# Risk of cancer after low doses of ionising radiation—retrospective cohort study in 15 countries

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## Abstract

**Objectives** To provide direct estimates of risk of cancer after protracted low doses of ionising radiation and to strengthen the scientific basis of radiation protection standards for environmental, occupational, and medical diagnostic exposures.
**Design** Multinational retrospective cohort study of cancer mortality.
**Setting** Cohorts of workers in the nuclear industry in 15 countries.
**Participants** 407 391 workers individually monitored for external radiation with a total follow-up of 5.2 million person years.
**Main outcome measurements** Estimates of excess relative risks per sievert (Sv) of radiation dose for mortality from cancers other than leukaemia and from leukaemia excluding chronic lymphocytic leukaemia, the main causes of death considered by radiation protection authorities.
**Results** The excess relative risk for cancers other than leukaemia was 0.97 per Sv, 95% confidence interval 0.14 to 1.97. Analyses of causes of death related or unrelated to smoking indicate that, although confounding by smoking may be present, it is unlikely to explain all of this increased risk. The excess relative risk for leukaemia excluding chronic lymphocytic leukaemia was 1.93 per Sv (< 0 to 8.47). On the basis of these estimates, 1-2% of deaths from cancer among workers in this cohort may be attributable to radiation.
**Conclusions** These estimates, from the largest study of nuclear workers ever conducted, are higher than, but statistically compatible with, the risk estimates used for current radiation protection standards. The results suggest that there is a small excess risk of cancer, even at the low doses and dose rates typically received by nuclear workers in this study.

## Introduction

The 15 country study, an international collaborative study of cancer risk among radiation workers in the nuclear industry, was carried out to directly estimate the risk of cancer after protracted low dose exposures and to strengthen the scientific basis of radiation protection.[1] We present risk estimates for mortality from all cancers, excluding leukaemia, and from leukaemia excluding chronic lymphocytic leukaemia, and compare them with estimates derived from data on survivors of the A bomb. We have used the term nuclear industry to refer to facilities engaged in production of nuclear power, manufacture of nuclear weapons, enrichment and processing of nuclear fuel, production of radioisotopes, or nuclear reactor or weapons research. Uranium mining is not included.

## Methods

This multinational retrospective cohort study used a common protocol in 15 countries and collected information on nearly 600 000 workers. Study cohorts were defined from employment and dosimetric records of participating facilities or, where available, from centralised national dose registries. The a priori eligibility criteria for inclusion of cohorts[2] were essentially complete and non-selective follow-up for mortality; availability of individual annual recorded estimates of dose for all monitored workers; and availability of information on historical monitoring policies and practices. We included all workers who had been monitored for external photon (x and γ) radiation exposure through the use of personal dosimeters. Details of country specific methods are described elsewhere.[3]

### Vital status and cause of death ascertainment

We established vital status through linkage with national or regional death registries or, where this was not possible, appropriate records of local authorities. Completeness of follow-up ranged from 87% to nearly 100%. Vital statistics registries provided cause of death, which was known for over 90% of workers who died.

### Adequacy of dosimetric records

We reconstructed each worker's dosimetric history using recorded doses from individual facilities or national dose registries. A study evaluated the comparability of dose estimates across facilities and time[3] and quantified sources of bias (see bmj.com). Doses from higher energy photons (100-3000 keV), which constituted most of the dose in most cohorts, were judged to have been measured in a comparable way over time and across facilities.[3 4] We excluded workers with potential for substantial doses (≥ 10% of their whole body dose) from other radiation types (neutrons, internal exposures).

### Main study population

The main study population was workers who had been employed in one or more facilities for at least one year, who had been monitored for external radiation exposure, and whose doses resulted predominantly from higher energy photon radiation (190 677 workers who did not fit these criteria were excluded).

### Dosimetric errors and derivation of organ doses

Organ doses were derived by dividing recorded doses by the appropriate organ dose bias factor (see bmj.com). We used doses to the colon and active bone marrow for analyses of mortality from all cancers excluding leukaemia and from leukaemia, respectively.

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### Statistical methods

Analyses were based on a linear relative risk Poisson regression model (see bmj.com). Analyses used only underlying cause of death. To allow for a latent period between exposure and death, doses were lagged by two years for leukaemia and 10 years for other cancers. Sensitivity analyses were conducted with a range of different lags.

We focused on the main causes of death for which radiation protection committees have provided risk estimates: all cancers excluding leukaemia and leukaemia excluding chronic lymphocytic leukaemia. Chronic lymphocytic leukaemia is thought to be less inducible by ionising radiation than other leukaemias.[5] We have also presented risk estimates for solid cancers to compare with recent data for A bomb survivors[6] and for all cancers excluding leukaemia, lung, and pleural cancers (which have the greatest potential for confounding by smoking, internally incorporated radionuclides, and other occupational carcinogens). We investigated confounding by smoking by separately analysing solid cancers related or unrelated to smoking and two groupings of smoking related outcomes other than cancer (all non-malignant respiratory diseases and chronic obstructive bronchitis and emphysema).

### Analysis of data from survivors of A bomb

We analysed mortality data from the A bomb survivors for solid cancer to 1997[6] and leukaemia to 1990[7] using similar methods to provide risk estimates for comparison.

## Results

The main study population comprised 407 391 workers (table 1). Most workers in the study were men (90%), and men received 98% of the collective dose. The distribution of recorded doses was skewed (fig 1). The average cumulative dose was 19.4 mSv. Ninety per cent of workers received cumulative doses <50 mSv and less than 0.1% received cumulative doses >500 mSv.

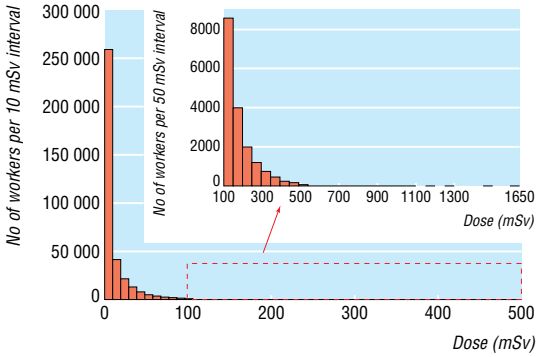


**Fig 1** Distribution of cumulative radiation doses among workers included in the analyses

For all cancers excluding leukaemia, the excess relative risk was significantly different from zero (table 2). This estimate corresponds to a relative risk of 1.10 for a radiation dose of 100 mSv. For solid cancers, the excess relative risk was higher than but statistically compatible with the estimate for A bomb survivors. The excess relative risk for leukaemia excluding chronic lymphocytic leukaemia corresponds to a relative risk of 1.19 for a dose of 100 mSv. This estimate is between the linear and linear quadratic extrapolations from data on A bomb survivors.

Indirect analyses of the possible confounding effect of smoking yielded excess relative risks that ranged between 0.59 per Sv (−0.29 to 1.70) for all cancers excluding leukaemia and lung and pleural cancer, and 0.91 per Sv (−0.11 to 2.21) for smoking related cancers (see bmj.com).

The increased risk for smoking related cancers was mainly due to an increased risk of lung cancer (1.86 per

**Table 1** Cohorts included in the 15 country study

| | No of facilities | First year of operations | Follow-up period | No of workers | Person years | Deaths | | | Collective cumulative dose (Sv) | Average individual cumulative dose (mSv) |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | All causes | All cancers excluding leukaemia | Leukaemia excluding CLL | | |
| Australia | 1 | 1959 | 1972-98 | 877 | 12 110 | 56 | 17 | 0 | 5.4 | 6.1 |
| Belgium | 5 | 1953 | 1969-94 | 5 037 | 77 246 | 322 | 87 | 3 | 134.2 | 26.6 |
| Canada | 4 | 1944 | 1956-94 | 38 736 | 473 880 | 1 204 | 400 | 11 | 754.3 | 19.5 |
| Finland | 3 | 1960 | 1971-97 | 6 782 | 90 517 | 317 | 33 | 0 | 53.2 | 7.8 |
| France CEA-COGEMA | 9 | 1946 | 1968-94 | 14 796 | 224 370 | 645 | 218 | 7 | 55.6 | 3.8 |
| France EDF | 22 | 1956 | 1968-94 | 21 510 | 241 391 | 371 | 113 | 4 | 340.2 | 15.8 |
| Hungary | 1 | 1982 | 1985-98 | 3 322 | 40 557 | 104 | 39 | 1 | 17.0 | 5.1 |
| Japan | 33* | 1957 | 1986-92 | 83 740 | 385 521 | 1 091 | 413 | 19 | 1526.7 | 18.2 |
| Korea (south) | 4 | 1977 | 1992-97 | 7 892 | 36 227 | 58 | 21 | 0 | 122.3 | 15.5 |
| Lithuania | 1 | 1984 | 1984-2000 | 4 429 | 38 458 | 102 | 24 | 1 | 180.2 | 40.7 |
| Slovak Republic | 1 | 1973 | 1973-93 | 1 590 | 15 997 | 35 | 10 | 0 | 29.9 | 18.8 |
| Spain | 10 | 1968 | 1970-96 | 3 633 | 46 358 | 68 | 25 | 0 | 92.7 | 25.5 |
| Sweden | 6 | 1954 | 1954-96 | 16 347 | 220 501 | 669 | 190 | 4 | 291.8 | 17.9 |
| Switzerland | 4 | 1957 | 1969-95 | 1 785 | 22 051 | 66 | 24 | 0 | 111.2 | 62.3 |
| UK | 32 | 1946 | 1955-92 | 87 322 | 1 370 101 | 7 983 | 2201 | 54 | 1810.1 | 20.7 |
| US Hanford | 1 | 1944 | 1944-86 | 29 332 | 678 833 | 5 564 | 1279 | 35 | 695.4 | 23.7 |
| US INEL | 1 | 1949 | 1960-96 | 25 570 | 505 236 | 3 491 | 886 | 26 | 254.6 | 10.0 |
| US NPP | 15 | 1960 | 1979-97 | 49 346 | 576 682 | 983 | 314 | 19 | 1336.0 | 27.1 |
| US ORNL | 1 | 1943 | 1943-84 | 5 345 | 136 673 | 1 029 | 225 | 12 | 81.1 | 15.2 |
| Total | 154 | — | — | 407 391 | 5 192 710 | 24 158 | 6519 | 196 | 7892.0 | 19.4 |

CEA-COGEMA=Commissariat à l'Energie Atomique-Compagnie Générale des Matières Nucléaires; EDF=Electricité de France; NPP=nuclear power plants; INEL=Idaho National Engineering Laboratory; ORNL=Oak Ridge National Laboratory; CLL=chronic lymphocytic leukaemia.
*No information available to allow separation of different facilities.

Sv, 0.26 to 4.01). Other smoking related cancers showed little evidence of an increased risk (0.21 per Sv, <0 to 2.01). Risk estimates for mortality from non-malignant respiratory diseases and from chronic obstructive bronchitis and emphysema were raised but not significantly different from zero (excess relative risk per Sv 1.16, −0.53 to 3.84, and 2.12, −0.57 to 7.46, respectively).

## Discussion

Results from our study suggest that in workers in the nuclear industry an excess risk of cancer exists, albeit small, even at low doses and dose rates. The 15 country study allowed the compilation of the largest body of direct evidence to date concerning the effects of low dose chronic exposure to ionising radiation.

### All cancer excluding leukaemia

We found a significantly increased risk for all cancers (excluding leukaemia). The central risk estimate was higher than the linear extrapolation from the A bomb survivors. It is unlikely that this could be due to ascertainment bias, as the excess relative risk for all non-cancer mortality was weakly positive (0.20, −0.26 to 0.72).

Information was not available to adjust directly for possible confounding by variables such as smoking, diet, and occupational exposures. Some of these factors—particularly smoking and diet—are strongly related to socioeconomic status and adjustment for this will have partially controlled for their effects. Some studies have found an association between radiation dose and smoking,[8 9] while others have not.[10–12]

The central risk estimate for cancers unrelated to smoking was higher than that for smoking related cancers other than lung cancer, indicating that confounding by smoking is unlikely to explain all of the relation found between all cancer risk and radiation dose. On the other hand, the non-significantly increased risks for mortality from non-malignant smoking related diseases indicate a possible effect of smoking. The risk estimates for mortality from cancers related and unrelated to smoking, however, are consistently two to three times higher than, but statistically compatible with the risk estimate for solid cancers from the A bomb analyses. Taken together, these findings indicate that a confounding effect by smoking may be partly, but not entirely, responsible for the estimated increased risk for mortality from all cancers other than leukaemia.

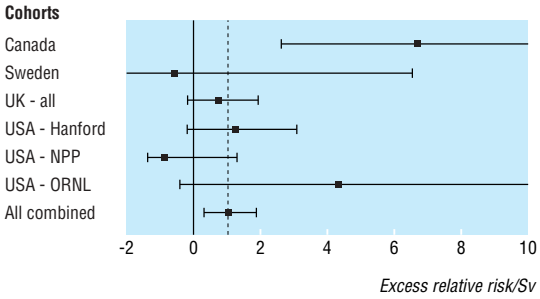


**Fig 2** Excess relative risks per Sv for all cancer excluding leukaemia in cohorts with more than 100 deaths (NPP=nuclear power plants, ORNL=Oak Ridge National Laboratory)

Formal tests for heterogeneity provided no evidence for differences in risk between countries, cohorts, or groups of facilities ($P>0.20$). Figure 2 shows the excess relative risk per Sv in the larger cohorts (>100 cancer deaths). Analyses excluding one cohort or country at a time produced excess relative risks per Sv ranging from 0.58 (excluding Canada) to 1.25 (excluding the UK), all consistently higher than but compatible with the estimate from A bomb analyses. Only when we excluded Canada was the excess relative risk no longer significantly different from zero (0.58, −0.22 to 1.55).

Sensitivity analyses of different lag periods showed that both the risk estimates and their uncertainties increased with increasing lag. The excess relative risk per Sv ranges from 0.76 (0.07 to 1.59) with a lag of five years to 1.68 (0.22 to 3.48) with a lag of 20 years. The estimates are all statistically compatible with the linear extrapolation from the A bomb survivors.

### Leukaemia excluding chronic lymphocytic leukaemia

Although our estimate of risk of leukaemia is not significantly different from zero, it is similar to estimates from previous large scale studies of nuclear workers.[13 14] Furthermore, it is intermediate between estimates obtained by fitting a linear and a linear quadratic dose-response model to data on men exposed to the A bomb at age 20-60. The excess relative risk per

**Table 2** Estimates of excess relative risk per Sv (95% confidence interval) for all cancers excluding leukaemia, solid cancers, and leukaemia excluding chronic lymphocytic leukaemia, for nuclear workers and survivors of A bomb in Japan*

| | 15 country study | | Atomic bomb survivors (men exposed at age 20-60) | |
|---|---|---|---|---|
| | No of cancers | Risk | No of cancers | Risk† |
| All cancers excluding leukaemia | 5024 | 0.97 (0.14 to 1.97) | | |
| Solid cancers | 4770 | 0.87 (0.03 to 1.88) | 3246 | 0.32‡ (0.01 to 0.50) |
| Leukaemia excluding CLL: | | | | |
| Linear model | 196 | 1.93 (<0§ to 8.47) | 83 | 3.15¶ (1.58 to 5.67) |
| Linear quadratic model | | | | 1.54** (−1.14 to 5.33) |

CLL=chronic lymphocytic leukaemia.
*Colon dose used for all cancers and solid cancer analyses, bone marrow dose for leukaemia.
†Note that because analyses were restricted to men aged 20-60 at exposure the confidence intervals are much wider than those presented by other investigators,[13 14] based on the full cohort.
‡Analyses carried out at IARC with excess relative risk model that allows for age at exposure modification, adjusted for attained age, calendar period, and city. Estimate for men exposed at age 35.
§Estimate on boundary of parameter space.
¶Analyses carried out at IARC with constant excess relative risk model, adjusted for attained age, calendar period, and city.
**Analyses carried out at IARC—linear term of linear quadratic model—preferred model for describing leukaemia mortality in analyses of data on A bomb survivors.[14]

## What is already known on this topic

Current radiation protection standards are based mainly on data from the survivors of the atomic bomb in Japan

The estimation of risks after low dose protracted or fractionated exposures to ionising radiation is controversial

## What this study adds

A small excess risk of cancer exists, even at the low doses typically received by nuclear industry workers in this study

Sv shows only a small increase with increasing lag periods, from 1.93 (<0 to 8.47) with a lag of two years to 2.53 (<0 to 10.45) with a lag of 10 years.

### Implications for radiation protection

Current recommendations are to limit occupational doses to 100 mSv over five years (not to exceed 50 mSv in any one year) and doses to the public to 1 mSv per year.[15] Our estimates suggest that a cumulative exposure of 100 mSv would lead to a 9.7% (1.4 to 19.7%) increased mortality from all cancers excluding leukaemia and a 5.9% (−2.9 to 17.0%) increased mortality from all cancers excluding leukaemia, lung, and pleura compared with background rates. The corresponding figure is 19% (<0 to 84.7%) for mortality from leukaemia excluding chronic lymphocytic leukaemia. Less than 5% of workers in this study received cumulative doses of the order of 100 mSv over their entire career. We estimate that 1-2% of deaths from cancer (including leukaemia) among workers in this cohort may be attributable to radiation.

### Conclusions

We have provided radiation risk estimates from the largest study of nuclear industry workers conducted so far. These estimates are higher than but statistically compatible with the current bases for radiation protection standards. The confidence intervals range from values lower than those derived by linear extrapolation from data from A bomb survivors up to values that exceed this extrapolation by a factor of six for cancers other than leukaemia and nearly three for leukaemia. These results suggest that an excess risk of cancer exists, albeit small, even at the low doses and dose rates typically received by nuclear workers in this study.

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Competing interests: C Hacker, B Heinmiller, H Hyvonen, M Marshall, A Rogel, J Bernar Solano, M Eklöf, and K Holan are (or have been in the past five years) employees of the nuclear industry or have links to the nuclear industry in their country. They were appointed to the international study group and/or the dosimetry subcommittee as experts because of their critical knowledge and experience in historical radiation protection practices and dosimetry. None of them had influence on decisions concerning analysis of the results.

Ethical approval: The study was approved by the IARC ethical review committee and by the relevant ethical committees of the participating countries.

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