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


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

Ionising radiation is one of the most studied and ubiquitous carcinogens in our environment. The main basis for radiation protection recommendations is the study of survivors of the Japanese atomic bomb (A bomb), a population exposed primarily at high dose rates.\(^1\) The primary public health concern, however, is the protection of people from relatively low dose, protracted or fractionated exposures such as those received by the public in the general environment, by patients through repeated diagnostic procedures,\(^3\) and by radiation workers.

The effects of low dose chronic exposure to external radiation have been directly estimated in several cohorts of workers in the nuclear industry,\(^4\) but the sample size has limited the precision of these estimates. Analyses of combined cohorts have improved precision.\(^5\)\(^6\) Estimates from these analyses, however, are compatible with a range of possibilities, from a reduction of risk at low doses to risks higher than those underlying current radiation protection recommendations.

The 15 country study, an international collaborative study of cancer risk among radiation workers in the nuclear industry, was carried out to further improve the precision of direct estimates of risk after protracted low dose exposures and to strengthen the scientific basis of radiation protection.\(^7\) 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 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 or dosimetric records of participating facilities or, where available, from centralised national dose registries. The a priori eligibility criteria for inclusion of cohorts' 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 y) radiation exposure through the use of personal dosimeters. Details of country specific methods are described elsewhere.\(^8\)

Ascertainment of vital status and cause of death

We established vital status through linkage with national or regional death registries. In a few countries where this was not
possible, appropriate records of local authorities were used. 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 of errors in recorded doses evaluated the comparability of dose estimates across facilities and time and identified and quantified sources of bias and uncertainties. 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. The adequacy of practices and technology to measure and record dose from other radiation types (neutrons, internal exposures), however, varied substantially, particularly in earlier years. We therefore excluded workers with potential for substantial doses (>10% of their whole body dose) from these radiation types.

**Main study population**

The main study population was defined as workers who had been employed in one or more facilities for at least one year (113,711 workers excluded), who had been monitored for external radiation exposure (38,521 workers excluded), and whose doses resulted predominately from higher energy photon radiation (59,730 workers with internal contamination and 19,041 with neutron exposures excluded).

**Dosimetric errors and derivation of organ doses**

The major sources of errors in higher energy photon doses were dosimetry technology, exposure conditions, and calibration practices. Errors from these sources were quantified and bias factors specific to the doses to each organ of interest calculated for each model of dosimeter used and by type of facility (nuclear power plants and mixed activities facilities). Organ doses were derived by dividing recorded doses by the appropriate organ dose bias factor. We used doses to the colon and active bone marrow for analyses of mortality from all cancers excluding leukaemia and from leukaemia, respectively. All doses are expressed as dose equivalents in sieverts (Sv).

**Statistical methods**

Analyses were based on a linear relative risk Poisson regression model, in which the relative risk is of the form 1+βZ, where Z is the cumulative dose equivalent in Sv and β is the excess relative risk per Sv; 95% likelihood based confidence intervals were calculated. We used 11 a priori categories of dose (<5, 5-<10, 10-<20, 20-<50, 50-<100, 100-<150, 150-<200, 200-<300, 300-<400, 400-<500, ≥500 mSv). Analyses used only underlying cause of death. Estimates of excess relative risk were stratified for sex, age, and calendar period (both in five year categories), facility, duration of employment (<10 years, ≥10 years), and socioeconomic status. In the analyses of all cancers we excluded cohorts for which socioeconomic information was unavailable or incomplete (Japan, Idaho National Engineering Laboratory (INEL), Ontario Hydro Canada), but we included them in analyses of leukaemia as the potential for confounding by socioeconomic status was thought to be less for leukaemia. To allow for a latent period between exposure and death, doses were lagged by two years for leukaemia and 10 years for other cancers, as in other studies of nuclear workers and assessments of radiation risk. Sensitivity analyses were conducted with a range of different lags. Attributable risks were estimated by multiplying the excess relative risks by the average dose in the cohort.

We have 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 excluded because it is thought to be less readily inducible by ionising radiation than other leukaemias. We have also presented risk estimates for solid cancers (that is, excluding lymphatic and haematopoietic malignancies) to compare with recent data for A bomb survivors 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 and leukaemia to 1990 using similar methods to provide risk estimates for comparison. Analyses were stratified for attained age, city, and calendar time and restricted to men aged 20-60 at exposure, the group most comparable to the workers.

**Results**

Overall, 598,068 workers were employed in at least one of 154 facilities. Most facilities were involved in nuclear power production; the rest specialised in different activities, including research, waste management, and production of fuel, isotopes, and weapons. The main study population comprised 407,391 workers (table 1). A total of 24,158 (5.9%) people were known to have died during the study period: 6,519 from cancers other than leukaemia and 196 from leukaemia excluding chronic lymphocytic leukaemia. 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 skewed (fig 1). Ninety per cent of workers received cumulative doses <50 mSv and less than 0.1% received cumulative doses >500 mSv.

For all cancers excluding leukaemia, the excess relative risk was 0.97 per Sv and was significantly different from zero (95% confidence interval 0.14 to 1.97) (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 0.87 (0.03 to 1.88), higher than but statistically compatible with the estimate for A bomb survivors (0.32 per Sv). The excess relative risk for leukaemia excluding chronic lymphocytic leukaemia was 1.93 per Sv (<0 to 8.47), which gives 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 (table 2).

Table 3 assesses the possible confounding effect of smoking. Excess relative risks 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.

The increased risk for smoking related cancers was mainly due to an increased risk of lung cancer (1.86 per 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 show 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. 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. Our risk estimates mainly reflect risks in men, as date concerning the effects of low dose chronic exposure to ionising radiation. Our risk estimates mainly reflect risks in men, as more likely to list cancer as the underlying cause of death for workers with higher exposures, as the excess relative risk for all non-cancer mortality was weakly positive (0.20, –0.26 to 0.72).

We could not adjust directly for possible confounding by variables such as smoking, diet, and occupational exposures as information was not available. 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. Factors such as smoking can confound the association between radiation dose and risk only if they are related both to risk of cancer and to dose. Some cohort studies have found an association between radiation dose and smoking, while others have not.

Although the estimated risk for mortality from lung cancer was particularly high, mortality from smoking related cancers other than lung cancer showed little evidence of a relation with dose. Indeed, 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 all groups of cancers related and unrelated to smoking were based on organ dose estimates, which we adjusted to account for the main sources of systematic errors.

**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, with physicians being more likely to list cancer as the underlying cause of death for workers with higher exposures, as the excess relative risk for all non-cancer mortality was weakly positive (0.20, –0.26 to 0.72).

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

<table>
<thead>
<tr>
<th>No of facilities</th>
<th>First year of operations</th>
<th>Follow-up period</th>
<th>No of workers</th>
<th>Person years</th>
<th>All causes</th>
<th>All cancers excluding leukaemia</th>
<th>Leukaemia excluding CLL</th>
<th>Collective cumulative dose (Sv)</th>
<th>Average individual cumulative dose (mSv)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Australia</td>
<td>1</td>
<td>1959-1972-98</td>
<td>12 110</td>
<td>577</td>
<td>17</td>
<td>0</td>
<td>5.4</td>
<td>19.5</td>
<td>6.1</td>
</tr>
<tr>
<td>Belgium</td>
<td>5</td>
<td>1953-1969-94</td>
<td>77 246</td>
<td>5 857</td>
<td>87</td>
<td>3</td>
<td>322</td>
<td>26.8</td>
<td>6.1</td>
</tr>
<tr>
<td>Canada</td>
<td>4</td>
<td>1944-1956-94</td>
<td>473 890</td>
<td>33 768</td>
<td>400</td>
<td>11</td>
<td>1 204</td>
<td>19.5</td>
<td>6.1</td>
</tr>
<tr>
<td>Finland</td>
<td>3</td>
<td>1960-1971-97</td>
<td>99 517</td>
<td>6 782</td>
<td>33</td>
<td>0</td>
<td>317</td>
<td>7.8</td>
<td>3.8</td>
</tr>
<tr>
<td>France CEA-COGEMA</td>
<td>9</td>
<td>1946-1968-94</td>
<td>224 370</td>
<td>14 796</td>
<td>218</td>
<td>7</td>
<td>645</td>
<td>3.8</td>
<td>3.8</td>
</tr>
<tr>
<td>France EDF</td>
<td>22</td>
<td>1956-1968-94</td>
<td>241 391</td>
<td>21 510</td>
<td>113</td>
<td>4</td>
<td>371</td>
<td>15.8</td>
<td>15.8</td>
</tr>
<tr>
<td>Hungary</td>
<td>1</td>
<td>1982-1985-98</td>
<td>40 557</td>
<td>3 222</td>
<td>39</td>
<td>1</td>
<td>104</td>
<td>5.1</td>
<td>5.1</td>
</tr>
<tr>
<td>Japan</td>
<td>33</td>
<td>1957-1986-92</td>
<td>385 521</td>
<td>83 740</td>
<td>413</td>
<td>19</td>
<td>1 091</td>
<td>18.2</td>
<td>18.2</td>
</tr>
<tr>
<td>Korea (south)</td>
<td>4</td>
<td>1977-1992-97</td>
<td>36 227</td>
<td>7 892</td>
<td>21</td>
<td>0</td>
<td>58</td>
<td>15.5</td>
<td>15.5</td>
</tr>
<tr>
<td>Lithuania</td>
<td>1</td>
<td>1964-1984-2000</td>
<td>38 458</td>
<td>4 429</td>
<td>24</td>
<td>1</td>
<td>102</td>
<td>40.7</td>
<td>40.7</td>
</tr>
<tr>
<td>Slovak Republic</td>
<td>1</td>
<td>1973-1973-93</td>
<td>15 997</td>
<td>1 580</td>
<td>10</td>
<td>0</td>
<td>35</td>
<td>18.8</td>
<td>18.8</td>
</tr>
<tr>
<td>Spain</td>
<td>10</td>
<td>1968-1970-96</td>
<td>46 358</td>
<td>3 633</td>
<td>25</td>
<td>0</td>
<td>68</td>
<td>25.5</td>
<td>25.5</td>
</tr>
<tr>
<td>Sweden</td>
<td>8</td>
<td>1954-1954-96</td>
<td>220 501</td>
<td>16 347</td>
<td>190</td>
<td>4</td>
<td>669</td>
<td>17.9</td>
<td>17.9</td>
</tr>
<tr>
<td>Switzerland</td>
<td>4</td>
<td>1957-1969-95</td>
<td>22 051</td>
<td>1 785</td>
<td>24</td>
<td>0</td>
<td>66</td>
<td>62.3</td>
<td>62.3</td>
</tr>
<tr>
<td>UK</td>
<td>32</td>
<td>1946-1955-92</td>
<td>220 101</td>
<td>87 322</td>
<td>220</td>
<td>54</td>
<td>7 983</td>
<td>20.7</td>
<td>20.7</td>
</tr>
<tr>
<td>US Hanford</td>
<td>1</td>
<td>1944-1944-86</td>
<td>1 370 101</td>
<td>29 332</td>
<td>1270</td>
<td>35</td>
<td>5 564</td>
<td>23.7</td>
<td>23.7</td>
</tr>
<tr>
<td>US INEL</td>
<td>1</td>
<td>1949-1960-96</td>
<td>1 204 36</td>
<td>25 570</td>
<td>886</td>
<td>26</td>
<td>3 491</td>
<td>10.0</td>
<td>10.0</td>
</tr>
<tr>
<td>US NPP</td>
<td>15</td>
<td>1960-1979-97</td>
<td>578 682</td>
<td>49 346</td>
<td>314</td>
<td>19</td>
<td>983</td>
<td>27.1</td>
<td>27.1</td>
</tr>
<tr>
<td>US ORNL</td>
<td>1</td>
<td>1943-1943-84</td>
<td>1 176 710</td>
<td>5 345</td>
<td>225</td>
<td>12</td>
<td>1 029</td>
<td>15.2</td>
<td>15.2</td>
</tr>
<tr>
<td>Total</td>
<td>154</td>
<td>—</td>
<td>21 510 400</td>
<td>407 391</td>
<td>5 192 710</td>
<td>24 158</td>
<td>186 789 2.0</td>
<td>710</td>
<td>53.2</td>
</tr>
</tbody>
</table>

CEA-COGEMA=Commissariat à l‘Energie Atomique-Compagnie Générale des Matières Nucléaires; EDF=Électricité de France; NPP=nucléar power plants; INEL=Idaho National Engineering Laboratory; ORNL=Oak Ridge National Laboratory; CLL=chronic lymphocytic leukemia.

*No information available to allow separation of different facilities.
by smoking may be partly, but not entirely, responsible for the estimated increased risk for mortality from all cancers other than leukaemia.

The findings for all cancers excluding leukaemia were not greatly influenced by data from any one country: 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); the risk estimate for Canada is the largest. 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. 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 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.

The preferred model for the A bomb data includes an effect of time since exposure. Patterns of risk of cancer after low dose protracted exposures are, however, not necessarily the same as those observed in A bomb studies. Indeed, the data for nuclear workers did not show evidence of a time since exposure effect (not shown).

Our results are not independent of previous combined analyses. Analyses excluding workers from these earlier cohorts, however, yielded similar conclusions.

Implications for radiation protection

The general practice in radiation protection is to estimate risks for protracted exposures to low doses by extrapolating from situations of acute exposure to high doses. For this, a linear dose response model with no threshold is assumed and risk estimates are divided by two to allow for the assumed reduced carcinogenicity of exposures received at low dose rates. For leukaemia, this is similar to using the linear term of a linear quadratic model. The central risk estimate for leukaemia from this study (and from previous studies of nuclear workers) would support this practice. The confidence interval is wide, however, and findings are also compatible with no reduction, as well as with greater reductions of risk at low doses.

For mortality from all cancers excluding leukaemia, the central risk estimates are two to three times higher than the linear extrapolation from the A bomb survivors. The confidence intervals are wide, however, and findings are statistically compatible with the current bases for radiation protection standards.

Current recommendations form the International Commission on Radiological Protection (ICRP) are to limit occupational

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**Table 3** Estimates of excess relative risk per Sv (95% confidence intervals) for specific causes of death

<table>
<thead>
<tr>
<th>Cause of death*</th>
<th>No of deaths</th>
<th>Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>All cancers excluding leukaemia</td>
<td>5024</td>
<td>0.97 (0.14 to 1.97)</td>
</tr>
<tr>
<td>All cancers excluding leukaemia, lung and pleural cancers</td>
<td>3528</td>
<td>0.59 (-0.29 to 1.70)</td>
</tr>
<tr>
<td>Solid cancers</td>
<td>4770</td>
<td>0.87 (0.03 to 1.88)</td>
</tr>
<tr>
<td>Smoking related solid cancer†</td>
<td>2737</td>
<td>0.91 (-0.11 to 2.21)</td>
</tr>
<tr>
<td>Solid cancers unrelated to smoking</td>
<td>2033</td>
<td>0.62 (-0.51 to 2.20)</td>
</tr>
</tbody>
</table>

*Colon dose used for all cancers excluding leukaemia; all cancers excluding leukaemia, lung and pleural cancers; solid cancers; and solid cancers unrelated to smoking. Lung dose used for smoking related solid cancers.
†Those cancers identified as having sufficient evidence for being caused by smoking in recent IARC monograph include cancers of lung, oral cavity, nasopharynx, oropharynx, and hypopharynx; nasal cavity and paranasal sinuses; larynx, esophagus, stomach, pancreas, liver, kidney (body and pelvis), ureter, urinary bladder, and uterine cervix. Category of cancers unrelated to smoking comprised all other solid cancers.
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.

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. 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 mortal-

ity 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, however, and most of these doses were received in the early years of the nuclear industry, when protection standards were less stringent than today. Overall, on the basis of our central risk estimates, 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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Contributors: ECs designed and coordinated the international study, took part in data analysis, interpretation, and writing of the paper, and is guaran-
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