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Mortality from diseases other than cancer following low doses of ionizing radiation: results from the 15-Country Study of nuclear industry workers

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Background Ionizing radiation at very high (radio-therapeutic) dose levels can cause diseases other than cancer, particularly heart diseases. There is increasing evidence that doses of the order of a few sievert (Sv) may also increase the risk of non-cancer diseases. It is not known, however, whether such effects also occur following the lower doses and dose rates of public health concern.

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Methods We used data from an international (15-country) nuclear workers cohort study to evaluate whether mortality from diseases other than cancer is related to low doses of external ionizing radiation. Analyses included 275 312 workers with adequate information on socioeconomic status, over 4 million person-years of follow-up and an average cumulative radiation dose of 20.7 mSv; 11 255 workers had died of non-cancer diseases.

Results The excess relative risk (ERR) per Sv was 0.24 [95% CI (confidence intervals) −0.23, 0.78] for mortality from all non-cancer diseases and 0.09 (95% CI −0.43, 0.70) for circulatory diseases. Higher risk estimates were observed for mortality from respiratory and digestive diseases, but confidence intervals included zero. Increased risks were observed among the younger workers (attained age <50 years, identified *post hoc*) for all groupings of non-cancer causes of death, including external causes. It is unclear therefore whether these findings reflect real effects of radiation, random variation or residual confounding.

Conclusions The most informative low-dose radiation study to date provides little evidence for a relationship between mortality from non-malignant diseases and radiation dose. However, we cannot rule out risks per unit dose of the same order of magnitude as found in studies at higher doses.

Keywords Radiation, ionizing, radiation effects, cohort studies, occupational diseases, cardiovascular diseases, digestive system diseases, respiratory tract diseases

Introduction

Ionizing radiation is a well-established human carcinogen. At high doses, ionizing radiation exposure is also known to cause non-cancer effects. Excess cardiovascular mortality has been observed in studies of patients treated with radiotherapy for breast cancer[1–4] and Hodgkin's disease[5] who received doses of 10 sievert (Sv) or more to the heart at high dose-rates (for simplicity, all doses in this article are expressed in terms of equivalent dose in Sv to a particular tissue (colon, lung). As this article 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[6]). Very high doses of radiation to the heart can result in fibrotic and small vessel damage in the pericardium, myocardium and coronary vasculature, with subsequent myocardial infarction being the most common fatal complication.[7]

Non-cancer late effects have been documented at lower doses among the atomic bomb survivors.[8–12] Radiation-related excess mortality and morbidity due to circulatory, digestive and respiratory diseases have been observed in this cohort at doses below 4 Sv; however, a threshold as high as 500 mSv could not be ruled out.[11] Other studies of populations with doses below 5 Sv have, to date, not shown a consistent pattern of increases in mortality from circulatory disease (reviewed by McGale and Darby),[13] although a dose-related increase in coronary heart disease was observed recently in patients receiving radiotherapy for peptic ulcer with cardiac doses ranging from 1.6 to 3.9 Sv.[14] Further, a recent study among Chernobyl clean-up workers, with an average whole-body dose of 100 mSv, reported an increased risk of ischaemic heart disease, essential hypertension and cerebrovascular disease; analyses were, however, not adjusted for smoking or alcohol consumption.[15]

Given the nature of the radiation damage to the heart and vessels observed following radiotherapy,[7] it is not known whether any increased risk is in fact expected following the low doses (of the order of a few tens of mSv) received in a protracted or fractionated fashion that are of public health concern. If such effects were confirmed, this would have important implications for radiation protection of medically, occupationally and environmentally exposed-populations, as well as for the understanding of the aetiology of circulatory and other non-cancer diseases.

Workers in the nuclear industry are a suitable population for the direct estimation of radiation effects at low doses: they form large, relatively stable populations with relatively well-measured and well-recorded external radiation doses. Large studies of combined cohorts of nuclear workers have previously reported no radiation-related excess in mortality from non-cancer diseases as a group.[16,17] A dose-related increased mortality from circulatory diseases has been observed in some studies of nuclear industry workers,[17,18] but it is unclear whether this reflects a real effect of radiation exposure or residual confounding.

This article evaluates whether mortality from diseases other than cancer is related to radiation dose in the 15-Country Study of nuclear industry workers.

Methods

The 15-Country Study is a multi-national retrospective cohort study, in which the mortality of nuclear industry workers from 15 countries was studied. In this article, 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, the production of radioisotopes or reactor or weapons research; uranium mining is not included. Radiation-related cancer risk estimates from the 15-Country Study have been published elsewhere,[19,20] as have the detailed methods of the follow-up[20] and dosimetry.[22] The main study population was defined[21] 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). For the non-cancer analyses presented here, workers also had to have been followed for non-cancer mortality (this excludes the Japanese cohort), and have adequate socioeconomic status (SES) information (this excludes the Japanese, US-Idaho National Laboratory and Canada-Ontario Hydro cohorts).[21]

For each worker monitored for external radiation exposure, individual annual recorded radiation doses were obtained from facility records and/or national dose registries. Doses to specific organs were derived by dividing the recorded doses by organ dose bias factors developed in a study of errors in doses.[22] In this article, lung doses are used for respiratory diseases and colon doses for all other diseases, as was done in the study of atomic bomb survivors.[11]

Statistical analysis

Consistent with previous analyses of this cohort,[20] doses and person-years at risk for each worker were accumulated over time from date of entry in the study to date of exit. To allow for a possible latent period between an exposure and its effect, cumulative doses were lagged by 10 years, for consistency with radiotherapy studies.[4,7] Sensitivity analyses used a range of different lag times.

Observed (O) and expected (E) numbers of deaths and person-years of follow-up were calculated by eleven dose categories (0–, 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 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 based on the linear relative risk model was used to test the statistical significance of the trend in O/E ratios.[23]

Analyses were based on a linear relative risk Poisson model, in which the relative risk is of the form $1+\beta Z$, where Z is the lagged cumulative dose in Sv, and β is the excess relative risk (ERR) per sievert. This model has been used commonly in analyses of nuclear workers studies[16,17] and radiation risk estimation.[6,24] The linear RR model has computational restrictions, however, as the relative risk cannot be negative. Log-linear models, in which the relative risk (RR) is assumed to be of the form $\exp(\beta Z)$, were therefore also fitted to the data. Resulting estimates of the RR at a dose of 100 mSv compared with 0 mSv are presented where β could not be estimated under the linear model. Linear RR and log-linear models give essentially the same results at low doses and low risks. Confidence intervals are 95% likelihood-based intervals.

All analyses (trend tests and regression models) were stratified on sex, age and calendar period (both in 5-year categories), facility, duration of employment (<10 years, ⩾10 years) and SES.

The risk of radiation-induced disease may vary among subgroups of the study population (gender, study-cohort, facility type) and by variables such as attained age, age at exposure and time since exposures.[11] Heterogeneity of risk estimates was tested using likelihood ratio tests for the interaction of gender, cohort, facility type and age with dose. A priori defined categorical variables were used to evaluate variation in risk by attained age (<60, 60–70, 70+ years), age-at-exposure (<35, 35–50 and 50+ years) and time-since-exposure (<10, 10–20 and 20+ years). For age-at-exposure and time-since-exposure, the cumulative doses received in each of the three categories were modelled jointly, and the likelihood of this model was tested against that of the standard model with one total cumulative dose.

Outcomes studied

Results are presented for mortality from all non-malignant (non-cancer) diseases combined and for the main groupings of specific non-cancer diseases: circulatory diseases, respiratory diseases excluding pneumonia and digestive diseases. Particular attention is paid to circulatory diseases, because of the evidence from high-dose studies discussed above. Mortality from chronic obstructive pulmonary disease, liver cirrhosis and external causes were also studied as indirect indicators of potential for confounding by, respectively, smoking, alcohol consumption and more general life-style related factors. The ICD codes defining these causes of death have been published elsewhere.[21] Only underlying causes of death were analysed. Because of limited statistical power, analyses of age-at-exposure and time-since-exposure were carried out only for all non-cancer diseases combined and for circulatory diseases.

Results

The study population for the non-cancer analyses included 275 312 workers with a total duration of follow-up of 4 067 861 person-years and a total collective recorded dose of 5690 Sv (Table 1). The average cumulative recorded dose was 20.7 mSv; <0.1% of workers had received cumulative doses >500 mSv over their entire career in the nuclear industry.[19] The average individual colon dose and lung dose were 16.9 and 17.9 mSv, respectively.

A total of 13 315 workers died from causes other than cancer, 2060 from external causes of death and 11 255 from non-cancer diseases; the majority of these latter deaths were from circulatory diseases ($n=8412$) (Table 2). The ERR per sievert for mortality from all non-cancer diseases was 0.24 (95% CI −0.23, 0.78) (Table 2). The corresponding trend test gave little evidence for an increase in risk with dose ($P=0.16$). There was no evidence of a dose–response for circulatory disease mortality overall (ERR/Sv = 0.09;

Table 1 Cohorts included in non-cancer analyses of the 15-Country Study (adapted from Cardis *et al*. 2005[19])

	Number of facilities	Earliest year of start of operations	Follow-up period	Number of workers	Person-years	Collective cumulative dose (Sv)	Average cumulative recorded dose (mSv)	Deaths from non-cancer diseases
Australia	1	1959	1972–98	877	12 110	5.4	6.1	31
Belgium	5	1953	1969–94	5037	77 246	134.2	26.6	142
Canada excl OH	4	1944	1956–94	15 967	239 789	333.3	20.9	323
Finland	3	1960	1971–97	6782	90 517	53.2	7.8	180
France								
CEA-COGEMA	9	1946	1968–94	14 796	224 370	55.6	3.8	252
France EDF	22	1956	1968–94	21 510	241 391	340.2	15.8	97
Hungary	1	1982	1985–98	3322	40 557	17.0	5.1	45
Korea (south)	4	1977	1992–97	7892	36 227	122.3	15.5	14
Lithuania	1	1984	1984–00	4429	38 458	180.2	40.7	35
Slovakia	1	1973	1973–93	1590	15 997	29.9	18.8	12
Spain	10	1968	1970–96	3633	46 358	92.7	25.5	17
Sweden	6	1954	1954–96	16 347	220 501	291.8	17.9	333
Switzerland	4	1957	1969–95	1785	22 051	111.2	62.3	17
UK	32	1946	1955–92	87 322	1 370 101	1810.1	20.7	5044
US Hanford	1	1944	1944–86	29 332	678 833	695.4	23.7	3673
US NPP	15	1960	1979–97	49 346	576 682	1336.0	27.1	412
US ORNL	1	1943	1943–84	5345	136 673	81.1	15.2	628
				275 312	4 067 861	5689.6	20.7	11 255

Note: Workers at OH (Canada), Idaho National Laboratories (USA) and in Japan have been excluded from this analysis for the reasons given in the Methods section. They were included in the leukaemia analyses presented elsewhere[19,20].

CEA-COGEMA, Commissariat à l'Energie Atomique – Compagnie Générale des Matières Nucléaires; EDF, Electricité de France; NPP, Nuclear Power Plants; OH, Ontario Hydro; ORNL, Oak Ridge National Laboratory.

95% CI −0.43, 0.70; P for trend = 0.37) or for mortality from specific circulatory diseases. Elevated ERRs/Sv were observed for cerebrovascular diseases (ERR/Sv = 0.88; 95% CI −0.67, 3.16) and for the category 'other circulatory diseases' (ERR/Sv = 0.29; 95% CI < 0, 2.40), but confidence intervals included zero.

Risk estimates for mortality from all non-malignant respiratory diseases (ERR/Sv = 1.16; 95% CI −0.53, 3.84), chronic obstructive pulmonary disease (ERR/Sv = 0.56; 95% CI < 0, 3.77), all digestive diseases (ERR/Sv = 0.96; 95% CI < 0, 4.52) and liver cirrhosis (ERR/Sv = 1.54; 95% CI < 0, 9.67) were elevated but confidence intervals included zero. External causes of death showed a negative ERR/Sv (–0.50, 95% CI < 0, 1.08) (Table 2).

There was little evidence for radiation-related increases in mortality from non-cancer diseases overall or from specific disease groups in individual countries, or for heterogeneity of risks between countries, cohorts or facility types (Supplementary Table A). However, numbers of deaths were small in many countries and the confidence intervals were wide. Elevated risks were, nevertheless, seen in the US-NPP cohort, for all non-cancer diseases (ERR/Sv = 5.99; 95% CI 1.75, 12.4) and for circulatory diseases (ERR/Sv = 6.04; 95% CI 1.36, 13.5).

The ERRs/Sv in men were very similar to those observed in the entire population for mortality from all non-cancer diseases as well as from circulatory, respiratory and digestive diseases (Table 3; Supplementary Table B), reflecting the fact that the study population consisted mainly of men (90%) who received 98% of the collective dose. There was no evidence for a difference in risk between men and women.

There was some evidence for heterogeneity of risk by attained age category for non-cancer diseases as a group although confidence intervals for the different age groups overlapped (heterogeneity $P = 0.10$); the ERR/Sv was highest for attained ages below 60 years (ERR/Sv = 1.25; 95% CI −0.03, 2.83) (Table 3). More detailed analyses conducted *post hoc* of attained age in four categories (Table 4) showed that the elevated risks were found mainly in the age group below 50 years, and that the increased risk in this age category was seen for each grouping of non-cancer causes of death, including external causes.

There was no evidence for a difference in radiation-related risk by age at exposure for all non-cancer diseases or for circulatory diseases (Table 3). Differences in ERR/Sv estimates were found, however, between time-since-exposure categories for both of these outcomes; this was due to negative ERRs/Sv for doses received <10 years previously (Table 3). Risk estimates tended to increase with increasing lag time for all non-cancer diseases overall, as well as for circulatory, respiratory and digestive diseases (Table 3; Supplementary Table B).

Table 2 Mortality from diseases other than cancer in relation to radiation dose: observed and expected numbers of deaths by cumulative radiation dose, trend test statistic and Poisson regression results

			Cumulative Dose (mSv)													
Cause of death	***N***		**<5**	**5–**	**10–**	**20–**	**50–**	**100–**	**150–**	**200–**	**300–**	**400–**	**500+**	**Trend (*P*-value)[b]**	**ERR/Sv (95% CI)**	**RR at 100mSv[a]**
All non-cancer causes[c]	13 315	Obs	8076	1465	1405	1248	587	204	114	133	55	20	8	0.87	0.20	1.02
		Exp	8164.7	1432.5	1378.6	1228.2	574.1	215.4	118.2	124.2	55.1	14.9	9.0	(0.19)	(−0.26, 0.72)	
External causes	2060	Obs	1605	133	122	111	51	20	7	9	2	0	0	−0.36	−0.50	0.95
		Exp	1622.6	129.7	113.6	104.3	50.3	18.1	8.4	9.4	2.5	0.6	0.4	(0.64)	(<0[d], 1.08[e])	
Non-cancer diseases	11 255	Obs	6471	1332	1283	1137	536	184	107	124	53	20	8	0.99	0.24	1.02
		Exp	6542.1	1302.8	1265.0	1123.9	523.8	197.2	109.8	114.8	52.6	14.3	8.7	(0.16)	(−0.23, 0.78)	
Circulatory diseases	8412	Obs	4818	995	972	853	398	139	82	95	43	11	6	0.32	0.09	1.01
		Exp	4854.2	978.9	952.9	845.5	400.5	150.5	84.1	88.9	39.1	10.8	6.7	(0.37)	(−0.43, 0.70)	
Ischaemic heart disease	5821	Obs	3334	683	679	586	276	100	55	65	30	8	5	−0.02	−0.01	1.00
		Exp	3333.6	681.8	665.8	588.5	283.8	106.7	59.1	61.6	27.7	7.8	4.6	(0.51)	(−0.59 0.69)	
Heart failure	130	Obs	81	17	13	10	5	1	0	1	2	0	0	0.01	−0.03	1.00
		Exp	77.4	15.9	15.5	11.4	5.0	1.9	1.1	1.2	0.4	0.2	0.1	(0.50)	(<0, 4.91[e])	
Deep vein thrombosis and pulmonary embolism	104	Obs	58	8	15	15	4	1	2	1	0	0	0	−0.92	<0	0.74[f]
		Exp	57.1	10.9	12.1	13.0	5.2	2.2	1.4	1.6	0.4	0.1	0.0	(0.82)	– (0.38,1.26)	
Cerebro-vascular diseases	1224	Obs	678	157	139	126	65	21	14	17	4	2	1	0.86	0.88	1.09
		Exp	700.7	144.5	125.7	128.5	59.6	20.9	12.0	14.0	5.6	1.5	1.1	(0.20)	(−0.67, 3.16)	
Other circulatory diseases	1133	Obs	667	130	126	116	48	16	11	11	7	1	0	0.32	0.29	1.03
		Exp	685.5	125.7	123.9	104.2	46.9	18.8	10.6	10.4	5.0	1.3	0.9	(0.38)	(<0, 2.40)	
Respiratory diseases[g]	792	Obs	381	107	118	103	46	14	8	8	3	3	1	1.23	1.16	1.12
		Exp	416.5	101.2	102.9	92.2	42.9	14.5	8.0	7.4	4.9	0.9	0.6	(0.11)	(−0.53, 3.84)	
Chronic obstructive pulmonary disease[h]	475	Obs	224	65	67	65	26	14	6	4	1	1	2	0.54	0.56	1.06
		Exp	244.6	59.1	55.9	60.9	28.4	11.1	5.3	4.8	3.0	1.1	0.7	(0.29)	(<0, 3.77)	
Digestive diseases	620	Obs	388	65	56	65	24	8	3	4	4	3	0	0.93	0.96	1.10
		Exp	400.1	62.6	59.5	50.3	23.3	9.8	5.6	5.5	2.3	0.7	0.4	(0.18)	(<0, 4.52)	
Liver cirrhosis	263	Obs	173	28	23	24	8	1	2	2	1	1	0	0.76	1.54	1.15
		Exp	183.1	23.7	23.4	16.8	7.6	3.3	2.0	2.0	0.8	0.2	0.1	(0.22)	(<0, 9.67)	

[a]Based on a linear excess relative risk model unless otherwise indicated—if RR could not be estimated under the linear model, the RR from a log-linear model is shown.

[b]1-sided *P*-values are presented as there was no reason to suspect that exposure to radiation would be associated with a reduction in risk.

[c]Total of external causes and non-cancer diseases.

[d]<0: The linear excess relative risk model has computational restrictions, as 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 the article.

[e]Wald-based upper confidence bound (likelihood-based bound could not be estimated).

[f]RR (95% CI) from a log-linear model.

[g]Excluding pneumonia.

[h]Including emphysema, chronic obstructive bronchitis, and chronic obstructive pulmonary diseases—not otherwise specified.

ERRs/Sv increased from 0.24 to 0.48 for all non-cancer diseases and from 0.09 to 0.39 for circulatory disease when analyses were not stratified for SES (Table 3). Removing stratification for duration of employment resulted in a reduction in estimated ERRs/Sv from 0.24 to 0.04 for all non-cancer diseases, and from 0.09 to −0.04 for circulatory diseases. Similar results were observed for respiratory and digestive diseases (Supplementary Table B).

Discussion

The 15-Country Study gives little evidence for a relation between mortality from non-malignant diseases and external radiation dose at the low doses received by nuclear industry workers. However, radiation-related non-cancer effects are expected to be small (if they exist at all) at the low doses received by most nuclear workers. Therefore, despite

Table 3 ERR per Sv and RR at 100 mSv by sex, attained age, age at exposure, time since exposure, lag time and alternative stratification strategies—mortality from all non-cancer diseases combined and circulatory diseases

	Non-cancer diseases					Circulatory diseases				
	N	ERR/Sv	95% CI		RR at 100 mSv[a]	*N*	ERR/Sv	95% CI		RR at 100 mSv
Overall	11 255	0.24	−0.23	0.78	1.02	8412	0.09	−0.43	0.70	0.01
Gender										
Men	10 700	0.25	−0.23	0.80	1.03	8067	0.10	−0.43	0.71	0.01
Women	555	<0	–		0.76[b] (0.30, 1.63)	345	<0	–		0.86[b] (0.29, 2.08)
LR test for homogeneity (1 df)		*P* = 0.51					*P* = 0.71			
Attained age										
<60 years	3777	1.25	−0.03	2.83	1.12	2810	0.75	−0.59	2.46	1.08
60–70 years	3464	−0.31	−0.91	0.45	0.97	2685	−0.49	−1.02	0.32	0.95
>70 years	4014	0.41	−0.31	1.30	1.04	2917	0.51	−0.35	1.61	1.05
LR test for homogeneity (2 df)		*P* = 0.10					*P* = 0.16			
Age at exposure										
Doses received:										
<35 years		0.52	−1.12	2.54	1.05		−0.01	−1.68	2.16	1.00
35-50 years		0.14	−0.68	1.07	1.01		0.10	−0.81	1.17	1.01
>50 years		0.14	−0.69	1.12	1.01		0.06	−0.84	1.15	1.01
LR test for homogeneity (2 df)		*P* = 0.93					*P* = 0.99			
Time since exposure										
Doses received:										
<10 years previous		−0.90	<0	−0.11[c]	0.91		<0	–		0.80[b] (0.70, 0.91)
10–20 years previous		0.29	<0	1.05[c]	1.03		0.08	<0	0.94[c]	1.01
>20 years previous		0.11	<0	0.86[c]	1.01		0.29	<0	1.16[c]	1.03
LR test for homogeneity (2 df)		*P* < 0.001					*P* = 0.01			
Lag time										
2 years	11 255	−0.10	−0.45	0.30	0.99	8412	−0.14	−0.53	0.32	0.99
5 years	11 255	0.05	−0.34	0.50	1.00	8412	−0.02	−0.46	0.48	1.00
10 years	11 255	0.24	−0.23	0.78	1.02	8412	0.09	−0.43	0.70	1.01
15 years	11 255	0.53	−0.09	1.25	1.05	8412	0.48	−0.23	1.31	1.05
Impact of stratification variables										
No stratification for SES	11 255	0.48	−0.01	1.04	1.05	8412	0.39	−0.16	1.02	1.04
No stratification for duration of Employment	11 255	0.04	−0.37	0.51	1.00	8412	−0.04	−0.51	0.49	1.00

[a]Based on a linear excess relative risk model unless otherwise indicated—if RR could not be estimated under the linear model, the RR from a log-linear model is shown.

[b]RR (95% CI) from a log-linear model.

[c]Wald-based upper confidence bound (likelihood-based bound could not be estimated).

the large size of this study, the power to detect a small increase in risk is limited. Indeed, the central risk estimates observed in this study for mortality from all non-cancer diseases and from circulatory diseases are similar to comparable estimates derived from the A-bomb survivors' data (Table 5), and thus statistically compatible with a linear extrapolation from these data. Hence, we can exclude neither the existence of a threshold for the induction of non-cancer effects, nor an effect of the same order of magnitude as found in the A-bomb survivors. These findings are consistent with most other low-dose studies, in which radiation-related excess in risk of circulatory disease have generally not been observed (reviewed by McGale and Darby).[13]

Larger increases in risk were observed for mortality from respiratory diseases and digestive diseases in this study. The A-bomb survivors' study has reported radiation-related increases in risk for these disease outcomes,[11] but, to our knowledge, no other large studies have reported such associations. The explanation for these results is unclear and may include chance (given the wide confidence intervals), as well as confounding by factors such as smoking and alcohol consumption.

Analyses in this study are not independent from those of the previous 3-Country Study which combined cohorts from Canada, the UK and the US.[17] The weakly positive risk estimates in this study were driven mainly by the cohorts and follow-up periods also included in the 3-Country Study (3-country cohorts: ERR/Sv for non-cancer diseases = 0.40; 95% CI −0.18, 1.08. Other cohorts: ERR/Sv = −0.11; 95% CI < 0, 0.85). These are also among the cohorts with the

Table 4 ERR per Sv and RR at 100 mSv by attained age in four categories

	N	ERR/Sv	95% CI		RR at 100 mSv[a]
Non-cancer diseases					
<50 years	798	9.10	2.02	19.7	1.91
50–60 years	2979	0.79	–0.41	2.32	1.08
60–70 years	3464	−0.31	–0.91	0.45	0.97
>70 years	4014	0.41	–0.31	1.30	1.04
LR test for homogeneity (3 df)		*P* = 0.02			
Circulatory diseases					
<50 years	516	9.36	1.64	21.5	1.94
50–60 years	2294	0.25	–0.99	1.89	1.03
60–70 years	2685	−0.49	<0	0.32	0.95
>70 years	2917	0.51	–0.35	1.61	1.05
LR test for homogeneity (3 df)		*P* = 0.03			
Respiratory diseases					
<50 years	27	20.35	<0	273	3.04
50–60 years	109	7.98	–0.47	27.9	1.80
60–70 years	279	1.23	<0	6.29	1.12
>70 years	377	0.33	<0	3.55	1.03
LR test for homogeneity (3 df)		*P* = 0.47			
Digestive diseases					
<50 years	82	5.67	<0	75.0	1.57
50–60 years	238	4.03	–0.76	15.2	1.40
60–70 years	176	−1.02	<0	1.08[b]	0.90
>70 years	124	2.03	<0	15.1	1.20
LR test for homogeneity (3 df)		*P* = 0.45			
External causes					
<50 years	1157	8.01	0.99	18.5	1.80
50–60 years	590	0.33	<0	4.06	1.03
60–70 years	198	<0	–		0.62 (0.35, 0.98)[c]
>70 years	115	<0	–		0.67 (0.30, 1.17)[c]
LR test for homogeneity (3 df)		*P* = 0.31			

[a]Based on a linear excess relative risk model unless otherwise indicated—if RR could not be estimated under the linear model, the RR from a log-linear model is shown.
[b]Wald-based upper confidence bound (likelihood-based bound could not be estimated).
[c]RR (95% CI) from a log-linear model.

Table 5 Comparison of ERR estimates per Sv between nuclear workers and atomic bomb survivors

	15-Country Study		Atomic bomb survivors (men exposed between the ages of 20 and 60)[a]	
Cause of death	*N*	ERR/Sv (95% CI)	*N*	ERR/Sv (95% CI)
Non-cancer diseases	11 255	0.24 (−0.23, 0.78)	4563	0.12 (0.01, 0.24)
Circulatory diseases	8412	0.09 (−0.43, 0.70)	2571[b]	0.16 (0.02, 0.32)
Respiratory diseases	792	1.16 (−0.53, 3.84)	911	0.04 (−0.17, 0.30)
Digestive diseases	620	0.96 (<0, 4.52)	370	−0.03 (−0.35, 0.40)
Liver cirrhosis	263	1.54 (<0, 9.67)	167	0.02 (<0, 0.73)

[a]Analyses of non-cancer disease mortality of A-bomb survivor data carried-out at IARC, using an excess relative risk model stratified for attained age, calendar period and city. Analyses were restricted to men, exposed between the ages of 20 and 60, the group most comparable to the nuclear workers in the 15-Country study. Analyses were restricted to follow-up data 1968–97 and to survivors proximal to the hypocenter (<3 km) as described in Report 13 by Preston *et al*[11].
[b]Categories heart disease and stroke from Report 13[11] combined.

longest follow-up periods and the largest numbers of workers who accumulated higher doses.

Time and age-related effects

Of interest is the dose–response observed for all groupings of non-cancer diseases, including external causes, among workers with younger attained ages (below 50 years of age). This result is consistent with the A-bomb survivors' data where a decrease in mortality from all non-cancers with increasing attained age is observed.[11] It is unclear, however, whether our finding reflects a real effect of radiation, random variation or residual confounding, particularly since it is not related to any particular cause of death and since this age group was identified *post hoc*. Given the elevated risk for external causes in the younger age group, a confounding effect of life-style related factors acting particularly at younger ages appears possible.

The current study finds no evidence for differences in risk for radiation doses received at different ages. The A-bomb survivors' study reports a trend of decreasing ERR with increasing age at exposure for all non-cancer diseases combined,[11] whereas a more recent re-analysis of these same data has indicated that the highest risk arose in the medium (30–49 years) age group.[25]

Analyses by time-since-exposure and different lag periods showed higher risk estimates for exposures 10 years or more in the past. These findings are consistent with higher-dose studies in which radiation-related effects were generally not seen until at least 10 years after exposure.[4,7] A-bomb survivors analyses have now documented non-cancer effects in the follow-up periods covering ~20–50 years after exposure.[11,25]

Confounding

A limitation of this study is that, as in most occupational cohort studies, information on factors such as smoking habits, alcohol intake and diet could not be obtained. Non-cancer disease risks are known to be strongly related to such risk factors.[26] Smoking surveys in seven of the study cohorts have shown no consistent association between radiation dose and smoking with three showing a positive association and four showing no association.[21] Nevertheless, lung cancer risks were particularly raised in the 15-Country Study[19,20] suggesting that confounding by smoking may have played a role; a similar confounding effect

in the analyses of non-cancer disease cannot be ruled out. The increased risk estimate for chronic obstructive pulmonary diseases, although its confidence interval includes zero, is compatible with this. Further, it is notable that risk estimates for respiratory diseases and liver cirrhosis in the 15-Country Study are much higher than comparable estimates from the A-bomb survivors (Table 5), possibly demonstrating confounding effects by, respectively, smoking and alcohol consumption. Increases observed in the younger attained age categories for all main causes of non-cancer disease as well as external mortality causes may also indicate a specific confounding effect of lifestyle-related risk factors at younger ages.

This study partially controlled for these effects through adjustment for SES. SES was found to be an important confounder in this study, as it was associated both with all cause mortality and exposure in most countries,[21] and removal of SES stratification in our analyses had a relatively large effect of increasing risk estimates. Nevertheless, a surrogate measure can never entirely compensate for lack of direct data, and confounding may explain some of the small increases in radiation-related risk reported for non-cancer diseases.

Duration of employment was considered a priori to be a possible confounder and was therefore included in all main analyses to control for the so-called 'healthy worker survivor effect'.[20] This negative confounding effect occurs when workers who are healthier and therefore have lower mortality rates, stay in employment longer and may accumulate higher doses.[27] When we removed adjustment for duration of employment in the analyses, ERR estimates reduced to below 0, indicating that a healthy worker survivor effect may be present in this cohort.

Outcome misclassification

Misclassification of vital status or of underlying cause of death can occur in mortality studies. Coverage of ascertainment of both vital status and cause of death were near complete in the study cohorts, limiting the potential of bias.[21] Misclassification of the cause of death recorded on death certificates is likely to have occurred, especially for specific causes of death,[28–31] and may have differed over time and between countries. Nevertheless, risk estimates for the group of all non-cancer diseases combined would remain relatively unaffected.

Errors in dosimetry

Nuclear workers studies benefit from relatively well-measured and well-recorded radiation doses. However, even these doses can be subject to errors. An extensive study of errors in dosimetry formed part of the 15-Country Study.[22] This study identified and quantified the main errors in recorded doses, and dose estimates in the main analyses have been adjusted to take these errors into account. Further, analyses were restricted to workers whose radiation dose was predominantly from relatively well-measured radiation types (external radiation from higher energy photons), and workers with substantial doses from other radiation types (neutrons, internal contamination) were excluded.[22]

Conclusions

In conclusion, results from the largest nuclear workers cohort study to date give little evidence for a relation between mortality from non-malignant diseases and external radiation dose at the low doses received by nuclear industry workers. However, we cannot rule out risks of the same order of magnitude as found in the A-bomb survivors' study. Dose–response relationships found in younger workers merit further exploration. The follow-up periods in most countries were relatively short (average 13 years) and the majority of workers were comparatively young at the end of the follow-up (average 46 years). Further follow-up of these populations will be useful to improve the precision of risk estimates.

Supplementary material

Supplementary data are available at *IJE* Online.

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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[32] (revision depending on the country). The study did not involve contact with study subjects.

Conflict of interest: None declared.

KEY MESSAGES

- The largest nuclear workers study to date finds little evidence for a relation between mortality from non-malignant diseases and low doses of external radiation.
- Risks per unit dose of the same order of magnitude as found in studies at higher doses cannot be ruled out.
- Radiation-related increased risks of non-malignant diseases were observed among the younger workers (attained age <50 years, identified *post hoc*), but it is unclear whether these findings reflect real effects of radiation, random variation or residual confounding.
- Further follow-up of the nuclear workers cohorts is needed to improve the precision of risk estimates.

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