)	1.07
4.8	2.3	2.5	1.4	0.3	0.2	(0.268)			
4	2	2	1	0	1	1.35	1.93	(<0, 7.14)	1.19
3.5	1.7	1.5	0.7	0.2	0.1	(0.089)			
1	0	1	0	0	0	−0.32	<0	—	0.90[d]
1.0	0.5	0.8	0.6	0.1	0.1	(0.626)			(*0.50*, *1.37*)
2	0	0	1	0	0	1.47	10.1	(−0.86, 40.2)	2.01
0.6	0.3	0.3	0.2	0.1	0.0	(0.070)			
2	2	2	0	0	1	0.91	1.16	(<0, 6.64)	1.12
2.5	1.3	1.1	0.6	0.2	0.1	(0.180)			
0	0	0	0	0	0	−0.42	<0	—	0.19[d]
0.4	0.2	0.1	0.0	0.0	0.0	(0.664)			(*0.18*, *1.99*)
1	0	1	0	0	0	−1.15	<0	—	0.59[d]
1.4	0.6	0.6	0.3	0.1	0.0	(0.876)			(*0.24*, *1.17*)
14	8	8	3	3	1	1.23	1.16	(−0.31, 3.33)	1.12
14.5	8.0	7.4	4.9	0.9	0.6	(0.109)			
4	0	2	1	0	0	−1.04	−0.72	(<0, 1.93[e])	0.93
2.6	1.7	2.4	1.3	0.4	0.3	(0.851)			
8	5	4	3	1	2	0.78	2.12	(−0.28, 6.37)	1.21
7.0	4.3	5.3	3.0	1.0	0.6	(0.218)			
5	1	1	0	0	0	−1.25	<0	—	0.77[d]
5.2	1.9	1.4	0.9	0.5	0.3	(0.894)			(*0.52*, *1.07*)

dividual facilities and/or national dose registries. A study of errors in dosimetry was carried out to evaluate the comparability of recorded dose estimates across facilities and time and to identify and quantify sources of bias and uncertainties in dose estimates (*25*). Errors related to dosimeter response, radiation fields and calibration practices were quantified, and organ-dose-specific dosimetric bias factors were calculated for each model of dosimeter in use in a participating facility and by facility type (nuclear power plants and other, mixed-activities facilities). Doses[3] to the colon, lung and active bone marrow were derived by dividing the recorded doses by the appropriate organ dose bias factor (*25*). The analyses described in the current paper are based on lung doses for lung, pleural and smoking-related cancers (see section on Outcomes Studied below for a definition) as well as for non-malignant respiratory diseases; bone marrow doses for leukemia, multiple myeloma, and lymphoma; and colon doses for all other causes of death.

Cumulative Dose and Person-Year Calculation

For each worker, cumulative dose and person-years at risk were accumulated over time from date of entry in the study (defined as the later of date of start employment plus 12 months, date of first monitoring, and date of start of vital status follow-up) to 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). Workers known to have received doses before entry into the study entered the follow-up with the corresponding dose. Doses, person years and other time variables such as age were updated every 15 days using the DATAB module of EPICURE (*26*) assuming annual doses were distributed uniformly over the year they were received. 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 all other causes of death, as in most previous nuclear worker studies (*2*). With a lag of x years, a dose was included in the calculation of the cumulative dose at time t if it had been received at or before time year $t - x$. 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. Sensitivity analyses were conducted using a range of different lag times (2, 5, 10 and 15 years).

Statistical Analysis

Observed (O) and expected (E) numbers of deaths and person-years of follow-up were calculated by 11 dose categories (<5, 5−, 10−, 20−, 50−, 100−, 150−, 200−, 300−, 400− and 500− mSv) chosen *a priori.* The expected numbers of deaths were calculated assuming that, within a stratum defined by levels of the stratification variables (see below), 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 comparison of observed and expected numbers is therefore based on an internal, not external, comparison population. The statistical significance of the trend in O/E ratios with cumulative dose was tested using the score statistic based on the linear relative risk model (*27, 28*) and the mean person-year weighted dose in each stratum. Since the main objective of radiation epidemiological studies is generally to test for an increased risk in relation to radiation exposure, one-sided P values and corresponding 90% confidence intervals are usually presented (*2, 7, 29*), and this is therefore the approach used here.

Estimates of the excess relative risk (ERR) per sievert were obtained using Poisson regression, based on a linear relative risk model in which the relative risk was assumed to be of the form $1 + \beta Z$, where Z is the lagged cumulative dose in sieverts, and β is the excess relative risk (ERR) per sievert. This model has been used in previous analyses of nuclear workers studies (*6*) and is commonly used in radiation risk estimation (*2*). The linear excess relative risk model has computational restrictions, since the relative risk cannot be negative. Hence the parameter is constrained to be larger than -1/maximum dose, and in some cases estimates and/or lower confidence bounds for β cannot be obtained; these are designated simply as <0 throughout this paper. Log-linear models, in which the relative risk is assumed to be of the form $\exp(\beta Z)$, were also fitted to the data, and resulting estimates of the relative risk at a dose of 100 mSv compared to 0 mSv are presented in this paper where β could not be estimated under the linear model. Linear and log-linear models give essentially the same results at low doses and low risks. Confidence intervals presented for the ERR and RR are likelihood based; where these could not be estimated, Wald-based upper confidence bounds are shown. As indicated above, they are 90% intervals, for consistency with other radiation epidemiological studies.[4] Departures from linearity of risk were explored by fitting polynomial equations in dose.

Stratification Variables and Potential Confounders

All analyses (trend tests and regression models) were stratified by sex, age and calendar period (both in 5-year categories), facility, duration of employment (<10 years, ≥10 years), and socio-economic status (SES). Stratification for duration of employment was used to control for a possible healthy worker survivor effect; alternative results are shown without this adjustment.

A socio-economic status indicator was derived in each country based on either occupational categories, education or pay scale (*14*). Cohorts for which SES information was either not available or not sufficiently complete (Japan, INL and Ontario Hydro cohort in Canada) were excluded from analyses of all cancers excluding leukemia and of single solid cancer types but were included in analyses of leukemia, lymphoma and multiple myeloma as the potential for confounding by SES was thought to be less for these outcomes [see for example ref. (*6*)] and as indicated by analyses of the effects of SES in this study. Results in this paper are also shown without SES stratification.

Since inadequate information was available on tobacco smoking, smoking-related and non-smoking-related solid cancers were analyzed separately to evaluate indirectly the potential effect of smoking confounding. Smoking-related cancers were those solid cancers identified as having sufficient evidence for being caused by smoking in the recent IARC monograph (*30*): cancers of the lung, oral cavity, naso-, oro- and hypopharynx, nasal cavity and paranasal sinuses, larynx, esophagus, stomach, pancreas, liver, kidney (body and pelvis), ureter, urinary bladder, and uterine cervix. The category of non-smoking-related cancers comprised all other solid cancers. The following groupings of smoking-related non-cancer outcomes were also studied as indirect indicators of confounding by smoking: all non-malignant respiratory diseases, emphysema alone and in combination with chronic obstructive bronchitis, and chronic obstructive pulmonary disease not otherwise specified (COPD-NOS) (*31*).

Effect Modifiers

Poisson regression analyses were carried out for subpopulations of the cohort (by country, cohort, facility type, sex and attained-age groups); likelihood ratio tests for the interaction of these variables with dose were used to test for heterogeneity of risk estimates between the subgroups.

Further analyses were conducted to evaluate the possible modifying effects of age at exposure and time since exposure. The relative contributions of doses received during three age-at-exposure periods—under 35, between 35 and 50, and over 50 years—were evaluated by modeling these three dose variables jointly in the Poisson regression models. Sim-

[3] All doses are expressed in terms of equivalent dose in sievert (Sv). Because this paper is mainly concerned with photon radiation, with a radiation-weighting factor of 1, the results could equally well be expressed in terms of absorbed dose to organs in grays with the same numerical values (*25*).

[4] It should be noted that the confidence intervals therefore differ slightly from those presented in Cardis *et al.* (*24*), which, for consistency with that journal's policy for publishing statistical results, were 95% confidence intervals.

ilarly, the joint effects of doses received in three different time-since-exposure periods were modeled: less than 10, 10–20 and more than 20 years previously. For these analyses, the person-years and deaths were stratified on three cumulative doses (corresponding to doses received in different age ranges or in different periods as appropriate).

Outcomes Studied

Observed and expected numbers of deaths, trend test statistics and ERR estimates were calculated for detailed causes of death as described in the accompanying methods paper (*14*). The main analyses used only underlying cause of death. Results including associated causes of death are given as an alternative analysis strategy. Analyses of subpopulations and effect modifiers are presented only for all cancers excluding leukemia, lung cancer and leukemia excluding CLL. Results of alternative analysis strategies are presented for all cancers excluding leukemia, for all cancers excluding leukemia, lung and pleural cancers, for lung cancer, and for leukemia excluding CLL.

Ethics

The study was approved by the IARC Ethical Review Committee and by the relevant ethics committees of the participating countries. The procedures followed were in accordance with the ethical standards of the responsible committees on human experimentation (institutional or regional) and with the Helsinki Declaration (1983 or more recent revision, depending on the country) (*32*).

RESULTS

Overall, 598,068 workers from 154 facilities were followed up in this study. Most workers were employed in facilities involved in nuclear power production; the remaining facilities (''mixed-activities facilities'') specialized in different activities, including research, waste management, and production of nuclear fuel, isotopes and weapons (*14*). The main study population included 407,391 workers. Detailed characteristics of these workers are described elsewhere (*14*). The total duration of follow-up was 5,192,710 person-years and the total collective recorded dose was 7,892 Sv. Most workers in the study were men (90%) and men received 98% of the collective dose. The overall average cumulative recorded dose was 19.4 mSv. The distribution of recorded doses was very skewed: 90% of workers received cumulative doses below 50 mSv and less than 0.1% received cumulative doses greater than 500 mSv. The distribution of doses varied across countries: the lowest average cumulative dose was recorded in France at CEA-COGEMA (3.5 mSv) and the highest in Switzerland (62.3 mSv) (*14*). Only in Canada, the UK and the U.S. were there sizable numbers of workers with cumulative doses above 500 mSv.

Radiation-Related Cause-Specific Mortality

There were 18,993 deaths from all causes in the cohort (Table 1A). The ERR for all causes of death was 0.42 per Sv (90% CI 0.07, 0.79), corresponding to a relative risk of 1.04 at 100 mSv. There was a statistically significant increasing trend with cumulative radiation dose ($P = 0.02$). The increased risk in all-cause mortality appears to be mainly due to an increase in mortality from all cancers (ERR/Sv = 0.97, 90% CI 0.28, 1.77), corresponding to a relative risk of 1.10 at 100 mSv; the corresponding estimate for all non-cancer causes of death combined was 0.20/Sv (90% CI −0.19, 0.63). The central estimate of the ERR for all cancers excluding leukemia was identical to that for all cancers; the ERR for solid cancers was slightly lower (ERR/Sv = 0.87), and both were statistically significantly greater than zero. Removing lung and pleural cancer reduced the number of deaths by 30%, and the ERR was somewhat lower (ERR/Sv = 0.59) and was no longer significantly different from zero. Smoking-related solid cancers showed a stronger association with cumulative radiation dose than non-smoking-related solid cancers (ERR/Sv respectively 0.91 and 0.62). The increase in risk for smoking related cancers was mainly due to an elevated lung cancer risk (Table 1B: ERR/Sv = 1.86, 90% CI 0.49, 3.63); smoking-related cancers other than lung cancer showed little evidence of an increased risk (ERR/Sv = 0.21, 90% CI <0, 1.68). Analyses using polynomials in dose (not shown) did not reveal significant departure from linearity for any of these causes of death. Analyses using continuous data and Cox proportional hazards model gave similar risk estimates (results not shown).

Figure 1 shows the ERR and 90% CI by dose category as well as the fitted ERR/Sv for all cancers excluding leukemia, for all cancers excluding leukemia, lung and pleural cancer, and for leukemia excluding CLL. Risk estimates for all cancers excluding leukemia and for all cancers excluding leukemia, lung and pleural cancers were very similar above 200 mSv, indicating that lung cancer was not entirely responsible for the increased ERR/Sv for all cancers excluding leukemia risk. It is noted that the ERR was significantly elevated in the 150–200 mSv category for both these causes of death. This increase, based on 74 deaths from all cancers excluding leukemia (including 29 lung cancer deaths), did not appear to be driven by any one country: Observed to expected ratios of similar magnitude were seen in Canada excluding OH (7 deaths), Sweden (2 deaths), UK (35 deaths), Hanford (18 deaths) and ORNL (5 deaths).

Results of analyses restricting doses to below 400, 200, 150 and 100 mSv showed that the risk estimates for all cancers excluding leukemia were not driven by the highest dose categories (Table 2).

No individual cancer type, apart from lung cancer, showed statistically significantly raised ERRs (Table 1B). The ERR for multiple myeloma was elevated but was not significantly different from zero (ERR/Sv = 6.15), as was the ERR for ill-defined and secondary cancers (ERR/Sv = 1.96); the trend tests showed associations of borderline statistical significance ($P = 0.06$). Other cancer subtypes that showed a weak but non-significant positive association with radiation dose were liver and pancreatic cancers.

The ERR for leukemia excluding CLL was 1.93 per Sv (90% CI <0, 7.14), which corresponds to a relative risk of 1.19 for a radiation dose of 100 mSv; this estimate was not significantly different from zero (Table 1C); there was no ev-

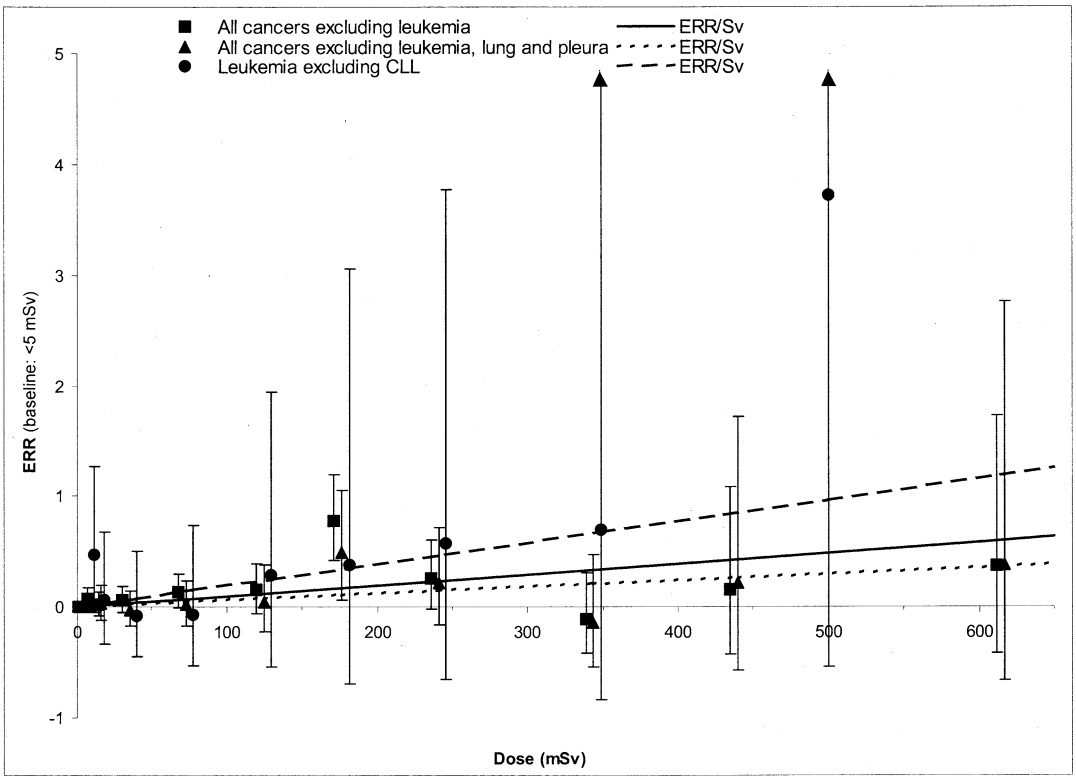

FIG. 1. Excess relative risk by dose category (relative to <5 mSv category) and 90% CI: all cancers excluding leukemia, all cancers excluding leukemia, lung and pleural cancers; leukemia excluding CLL. For leukemia excluding CLL, the 400–500 and >500 mSv categories have been combined because these two categories had very extreme values, based on very small numbers of death. In the combined >400 mSv category, the ERR/Sv was 3.73 (90% CI −0.54, 20.9).

idence for non-linearity in the dose response (results not shown). Figure 1 shows the ERR and 90% CI by dose category. Analyses by subtype showed no association between radiation dose and mortality from CLL, acute lymphocytic leukemia (ALL), and acute myeloid leukemia (AML). An association of borderline significance was seen for chronic myeloid leukemia (CML), however (ERR/Sv = 10.10). Mortality from all acute leukemia subtypes combined was positively but not significantly associated with radiation dose (ERR/Sv = 1.16), mainly due to a non-significant association with acute unspecified leukemia (not shown).

No statistically significant association was seen between radiation dose and any of the groups of non-malignant respiratory diseases examined (Table 1D): Risk estimates for mortality from all non-malignant respiratory disease (ERR/Sv = 1.16) and chronic obstructive bronchitis and emphysema (ERR/Sv = 2.12) were elevated but were not significantly different from zero, while a negative trend was reported for COPD-NOS.

Risk Estimates in Subpopulations of the Cohort

Results by country (Table 3) show that, for all cancers excluding leukemia, the ERR and RR were significantly raised only in Canada, where the ERR estimate was in fact considerably higher (6.65, 90% CI 2.56–13.0) than in the most other countries with sizable numbers of deaths. The test for heterogeneity (5 *df*) provided little evidence for

TABLE 2
ERR per Sv for all Cancers Excluding Leukemia: Results of Analyses Restricted to Different Dose Levels

	No.	ERR/Sv	90% CI	RR at 100 mSv
All doses	5,024	0.97	0.27 1.80	1.10
Cumulative doses <400 mSv	5,012	1.18	0.37 2.11	1.12
Cumulative doses <200 mSv	4,937	2.52	1.31 3.87	1.25
Cumulative doses <150 mSv	4,863	1.39	0.02 2.92	1.14
Cumulative doses <100 mSv	4,772	1.51	−0.29 3.51	1.15

Note. Results from linear models.

heterogeneity of risk between countries when countries with fewer than 100 cancer deaths were grouped (P = 0.19). Risk estimates in the two countries with the largest numbers of deaths, the UK and U.S., were of similar magnitude and were close to the overall risk estimate. A significantly reduced risk was seen for the cohorts of CEA-COGEMA and INL; the latter cohort was not included in the combined risk estimate because of lack of SES data. Analyses excluding one country at a time from the overall analysis population (not shown) gave ERRs that ranged between 0.58 per Sv (90% CI −0.10, 1.39) when Canada was excluded to 1.25 per Sv (90% CI 0.26, 2.43) when the UK cohorts were excluded. Only when Canada was included, however, was the ERR significantly different from zero.

Analyses of mortality from all cancers excluding leukemia, lung and pleural cancers (not shown) similarly showed little evidence of heterogeneity across countries (P = 0.73 when countries with fewer than 100 cancer deaths were grouped). The ERR for Canada was high (ERR/Sv = 3.69, based on 138 deaths) but was not significantly elevated. Again, analyses excluding one country at a time from the overall analysis population demonstrated that risk estimates were not greatly influenced by any one country: The ERRs ranged between 0.44 per Sv (90% CI −0.30, 1.36) when Canada was excluded to 0.67 per Sv (90% CI −0.25, 1.87) when the U.S. cohorts were excluded.

Lung cancer risk estimates showed greater variability between countries (Table 3). Significantly increased risk estimates were found in Canada, Spain and ORNL. A significantly reduced risk was found in the log-linear model for INL. The combined ERRs ranged (not shown) from 0.91 per Sv (90% CI −0.39, 2.62) when Canada was excluded to 3.19 (90% CI 1.18, 5.89) when the UK was excluded. There was little evidence of heterogeneity of risk across countries when countries with fewer than 100 deaths from all cancers were grouped (P = 0.24).

For leukemia excluding CLL, all countries/cohorts with at least 10 deaths, except Japan and ORNL, showed ERRs above 0 (Table 3). Risk estimates did not differ significantly between countries ($P < 0.1$). A statistically significantly elevated relative risk was seen only in France (ERR/Sv = 242, 90% CI 42.2, 1510; RR at 100 mSv = 6.42, 90% CI 1.88, 21.3), but the confidence intervals were very large and the observation was based on only 11 deaths. A significantly reduced relative risk was seen for ORNL based on 12 deaths. The overall ERR for leukemia excluding CLL ranged between 1.06 per Sv (90% CI <0, 5.42) when France was excluded and 2.72 per Sv (90% CI <0, 14.4) when the U.S. cohorts were excluded.

The ERRs for men were very similar to those observed in the entire population for all outcomes, reflecting the preponderance of men in the study cohorts (Table 4). The point estimates for women were lower, but confidence intervals were very wide, and the tests for homogeneity provided no evidence for a difference in risk between men and women.

The ERRs for all cancers excluding leukemia (ERR/Sv = 1.23, 90% CI 0.41, 2.20) and for lung cancer (ERR/Sv = 2.71, 90% CI 1.00, 4.95) were significantly elevated in mixed activities facilities but not in nuclear power plants (Table 4). For lung cancer, the homogeneity test was of borderline significance (P = 0.06). For all cancers excluding leukemia, lung and pleural cancers (not shown), there was no evidence for a difference between facility types (ERR/Sv 0.64 and 0.58, respectively, for mixed-activities facilities and nuclear power plants; P for homogeneity = 0.96). For leukemia excluding CLL, the ERR was higher in nuclear power plants (ERR/Sv = 3.58) than in mixed-activities facilities (ERR/Sv = 1.50), but this difference was not statistically significant (P = 0.72).

Time- and Age-Related Effects

For all cancers excluding leukemia, lung and pleural cancers (not shown), and for leukemia excluding CLL, the highest ERRs were found in workers with the highest attained age (over 70 years; Table 5). For lung cancer, both the younger (less than 60 years) and older (over 70 years) workers had significantly raised ERRs (of 4.47 and 3.67, respectively). Differences between age groups were not statistically significant, however, for any of these outcomes. Similar results were found when using different cut-offs for attained age categories (65 and 75 years).

In analyses jointly modeling doses received at different ages (Table 5), doses received before age 35 appear to entail a lower risk for all cancers excluding leukemia than doses received later (ERR/Sv respectively −1.07, 1.32 and 1.74 per Sv for exposures below age 35, between 35 and 50, and over 50 years of age); there was no evidence of statistically significant heterogeneity between the risk estimates for doses received at different ages at exposure (P = 0.23). Since the ERR estimates for the two older groups were similar in magnitude, an analysis in which these groups were combined was conducted *post hoc*. The estimates of ERR/Sv were respectively −1.11 (90% CI <0, 1.18) and 1.49 (90% CI 0.64, 2.48) for exposures below age 35 and at ages 35 or above; the homogeneity P value was 0.09. Similarly, for all cancers excluding leukemia, lung and pleural cancer (not shown), no association was found for exposures below the age of 35 (ERR/Sv −2.06), while non-significantly increased risks were seen for exposures at later ages (ERR/Sv, respectively, 1.21 and 0.69 for exposures between 35 and 50 and over 50 years old).

For lung cancer, patterns of risk differed from those described above (ERR/Sv 2.51, 1.52 and 3.87, respectively, for exposures below age 35, between 35 and 50, and over 50 years old); there was no evidence for heterogeneity of risk by age at exposure (P = 0.68). For leukemia excluding CLL (Table 5), a statistically significantly increased risk was seen in relation to doses received above the age of 50 but not below. Risk estimates did not differ significantly between categories of age at exposure (P = 0.38). A *post hoc* evaluation of heterogeneity in the effects of doses re-

TABLE 3
Country Specific ERR per Sv and RR at 100 mSv and Corresponding 90% Confidence Intervals (CI) for Deaths from all Cancers Excluding Leukemia and from Leukemia Excluding CLL

	All cancers excluding leukemia				
Country grouping	No.	ERR/ Sv	90% CI		RR at 100 mSv[a]
Overall	5,024	0.97	0.27	1.80	1.10
Australia	17	13.4	−5.99	119	2.34
Belgium	87	−0.59	<0	6.24	0.94
Canada-excluding OH	204	6.65	2.56	13.0	1.66
Canada-including OH[d]	*400*	*3.60*	*1.03*	*7.27*	*1.36*
Finland	33	174	<0	1,070	18.4
France	331	<0	—		0.61[c] (*0.24, 1.23*)
EDF	*113*	*−1.71*	*<0*	*4.20*[b]	*0.83*
CEA-COGEMA	*218*	*<0*	—		0.08[c] (*0.00, 0.80*)
Hungary	39	<0	—		0.03[c] (*0.00, 25.1*)
Japan[d]	*413*	*0.92*	−3.81	8.37	*1.09*
Korea	21	<0	—		0.00[c] (*0.00, 0.17*)
Lithuania	24	<0	—		0.96[c] (*0.02, 2.92*)
Slovakia	10	<0	—		0.00[c] (*0.00, 0.00*)
Spain	25	1.02	<0	13.9	1.10
Sweden	190	−0.58	<0	6.49	0.94
Switzerland	24	<0	—		0.88[c] (*0.35, 1.86*)
UK	2,201	0.66	−0.25	1.86	1.07
USA; excluding INL	1,818	0.78	−0.33	2.15	1.08
USA; including INL[d]	*2,704*	*−0.29*	*−1.04*	*0.63*	*0.97*
Hanford	*1,279*	*1.17*	*−0.23*	*2.99*	*1.12*
INL	*886*	*<0*	—		0.66[c] (*0.51, 0.83*)
NPPs	*314*	*−0.92*	*<0*	*0.78*[b]	*0.91*
ORNL	*225*	*4.28*	*−0.40*	*11.6*	*1.43*
LR test for homogeneity (13 *df*)[f]					*P = nd*
Countries with <100 deaths from all cancers grouped					
	280	−0.20	<0	3.82	0.98
LR test for homogeneity (*5 df*)					*P = 0.19*

[a] Based on a linear excess relative risk model unless otherwise indicated.
[b] Wald based upper confidence bound.
[c] RR (90% CI) from a log-linear model.
[d] Ontario Hydro, INL and Japan not included in overall risk estimate or homogeneity test because of lack of SES data.
[e] nd: not determined: the confidence bound or *P* value could not be calculated.
[f] Between countries.
[g] Based on a linear excess relative risk model unless otherwise indicated.
[h] Wald based upper confidence bound.
[i] RR (90% CI) from a log-linear model.

ceived at older (≥50 years) compared to younger (<50 years) ages provides some evidence of variation in these risk estimates (homogeneity *P* value = 0.08 for log-linear model; RR at 100 mSv 0.88, 90% CI 0.92, 1.25 for exposures before age 50, and 2.03, 90% CI 1.06, 2.82 for exposures at ages 50 or above).

Patterns of risk varied significantly with time since exposure for all cancers excluding leukemia in the log-linear model ($P = 0.03$) and showed borderline significance ($P = 0.07$) in the linear model. This was due to a negative dose–response relationship for doses received less than 10 years previously (ERR/Sv < 0; RR at 100 mSv = 0.85, 90% CI 0.73, 0.97). These doses are excluded in the overall analysis of cancer risk because of the 10-year lag time used. All cancers excluding leukemia, lung and pleural cancers (not shown) showed a similar pattern of risk with time since exposure, although no significant heterogeneity was found, $P = 0.17$). The ERR/Sv for lung cancer increased with increasing time since exposure, but there was no evidence of significant heterogeneity ($P = 0.28$). For leukemia excluding CLL, the ERR/Sv increased from −1.02 for doses received less than 10 years previously to 2.73 for doses received more than 20 years previously.

Increasing the lag periods increased the risk estimates for each outcome (Table 5). For all cancers except leukemia, the ERR/Sv increased from 0.57 per Sv for a 2-year lag to 1.03 per Sv for a 15-year lag. All these estimates are statistically significantly different from zero. For all cancers excluding leukemia, lung and pleural cancers (not shown), the ERR/Sv increased from 0.27 with a lag of 2 years to 0.59 with a lag of 10 years; it was 0.50 with a lag of 15 years. For lung cancer, the ERR/Sv increased from 1.46 to

TABLE 3
Extended

Lung cancer					Leukemia excluding CLL				
No.	ERR/Sv	90% CI		RR at 100 mSv	No.	ERR/Sv	90% CI		RR at 100 mSv
1,457	1.86	0.49	3.63	1.19	196	1.93	<0	7.14	1.19
3	—			—	0	—			—
26	−1.48	<0	1.66[b]	0.85	3	<0	—		0.00[c] (<0, 3.37)
65	11.6	3.63	27.8	2.16	—				
154	*4.57*	*0.84*	*11.1*	*1.46*	11	2.75	<0	49.5	1.28
Idl	8.04	<0	160[b]	1.80	0	—			—
69	2.17	−2.25	30.7	1.22	11	242	42.2	1,510	25.3
22	*13.8*	*<0*	*75.0*	*2.38*	*4*	*179*	*<0*	*716[b]*	*18.9*
47	*<0*	—		0.00[c] (*0.00, 2.03*)	*7*	*280*	*30.7*	*2,390*	*29.0*
10	<0	—		0.00[c] (*0.00, 265,000*)	1	<0	—		0.00[c] (<0, nd[e])
69	*0.40*	<0	12.3	*1.04*	19	−3.11	<0	7.17[b]	0.69
3	<0	—		0.00[c] (*nd, 4.30*)	0	—			—
4	<0	—		0.00[c] (*0.00, 2.49*)	1	<0	<0	27.5	0.00[c] (0.00, 4.06)
0	—			—	0	—			—
4	82.3	1.22	1,530	9.23	0	—			—
43	<0	—		0.61[c] (*0.11, 1.63*)	4	7.83	<0	61.1[b]	1.78
9	<0	—		0.85[c] (*0.19, 2.50*)	0	—	—		—
674	0.01	<0	2.27	1.00	54	1.17	<0	9.82	1.12
536	1.93	−0.17	4.90	1.19	—				
816	*−0.15*	−1.33	1.56	*0.99*	92	1.17	<0	8.67	1.12
366	*2.60*	*−0.08*	*6.79*	*1.26*	*35*	*1.18*	*<0*	*15.8*	*1.12*
280	*<0*	—		0.42[c] (*0.22, 0.69*)	*26*	*2.21*	*<0*	*23.7*	*1.22*
103	*<0*	—		0.87[c] (*0.56, 1.23*)	*19*	*12.98*	*<0*	*73.5*	*2.30*
67	*10.2*	*0.23*	*32.5*	*2.02*	*12*	*<0*	—		*0.01[c] (0.00, 0.52)*
				P = nd					*P = nd*
70	2.44	−1.62	13.9	1.24	5	<0	—		0.63[c] (0.00, 1.39)
				P = 0.24					*P = 0.59*

TABLE 4
Sex and Facility Type Specific ERR per Sv and RR at 100 mSv and Corresponding 90% Confidence Intervals (CI) for Deaths from all Cancers Excluding Leukemia, from Lung Cancer and from Leukemia Excluding CLL

	All cancers excluding leukemia			RR at 100	Lung cancer			RR at 100	Leukemia excluding CLL			
	No.	ERR/Sv	90% CI	mSv[a]	No.	ERR/Sv	90% CI	mSv	No.	ERR/Sv	90% CI	RR at 100 mSv
Overall	5,024	0.97	0.27 1.80	1.10	1,457	1.86	0.49 3.63	1.19	196	1.93	<0 7.14	1.19
Sex												
Men	4,619	1.01	0.30 1.85	1.10	1,392	1.88	0.50 3.66	1.19	181	2.07	<0 7.45	1.21
Women	405	−1.11	<0 5.50[b]	0.90	65	−1.04	<0 11.1[b]	0.90	15	<0	−	0.01[c] (0.00, 10.6)
LR test for homogeneity (1 df)			*P = 0.41*			*P = 0.73*		*P = 0.68*				
Facility type												
Nuclear power plants	1,186	−0.02	−1.29 1.70	1.00	316	−1.23	<0 0.49[b]	0.88	65	3.58	<0 18.0	1.36
Mixed activities	3,838	1.23	0.41 2.20	1.12	1,141	2.71	1.00 4.95	1.27	131	1.50	<0 7.37	1.15
LR test for homogeneity (1 df)			*P = 0.26*			*P = 0.06*		*P = 0.72*				

[a]Based on a linear excess relative risk model unless otherwise indicated.
[b]Wald-based upper confidence bound.
[c]RR (90% CI) from a log-linear mode.

TABLE 5
Effects of Attained Age, Age at Exposure, Time since Exposure and Lag Time on ERR per Sv and RR at 100 mSv and Corresponding 90% Confidence Intervals (CI) for Deaths from All Cancers Excluding Leukemia, from Lung Cancer and from Leukemia Excluding CLL

	All cancers excluding leukemia			RR at 100	Lung cancer			RR at 100	Leukemia excluding CLL			RR at 100
	ERR/Sv	90% CI		mSv[a]	ERR/Sv	90% CI		mSv	ERR/Sv	90% CI		mSv
Overall	0.97	0.27	1.80	1.10	1.86	0.49	3.63	1.19	1.93	<0	7.14	1.19
Attained age												
<60	1.07	−0.43	2.96	1.11	4.47	0.79	9.85	1.45	0.15	<0	8.88	1.01
60–70	0.23	−0.67	1.36	1.02	0.13	<0	2.05	1.01	0.03	<0	6.36[a]	1.00
>70	1.96	0.61	3.75	1.20	3.67	0.84	8.12	1.37	5.85	−0.56	27.5	1.58
LR test for homogeneity (2 *df*)	*P = 0.27*				*P = 0.11*			*P = 0.62*				
Age at exposure												
<35	−1.07	<0	1.24	0.89	2.51	−1.96	8.89	1.25	1.51	<0	11.6[b]	1.15
35–50	1.32	0.12	2.71	1.13	1.52	−0.71	4.36	1.15	−1.59	<0	3.02[b]	0.84
>50	1.74	0.24	3.58	1.17	3.87	0.92	7.93	1.39	5.01	<0	14.7[b]	1.50
LR test for homogeneity (2 *df*)	*P = 0.23*				*P = 0.68*			*P = 0.38*				
Time since exposure doses received:												
<10 years previous	−0.90	<0	0.35[b]	0.91	−0.44	<0	1.90[b]	0.96	−1.02	<0	nd[c]	0.90
10–20 years previous	0.56	<0	1.74[b]	1.06	0.96	<0	3.19[b]	1.10	0.28	<0	8.13[b]	1.03
>20 years previous	0.50	<0	1.70[b]	1.05	2.83	0.37	5.98	1.28	2.73	<0	24.1[b]	1.27
LR test for homogeneity (2 *df*)	*P = 0.07*				*P = 0.28*			*P = 0.64*				
Different lags												
2 years	0.57	0.03	1.19	1.06	1.46	0.38	2.84	1.15	1.93	<0	7.14	1.19
5 years	0.76	0.17	1.45	1.08	1.62	0.43	3.13	1.16	2.47	−0.78	8.61	1.25
10 years	0.97	0.27	1.80	1.10	1.86	0.49	3.63	1.19	2.53	−0.77	8.80	1.25
15 years	1.03	0.18	2.04	1.10	2.16	0.47	4.35	1.22	4.69	−0.33	13.9	1.47

[a]Based on a linear excess relative risk model unless otherwise indicated.
[b]Wald-based upper confidence bound.
[c]nd: not determined; the confidence bound could not be calculated.

2.16, all estimates being statistically significantly elevated. The ERR/Sv for leukemia excluding CLL increased from 1.93 per Sv for a 2-year lag to 4.69 per Sv for a 15-year lag; it was statistically significantly elevated with a 15-year lag in the log-linear analysis.

Impact of Different Analytical Strategies

Stratification for socio-economic status reduced the ERRs for all four main causes of death shown in Table 6. Without adjustment for SES, the ERR/Sv was 1.24 (90% CI 0.52, 2.07) for all cancers excluding leukemia and 2.88 (90% CI 1.34, 4.79) for lung cancer. The effect of not adjusting for SES was much smaller for all cancers excluding leukemia, lung and pleural cancers (ERR/Sv 0.61, 90% CI −0.12, 1.50), and leukemia excluding CLL (ERR/Sv 2.19, 90% CI <0, 7.59). Including Ontario Hydro, Japan, and INL—the cohorts for which SES classification was not available or not complete—reduced the non-SES-adjusted ERR for the cancer outcomes by about half. This reduction was attributable to a strong and statistically significant negative correlation between radiation dose and cancer risk found at INL and Ontario Hydro.

Stratification for duration of employment had a large effect on the ERR/Sv for all outcomes shown, reflecting a strong healthy worker survivor effect in these cohorts. Removing duration of employment from the analysis resulted in a reduction in estimated ERR/Sv from 0.97 to 0.31 for all cancers excluding leukemia, from 0.59 to 0.21 for all cancers excluding leukemia, lung and pleural cancer, from 1.86 to 0.48 for lung cancer, and from 1.93 to 0.82 for leukemia excluding CLL. None of these ERRs was significantly different from zero.

The inclusion of cancers listed as associated causes of death (i.e. cancer listed on the death certificate but not judged to be the underlying cause of death) had little influence on the risk estimates; it is noted that there were only 322 additional cancer deaths from associated causes. All cancers excluding leukemia, lung and pleural cancers showed the largest relative change in ERR: When cancer deaths coded as associated causes of death were included, the ERR decreased from 0.59 to 0.38.

DISCUSSION

The study reported here included cohorts of nuclear workers from 15 countries, studied using a common core protocol, and is the largest epidemiological study to date with individual estimates of doses from protracted expo-

TABLE 6
Effects of Socio-economic Status (SES), Duration of Employment, Excluded Cohorts, and Associated Causes of Death on ERR per Sv and RR at 100 mSv and Corresponding 90% Confidence Intervals (CI) for Deaths from all Cancers Excluding Leukemia, from all Cancers Excluding Leukemia, Lung and Pleural Cancer, from Lung Cancer, and from Leukemia Excluding CLL: Results from Linear Models

	No.	ERR/Sv	90% CI	RR at 100 mSv
All cancers excluding leukemia				
standard analysis	5,024	0.97	0.27 1.80	1.10
no adjustment for SES	5,024	1.24	0.52 2.07	1.12
no adjustment for SES, including OH, Japan, INEL	6,519	0.64	0.04 1.29	1.06
no adjustment for duration of employment	5,024	0.31	−0.23 0.93	1.03
including associated causes	5,346	0.94	0.26 1.72	1.09
All cancers excluding leukemia, lung, and pleura				
standard analysis	3,528	0.59	−0.16 1.51	1.06
no adjustment for SES	3,528	0.61	−0.12 1.50	1.06
no adjustment for SES, including OH, Japan, INEL	4,578	0.33	−0.31 1.08	1.03
no adjustment for duration of employment	3,528	0.21	−0.41 0.96	1.02
including associated causes	3,760	0.38	−0.31 1.24	1.04
Lung cancer				
standard analysis	1,457	1.86	0.47 3.81	1.19
no adjustment for SES	1,457	2.88	1.34 4.79	1.29
no adjustment for SES, including OH, Japan, INEL	1,895	1.33	0.23 2.68	1.13
no adjustment for duration of employment	1,457	0.48	−0.42 1.62	1.05
including associated causes	1,545	2.24	0.86 3.99	1.22
Leukemia excluding CLL				
standard analysis	196	1.93	<0 7.14	1.19
no adjustment for SES	196	2.19	<0 7.59	1.22
no adjustment for duration of employment	196	0.82	<0 4.62	1.08
including associated causes	205	1.74	<0 6.75	1.17

sures to low levels of photon (X and γ) radiation. It provides direct estimates of the risk of mortality from all cancer, and from specific cancer causes of death, related to low-dose occupational radiation exposure.

All Cancers Excluding Leukemia

This study finds evidence for an increased risk of mortality from all cancers excluding leukemia with increasing radiation dose. The ERR for all cancers excluding leukemia (0.97 per Sv) is higher than, but statistically compatible with, the estimate derived from male adult A-bomb survivors (0.32 per Sv for solid cancer) and the recent BEIR VII (*3*) estimate of 0.26 per Sv for exposure at ages 30 or above and attained age 50 (Table 7). This remains true if the atomic bomb survivor estimates are reduced by a dose and dose-rate effectiveness factor (DDREF) of 1.5 or 2 as has been done when these estimates were used for risk assessments (*3, 4*). It is also higher than central risk estimates obtained in the previous 3-Country nuclear workers combined analyses (ERR/Sv = −0.02) and in the UK NRRW (ERR/Sv = 0.09) (Table 7). Higher risk estimates than that found in the present study have been reported in a small number of studies of nuclear workers (*8, 9, 33*) and of radiation workers in general (*10*). Some of the workers in those studies have been included in the 15-Country Study.

Comparisons of observed and expected numbers of death from all causes, all cancers excluding leukemia, leukemia excluding CLL and multiple myeloma by cumulative dose category in the current study and in the 3-Country Study are shown in Table 8. Despite the more than fourfold increase in numbers of subjects included in the analysis, the total number of deaths from all cancers excluding leukemia increased by only 31%. This small increase is related proportionally to the inclusion of many relatively ''young'' cohorts of nuclear power plants workers (all but a few percent were below the age of 65 at the end of follow-up), few of whom (less than 20%) had more than 20 years of follow-up or received cumulative doses of the order of 50 mSv or more. Indeed, all of the increase in deaths from all causes and all cancers is for doses of less than 50 mSv; in these dose categories, the current study includes 52% more cancer deaths than the 3-Country Study.

One of the major differences between the 3-Country and the 15-Country Studies is the exclusion of workers with potential for substantial (i.e. >10% of the whole-body dose) dose from neutrons and/or internal contamination with nuclides other than tritium, doses that have not been adequately measured. This has resulted in a notable decrease in the number of deaths in the higher dose categories in the current study: There are 27% fewer deaths from all

TABLE 7
ERR Estimates per Sv for all Cancers Excluding Leukemia, Solid Cancers and Leukemia Excluding CLL, for Nuclear Workers and Atomic Bomb Survivors

			Atomic bomb survivors				Previous Nuclear Workers Studies			
	15-Country Study[a]		BEIR VII (*3*)[a,b]		IARC (*24*)[a,c]		3-Country Study (*6*)[d]		UK NRRW (*7*)[d]	
	No.	ERR/Sv (90% CI)	No.	ERR/Sv (90% CI)	No.	ERR/Sv (90% CI)	No.	ERR/Sv (90% CI)	No.	ERR/Sv (90% CI)
All cancers excluding leukemia	5,024	0.97 (0.27, 1.80)					3,830	−0.02 (−0.34, 0.35)	3,490	0.09 (−0.28, 0.52)
Solid cancers	4,770	0.87 (0.16, 1.71)	10,127	0.26[e] (0.15, 0.41)	3,259	0.32[f] (0.07, 0.47)				
Leukemia excluding CLL										
Linear model	196	1.93 (<0[g], 7.14)			83	3.15[h] (1.79, 5.18)	119	2.21 (0.1, 5.8)	91	2.55 (−0.03, 7.2)
Linear-quadratic model			296	2.3[i,j] (0.2, 7.9)[k] 1.4[m] (0.1, 3.4) 1.1[n] (0.1, 2.6)		1.54[i] (−0.76, 4.61)				

[a] Based on colon dose for all cancers excluding leukemia and for solid cancers; on bone marrow dose for leukemia.
[b] Based on mortality data 1950–2000 (*30*).
[c] Men exposed between the ages of 20 and 60; analyses conducted at IARC (*24*).
[d] Based on recorded doses.
[e] For exposures at ages 30+ and attained age 50.
[f] Based on solid cancer mortality data 1950–1997 (*24*); estimate is for men exposed at age 35.
[g] <0: Lower confidence bound is on boundary of parameter space (−1≈maxdose).
[h] Based on leukemia mortality data 1950–1990 *(24)*; estimate is for men.
[i] Linear term of linear-quadratic ERR model with modification by sex, age at exposure and time since exposure.
[j] Estimate is for males, exposed at age 30 or more, 5 years since exposure.
[k] These confidence limits apply to models in which both linear and quadratic coefficients are estimated. If the curvature (ratio of quadratic to linear coefficient) is fixed, the confidence intervals are much tighter 2.3 (0.8, 5.9), 1.3 (0.7, 2.3), 1.1 (0.6, 1.8).
[l] Linear term of linear-quadratic model.
[m] Estimate is for males, exposed at age 30 or more, 15 years since exposure.
[n] Estimate is for males, exposed at age 30 or more, 25 years since exposure.

cancers excluding leukemia and leukemia excluding CLL in the 15-Country Study compared to the 3-Country Study in the 50 mSv or above category; these percentages increase to 60 and 82%, respectively, in the 200 and 400 mSv and above categories (Table 8). Therefore, many of the higher-dose workers from the previous UK, U.S. and Canadian analyses have been excluded from the current analyses. These workers also tended to have lower mortality rates (RR in the current study for excluded compared to included workers 0.85, 95% CI 0.81–0.89 for all-cause

TABLE 8
Comparison of Observed and Expected Numbers of Death from Selected Causes of Death in the 3- and 15-Country Studies

Cancer category	Total	Dose category (mSv) 0−	10−	20−	50−	100−	200−	400+
All causes								
3-Country	15,825	9,582/9,506.3	1,848/1,916	1,880/1,910	989/986.5	702/719.2	586/549.2	238/238.2
15-Country	18,993	13,608/13,692	1,960/1947	1,768/1752	855/831.8	492/476.7	268/258.2	42/35.3
All cancer but leukemia								
3-Country	3,830	2,234/2,228	462/465.4	445/476.9	276/254	196/190.5	161/147.5	56/67.3
15-Country	5,024	3,547/3,581.3	500/513.6	476/475.4	249/236.2	165/133.3	75/73.6	12/10.8
Leukemia excluding CLL								
3-Country	119	60/62.0	19/17.2	14/17.4	8/9.0	8/6.4	4/4.7	6/2.3
15-Country	196	135/132.2	23/23.6	19/22.2	9/10.4	6/5.2	3/2.2	1/0.3
Multiple myeloma								
3-Country	44	28/26.6	3/5.2	1/4.7	5/2.7	3/2.1	2/1.9	2/0.8
15-Country	83	68/66.6	4/6.3	3/6.0	4/2.5	3/1.2	1/0.4	0/0.0

mortality and 0.88, 95% CI 0.80–0.96 for all cancers excluding leukemia), as also observed previously in Hanford workers (*34, 35*). The reasons for this are unclear and include a possibly stronger healthy worker survivor effect and/or a different smoking behavior relative to other radiation workers. Workers with potential for substantial dose from neutron exposure and/or internal contamination therefore had a large impact on the relationship between external photon doses and cancer risk, and their exclusion changes the risk estimates.

Other differences from previous analyses are the exclusion of workers employed for less than 1 year (this criterion was less than 6 months in the 3-Country Study), the longer follow-up in some of the cohorts, and the stratification by duration of employment. The latter, which was used in this study but not in the previous one, has a large impact on the risk estimate for all cancers excluding leukemia. Analysis of the sub-cohorts and their years of follow-up from the main study population who were also included in the 3-Country analyses gave an ERR/Sv of 0.67 (90% CI −0.24, 1.79) for all cancers excluding leukemia based on 2662 deaths. Analyses excluding the sub-cohorts and years included in the 3-Country Study also yielded an elevated risk estimate (ERR/Sv: 1.31, 90% CI 0.27, 2.59), based on 2,362 deaths.

As discussed elsewhere (*23*), formal tests for heterogeneity did not provide statistically significant evidence of differences in risk estimate for all cancers excluding leukemia between countries, cohorts or groups of facilities. Exclusion of Canada had the highest impact on the ERR/Sv, reducing the combined estimate by about 40%, to a level that was no longer statistically significantly different from 0. The ERR for Canada in the current study (6.65 per Sv) is larger than that reported (2.80 per Sv) by Zablotska *et al.* (*12*). Differences are mainly related to the exclusion of Ontario Hydro (Table 3), a facility in which SES was missing for a large proportion of the workers and in which there was a significant negative trend in mortality with dose (ERR/Sv −1.97). Including Ontario Hydro in the international combined analyses, however, had little impact on the overall risk estimate: ERR 0.89 per Sv (90% CI 0.21, 1.69). While the ERR for Canada appears to be unusually high and the lower confidence bound does not include the combined estimate, reviews of historical dosimetric practices and records have not provided any explanation for this. Analyses excluding Canada, as well as analyses excluding one country at a time, all yielded ERRs consistently higher than, but compatible with, the risk estimate from A-bomb analyses and the BEIR VII estimate; the study therefore provides important evidence for cancer risks due to low-dose protracted exposures.

Excluding lung and pleural cancer from the all cancers excluding leukemia group—to assess possible confounding by smoking and/or other occupational exposures—reduced the statistical power since it removed almost a third of all deaths and hence broadened the confidence interval around the risk estimate. As shown in Fig. 1, however, risk estimates for all cancers excluding leukemia and for all cancers excluding leukemia, lung and pleural cancers are very similar above 200 mSv. Further, all groups of smoking- and non-smoking-related cancer causes of death that were analyzed give central risk estimates per unit dose that are consistently two- to threefold higher than, but statistically compatible with, the risk estimate per unit dose for solid cancers from the A-bomb analyses and from BEIR VII. As discussed previously (*23*), we cannot exclude the possibility that a confounding effect by smoking or other occupational exposures was partly responsible for the increased risk found for mortality from all cancers other than leukemia and hence that the risk estimates for all cancers excluding leukemia in this study are overestimated. The balance of findings indicates, however, that it is unlikely that the entire increase can be explained by confounding due to smoking.

A statistically significantly increased risk was seen only among workers in mixed-activity facilities. Although this may reflect a difference in exposure conditions, it should be noted that the power to find an increase among nuclear power plant workers was low. There were three times fewer deaths among those workers, a shorter follow-up (4% of the person-years were accumulated in the 20 years or more since start of follow-up category, compared to 20% in the mixed-activities cohort), and the cumulative doses were generally lower than in mixed-activity facilities.

Studies of the temporal behavior of risk have been carried out in a number of cohorts of nuclear workers previously. An association between age at exposure and/or attained age and the risk of radiation-induced cancer has been reported in three cohorts in the U.S., Hanford (*36–38*), ORNL (*39*) and Rocketdyne (*33*), but not in the other cohorts included in the 3-Country Study (*6*). In the current study, the highest ERRs per Sv were found for attained ages of 70 or above for all cancers excluding leukemia, all cancers excluding leukemia, lung and pleural cancers, lung cancer as well as leukemia excluding CLL. However, differences between age groups were not statistically significant. Analyses of age at exposure also indicated that doses received later in life might entail a higher risk than doses received earlier in this adult population. Indeed, *post hoc* analyses comparing the effects of exposures received before age 35 and at or after age 35 provided some evidence, of marginal statistical significance, for heterogeneity of risk. Analyses excluding Hanford and ORNL gave very similar results. It is unclear whether these results reflect a greater susceptibility with age or a pattern of residual confounding that is related to cumulative doses accrued at older ages. Patterns of risk varied significantly with time since exposure due to negative risk estimates for doses received less than 10 years previously.

Leukemia

The risk estimate for leukemia excluding CLL derived from this study is raised (ERR/Sv = 1.93) but is not sig-

nificantly different from zero. The central estimate of the risk is intermediate between the risk estimates derived from a linear (ERR/Sv = 3.15) and linear-quadratic (ERR/Sv = 1.54) dose–response model fitted to the A-bomb survivors' data on men exposed as adults (Table 7) and is similar to the BEIR VII estimates (ERR/Sv = 1.1–2.3 for exposures at age 30 or above, received 5–25 years in the past). In addition, it is very similar to estimates obtained from the 3-Country Study (ERR/Sv = 2.21) (*6*) and the NRRW study (ERR/Sv = 2.55) (*7*) (Table 7).

As seen in the 3-Country Study and the UK NRRW study (*6*), the main leukemia subtypes showing a positive association with radiation dose were chronic myeloid leukemia and combined acute leukemia. No evidence for an association with radiation dose was found for CLL or for the acute leukemia subtypes (ALL, AML) analyzed separately; the power of these analyses was low, however, and for a large proportion of acute leukemia (37/137) it was not possible to classify whether they were ALL or AML.

Results of the 15-Country Study are not independent of those from the other studies of nuclear workers shown in Table 7. Indeed, the analyses presented here included 79 deaths from leukemia excluding CLL from the cohorts and years of follow-up included in the 3-Country analyses and 54 from the NRRW (note that these two studies are also not independent). When analyses were restricted to the subcohorts and years of follow-up not included in the 3-Country analyses, the leukemia ERR was 2.16 per Sv (90% CI <0, 10.6), based on 117 deaths. Excluding the UK data led to an estimate of 2.61 per Sv (90% CI <0, 10.3), based on 142 deaths. Therefore, although there is an overlap between these studies, similar conclusions would be drawn if analyses were based only on the new cohorts.

The difference in the statistical significance of the leukemia results reported here and that reported in the 3-Country Study is likely to be due to the smaller number of subjects with relatively high doses in the current study. Although the number of leukemia deaths in the main study population in the 15-Country Study is nearly twice the number from the previous 3-Country Study, most of the additional leukemia deaths occurred in subjects with low doses (Table 8). In addition, and as discussed above, there was a reduction in the number of high-dose leukemia deaths due to the exclusion of workers with potential for substantial doses from neutrons and/or internal contamination. The current analyses included 60% fewer leukemia deaths in the 200 mSv or more category than the 3-Country Study as shown in Table 8, and only one death above 400 mSv (compared with six in the previous study).

Furthermore, although no significant relationship was observed overall between radiation dose and mortality from leukemia excluding CLL, a significantly increased risk was seen for those with ages at exposure above 50. Higher risk estimates were also seen among subjects with highest attained age (above 70) for doses received 20 years or more previously, as well as with increasing lag times. However, these differences in risk by age and time were not statistically significant. It should be noted that the preferred ERR models for the A-bomb data and for BEIR VII include effects of age at exposure and time since exposure (*40*), whereby exposures at an early age confer a higher risk than exposures later in life (with little decrease in risk, however, after age 30 in BEIR VII) and the ERR decreases with time since exposure. While these results are not incompatible with the findings from this study, it should be noted that patterns of cancer risk after low-dose protracted exposures may not necessarily be the same as those observed in the A-bomb study.

Specific Cancer Types

Most of the 31 cancer types or groupings of cancer studied showed little or no association with radiation dose. Despite the size of the study, power to detect such associations was low because of the relatively small number of deaths for many specific cancer types.

Lung cancer was the only cancer to show a statistically significantly raised ERR. Previous nuclear workers studies have found both positive (*9, 10, 12, 39*) and negative (*6, 7, 22*) dose–response relationships between lung cancer and radiation dose. Lung cancer has been observed to be related to radiation dose in the A-bomb survivors (*41*) and in some studies of medically exposed populations [reviewed in ref. (*3*)] as well as among workers exposed to external radiation at Mayak in the former USSR (*42*), although the risk estimates were generally lower than that found in the current study. The BEIR VII estimate is 0.32 per Sv for men exposed at age 30 or above and attained age 60 (*3*).

Smoking confounding has been postulated as an explanation for the positive association found for lung cancer incidence and mortality in radiation workers included in the Canadian National Dose Registry (*10, 11*) as well as for the negative association between lung cancer and radiation dose in the NRRW and INL cohorts (*7*, *22*). The association found for lung cancer in this study should therefore be interpreted with caution, but it warrants further investigation in studies that can collect information about individual smoking habits and other occupational exposures.

Apart from lung cancer, multiple myeloma was the only specific type of malignancy to exhibit a borderline statistically significant association with radiation dose in this study. The ERR for multiple myeloma was 6.15 per Sv in the combined data set, larger than the estimate for leukemia and much larger than the estimate for all cancers excluding leukemia. Evidence exists for radiation-induced multiple myeloma from other studies, but it is not consistent (*2, 43*).

Among nuclear industry workers, statistically significant associations between multiple myeloma mortality and radiation dose have previously been reported for workers at Hanford (*44*) and Sellafield (*45*) as well as in the 3-Country Study (*6*), where the association largely reflected the previously reported associations in the Hanford and Sellafield

cohorts. In the current study, significant positive associations with radiation dose were seen in Sweden based on three deaths and Hanford based on 22 deaths. Most (N = 34) of the additional multiple myeloma deaths came from new cohorts, but the numbers of deaths in most cohorts and countries were very small (only the UK and the U.S. had more than 10 multiple myeloma deaths). Most of the previously reported high-dose multiple myeloma deaths, particularly from Sellafield, were excluded from the current study (Table 8). Since multiple myeloma is a disease with a relatively late age at onset, many of the new cohorts included in this study are in fact too young to provide much information about this risk.

Dosimetric Measurement Errors

Reliable estimates of dose were available systematically only for dose from external exposure to higher-energy photons. Since some workers could have received significant doses from other types of radiation, which were not always included in the dose estimates, substantial efforts were made to identify such workers and exclude them from the main study population. Results presented here are therefore restricted to those workers whose radiation dose is predominantly from relatively well-measured radiation types. Recorded doses from these radiation types were subject to systematic and random errors, related to dosimetry technology and administrative practices to monitor and record doses. A detailed study of historical practices and technology allowed the identification and quantification of the major dosimetric errors (*25*). As mentioned above, analyses are based on estimates of organ doses, which have been adjusted to take into account systematic errors related to dosimetry technology, radiation fields and calibration. However, uncertainties in the systematic errors have not been taken into account. Models to incorporate the uncertainties have been developed (Stayner *et al.,* manuscript submitted for publication), and detailed analyses are under way. Preliminary results indicate that they are likely to have little effect on the central risk estimates but will lead to somewhat wider confidence intervals.

Dosimetric errors from monitoring and recording practices, although considered, were not quantified in the current study, since no practice was identified which would lead to a substantial bias (*25*). It is noted that consideration of such errors by other authors have shown that their impact on risk estimates is often minor (*46–48*).

Errors in Outcome Data

Both vital status and cause-of-death ascertainment were estimated to be nearly complete in the study cohorts. As noted in the accompanying paper, however, a number of countries conducted passive follow-up, and SMRs in some countries are quite low; hence the possibility that vital ascertainment is in fact lower than reported cannot be excluded. Such underascertainment could induce bias and additional variability in risk estimates (*49*). Since follow-up was based on population registration systems in these countries, however, it is unlikely that any underascertainment would be differential with respect to dose, except possibly for workers who may have died or emigrated in the early part of the follow-up when population registration may have been incomplete. Further, all analyses were adjusted for calendar period, and additional analyses, restricted to person-years and deaths accrued since 1970 (not shown), yielded essentially identical results to those based on the full study population.

The likelihood of errors in outcome data is discussed in the accompanying methods paper (*14*). Since the study is based on cause of death recorded on death certificates, and since the majority of deaths occurred after the worker left employment or retired, it is unlikely that any misclassification of underlying cause of death would have been related to radiation dose. This is supported by the observation that risk estimates changed very little when cancers coded as associated causes of deaths (information available in eight countries) were included, although the number of such deaths was relatively small. Among the leukemia deaths in this study, only nine were listed as associated cause of death (five of these had another type of cancer as the underlying cause of death); hence the potential for misclassification of leukemia deaths seems minimal. Based on results of previous studies of death certificate coding (*50*), however, it is likely that misclassification of specific cancer causes occurred and this may have affected risk estimates for these specific causes; however, this would not affect the risk estimates for the group of all cancers combined.

Potential Confounding Factors

A limitation of this study is that it was not possible to directly adjust for potential confounding by variables such as smoking habits, diet and occupational exposure to other carcinogens, since information on these exposures was not available. This is of concern since, when evaluating *a priori* small increases in risk, even a small amount of confounding can seriously bias risk estimates (*51*). As discussed previously, however (*23*), although confounding by smoking may be present, it is unlikely to explain all of the increased risk for all cancers excluding leukemia in this study.

A major strength of the current study is that an SES measure was developed for most countries and that all analyses of solid cancer categories were stratified on this measure. This measure, which is meant as a surrogate for lifestyle factors (in particular tobacco smoking and also diet) was found to be an important confounder in this study since it was associated with both cancer mortality and exposure potential in most countries (*14*). The SES classification unavoidably differed in different countries, both in the measure on which it was based (occupation or educational level) and in the level of detail of the available measure (*14*). Stratification on SES in the analyses allowed the effect of

SES to be different in different countries/cohorts, however. Cohorts with an unsatisfactory level of SES information were excluded from the main analyses of cancer risk. Adjustment for SES had a substantial effect on the risk estimates for all cancers excluding leukemia, for lung cancer, and for all non-cancers. Although residual confounding cannot be excluded (since a surrogate measure cannot entirely compensate for lack of direct data), the fact that the risk estimates for all cancers excluding leukemia, lung and pleura cancers, and the estimates for leukemia excluding CLL appear relatively insensitive to the effects of SES, indicate that it is unlikely that residual confounding would explain the increased risk estimates for these outcomes. Inclusion of the cohorts with inadequate levels of SES information (Ontario Hydro in Canada, Japan, and INL in the U.S.) led to lower risk estimates for all cancers and lung cancer. These results, however, were driven mainly by strongly negative risk estimates in the INL and Ontario Hydro cohorts, and negative confounding by smoking has been postulated as an explanation for this at INL (*22*).

Duration of employment was considered *a priori* to be a possible confounder in the relationship between radiation dose and mortality and was therefore included in the main analyses in this study. A potential confounding effect related to duration of employment would work through the so-called healthy worker survivor effect, an effect that occurs in occupational studies using cumulative doses when workers who stay in employment longer, and may have accumulated higher doses, are those who are healthier and therefore have lower mortality rates (*52*); this effect is consistent with the finding of decreasing SMRs with increasing duration of employment seen in a number of the study cohorts (*14*). Any such confounding would bias risk estimates toward no effect. There was strong evidence of confounding by duration of employment in this study: Duration of employment was seen to be related both to cumulative dose and to cancer risk, and risk estimates for the main study outcomes (all cancers excluding leukemia, all cancers excluding leukemia, lung and pleural cancers, leukemia excluding CLL, and lung cancer) were increased by adjustment for duration of employment.

Implications for Radiation Protection

The U.S. National Academy of Sciences Committee on the Biological Effects of Ionizing Radiation, BEIR VII (*3*), has recently reviewed the scientific evidence concerning health effects of low levels of low-LET ionizing radiation. The Committee concluded that the current evidence is ''consistent with the hypothesis that there is a linear, no-threshold dose–response relationship between exposure to ionizing radiation and the development of cancer in humans.'' Results presented here, providing evidence of risk from the protracted low doses received by nuclear workers in this study, are consistent with the BEIR VII conclusions. The study, however, cannot address effects at very low doses, of the order of tens of mSv. Further, the power of the study is inadequate to investigate the shape of the dose response, even in the dose range under study.

This study is useful in that it provides specific direct information about the effects of dose rate and exposure protraction that complements the studies on which current risk estimates are based, in particular that of the atomic bomb survivors. Caution, however, should be exercised in the use of these risk estimates for radiation protection because of the potential overestimation of the risk due to possible confounding, particularly by smoking. Future studies, in particular a case–control study of lung cancer nested within the cohort, using detailed individual data on smoking and other potential occupational carcinogens, will be important to better quantify the effect of residual confounding on the radiation risk estimates.

CONCLUSIONS

This paper examines the relationship between radiation dose and cancer mortality and presents radiation risk estimates from the largest study of low-dose protracted exposures to photon radiation conducted so far. The paper also assesses the influence of confounding factors, effect modifiers, and different analytical strategies on the risk estimates. Significantly increased risks were found for mortality from all cancers excluding leukemia and from lung cancers. Analyses of smoking- and non-smoking-related causes of death indicate that, although confounding by smoking may be present, it is unlikely to explain all of this increased risk. Both SES and duration of employment were found to be important confounders of the association between radiation dose and mortality from all cancers excluding leukemia in this study.

Risk estimates per unit dose from this study are statistically compatible with estimates that serve as the basis for current radiation protection standards. They range from values lower than the BEIR VII estimates up to values that exceed these estimates by a factor of about six for both solid cancers and leukemia.

This is the largest analytical epidemiological study of the effects of low-dose protracted exposures to ionizing radiation to date. Further studies will be important to better assess the role of tobacco and other occupational exposures in our risk estimates

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