Risk of cancer from occupational exposure to ionising radiation: retrospective cohort study of workers in France, the United Kingdom, and the United States (INWORKS)

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ABSTRACT

STUDY QUESTION

Is protracted exposure to low doses of ionising radiation associated with an increased risk of solid cancer?

METHODS

In this cohort study, 308 297 workers in the nuclear industry from France, the United Kingdom, and the United States with detailed monitoring data for external exposure to ionising radiation were linked to death registries. Excess relative rate per Gy of radiation dose for mortality from cancer was estimated. Follow-up encompassed 8.2 million person years. Of 66 632 known deaths by the end of follow-up, 17 957 were due to solid cancers.

STUDY ANSWER AND LIMITATIONS

Results suggest a linear increase in the rate of cancer with increasing radiation exposure. The average cumulative colon dose estimated among exposed workers was 20.9 mGy (median 4.1 mGy). The estimated rate of mortality from all cancers excluding leukaemia increased with cumulative dose by 48% per Gy (90% confidence interval 20% to 79%), lagged by 10 years. Similar associations were seen for mortality from all solid cancers (47% (18% to 79%)), and within each country. The estimated association over the dose range of 0-100 mGy was similar in magnitude to that obtained over the entire dose range but less precise. Smoking and occupational asbestos exposure are potential confounders; however, exclusion of deaths from lung cancer and pleural cancer did not affect the estimated association. Despite substantial efforts to characterise the performance of the radiation dosimeters used, the possibility of measurement error remains.

WHAT THIS STUDY ADDS

The study provides a direct estimate of the association between protracted low dose exposure to ionising radiation and solid cancer mortality. Although high dose rate exposures are thought to be more dangerous than low dose rate exposures, the risk per unit of radiation dose for cancer among radiation workers was similar to estimates derived from studies of Japanese atomic bomb survivors. Quantifying the cancer risks associated with protracted radiation exposures can help strengthen the foundation for radiation protection standards.

FUNDING, COMPETING INTERESTS, DATA SHARING

Support from the US Centers for Disease Control and Prevention; Ministry of Health, Labour and Welfare of Japan; Institut de Radioprotection et de Sûreté Nucléaire; AREVA; Electricité de France; US National Institute for Occupational Safety and Health; US Department of Energy; and Public Health England. Data are maintained and kept at the International Agency for Research on Cancer.

WHAT IS ALREADY KNOWN ON THIS TOPIC

Ionising radiation is an established cause of cancer

The primary quantitative basis for radiation protection standards comes from studies of people exposed to acute, high doses of ionising radiation

WHAT THIS STUDY ADDS

In a study of workers exposed to radiation at low dose rates typically encountered in nuclear industries in France, the United Kingdom, and the United States, the results suggest a linear increase in the relative rate of cancer with increasing exposure to radiation

Contrary to the belief that high dose rate exposures are substantially more dangerous than low dose rate exposures, the risk per unit of radiation dose for cancer among radiation workers was similar to estimates derived from studies of Japanese atomic bomb survivors

Cancer risks that are associated with protracted radiation exposures can help strengthen the foundation for radiation protection standards

Introduction

In 1943, a large scale programme to develop nuclear weapons, and later nuclear power, began in the United States.[1] Soon afterwards, nuclear programmes also began in the United Kingdom and France. These programmes have employed hundreds of thousands of workers over the past 70 years. In the 1990s, an international study of cancer risk among radiation workers in three countries was carried out using a common core protocol, and this study subsequently was expanded to include 15 countries.[2 3] Cohorts of workers from France, the UK, and the USA provided the vast majority of the information available on early nuclear workers included in that study,[3] and each of these cohorts has been updated recently.[4-6]

The updated cohorts of nuclear workers from France, the UK, and the USA have been pooled, and an epidemiological analysis of cancer mortality conducted, as part of the International Nuclear Workers Study (INWORKS). These cohorts are among the largest, oldest, and most informative groups of nuclear workers in the world. They include men and women who have been monitored for external exposure to radiation using personal dosimeters and have been followed up over decades to

collect information on causes of death. Here, we report on analysis of all cancer mortality, and solid cancer mortality. Analyses of death due to lymphatic and haematopoietic cancer (including leukaemia) have been reported previously,[7] and analyses of deaths due to non-malignant disease and specific types of solid cancer will be reported subsequently.

We aimed to strengthen the scientific basis for the protection of adults from exposures to ionising radiation with low doses and low dose rates. Despite strong evidence of low dose radiation effects on cancer after exposure in utero[8-10] and supportive evidence of such associations following low dose exposures of diagnostic radiation in childhood,[11 12] epidemiological evidence of low dose radiation effects following exposure in adulthood has been more limited.[13]

Methods

International consortium

INWORKS was established to provide a basis for deriving more precise quantitative estimates of the risk of chronic, low level, exposure to ionising radiation. To be included, workers must have been employed in the nuclear industry for at least one year and monitored for external radiation exposure through the use of personal dosimeters. From France, data were obtained from three major employers: Commissariat à l'Energie Atomique, AREVA Nuclear Cycle, and Electricité de France.[4] From the UK, data were obtained through the National Registry for Radiation Workers, which includes information provided by major employers of nuclear workers including the Atomic Weapons Establishment, British Nuclear Fuels, UK Atomic Energy Authority, British Energy Generation, Magnox Electric, and the Ministry of Defence, among others.[5] From the USA, data were obtained from the US Department of Energy's Hanford site, Savannah River site, Oak Ridge National Laboratory, and Idaho National Laboratory, as well as from the Portsmouth Naval Shipyard.[6]

In France, as required by the French Data Protection Authority, workers were given the opportunity to refuse participation; however, none did. In the USA, worker information was taken from existing records, with no direct contact with any participants; because there is minimal risk to participants, the National Institute for Occupational Safety and Health institutional review board waived requirements for informed consent. UK workers can refuse to participate in the National Registry for Radiation Workers and associated studies; less than 1% refused.

Dosimetric data

Personal monitoring data for occupational exposure to ionising radiation were available from company records for UK workers and government and company records for US and French workers, providing individual annual quantitative estimates of whole body dose due to external exposure to penetrating radiation in the form of photons.[14] Unless otherwise stated, any reference to dose in this paper implies absorbed dose to the colon expressed in grays (Gy).

These analyses use estimated colon dose to facilitate comparison with other recent major analyses of associations between radiation dose and solid cancer mortality.[3 15] Under most working conditions, absorbed doses from external exposures were due to photons of energies between 100 and 3000 kiloelectron volts (1.6e-14 J and 4.8e-13 J, respectively), with a radiation weighting factor of 1. Thus, estimates of absorbed dose in Gy could well be expressed in terms of equivalent dose in sievert (Sv) with similar numerical values.

We used available records of estimated neutron doses, which were recorded in a unit of measure for equivalent dose (that is, rem or Sv), only to construct categories of neutron monitoring status: whether a worker had a positive recorded neutron dose, and if so, whether their recorded neutron dose ever exceeded 10% of their total external radiation dose of record.[14 16] We did not add recorded estimates of doses from tritium intakes to recorded estimates of dose due to external exposures.

Available measures of incorporated radionuclides were varied and included positive bioassay results, indication of confirmed uptake (for example, fraction of a body burden or annual limit on intake), or an assigned committed dose. For our purposes, we grouped these measures as an indication of a known or suspected internal contamination. French and US workers with a known or suspected uptake were identified, as were UK workers who were known to have been monitored for internal exposure.

Follow-up and ascertainment of causes of death

Vital status was ascertained through 2004, 2001, and 2005 for the French, UK, and US cohorts, respectively, through linkage with national and regional death registries, employer records, and Social Security Administration records. Information on underlying cause of death was abstracted from death certificates and coded according to ICD-9 (international classification of diseases, 9th revision) in effect at the time of death. All cancer mortality (ICD-9 codes 140-208) was examined because radiation induced cancers could occur at most, if not all, sites following whole body exposure to ionising radiation, and because death certificate data could be more accurate for identifying all cancers as a group than for identifying specific types of cancer.

We examined all cancer excluding leukaemia (ICD-9 codes 140-203) and solid cancer (codes 140-199) because these groups are typically used in studies that underlie radiation protection recommendations. Solid cancer excluding lung cancer (codes 140-199 except 162) was examined because lung cancer is strongly related to cigarette smoking. The exclusion of lung cancer offers an indirect method to address concerns that smoking might be associated with occupational radiation exposure among nuclear industry workers, leading to bias in estimates of radiation-cancer associations.[17 18]

We also examined the association between radiation dose and solid cancer excluding three main groups. Firstly, a large of group of smoking related cancers were excluded: cancers of the oral cavity and pharynx,

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oesophagus, stomach, colon, rectum, liver, gallbladder, pancreas, nasal cavity, larynx, lung, cervix, ovary, bladder, kidney, and ureter (ICD-9 codes 140-199 except 140-151, 153-157, 160-162, 180, 183, and 188-189).[19] The second group to be excluded was cancers of the lung, liver, and bone (codes 140-199 except 155, 162, and 170), which are three sites that receive substantial doses from incorporated plutonium.[20] The third exclusion group was cancers of the lung and pleura (codes 140-199 except 162 and 163), to address concerns regarding potential bias due to occupational asbestos exposure.

A person entered the study on the date of first dosimetric monitoring, or one year after the date of first employment, whichever was later. The national death registry in France provides individual information on causes of death only from 1968 onwards; therefore French workers entered follow-up on 1 January 1968 or later. A person exited the study on the earliest date of the following: date of death, date lost to follow-up, or end of follow-up.

Statistical methods

The statistical methods used were similar to those in previous international studies of nuclear workers.[2 3] The estimated colon dose due to external exposure to penetrating photons was the exposure of primary interest. We quantified radiation dose-mortality associations using a Poisson regression model (relative rate=1+βZ, where Z is the cumulative dose in Gy and β is excess relative rate (the relative rate minus 1) per Gy).[21] Estimates of excess relative rate per Gy were adjusted, through stratification, for the effects of:

- Country
- Attained age (in five year intervals)
- Sex
- Year of birth (in 10 year intervals)
- Socioeconomic status:
  - French, US, and UK workers employed by the Atomic Energy Authority and Atomic Weapons Establishment classified into five categories, based on job title: professional and technical workers, administrative staff, skilled workers, unskilled workers, and uncertain
  - Other UK workers classified into two broader categories of non-industrial and industrial employees
- Duration of employment or radiation work (in 10 year intervals)
- Neutron monitoring status.[14 16]

To allow for a minimal induction and latency period between exposure and death,[22] cumulative doses were lagged by 10 years, facilitating comparison with other studies of solid cancer among nuclear workers.[2 3 5] We undertook sensitivity analyses in which cumulative doses were lagged five years or 15 years, cumulative doses were restricted to the lower dose range, and women and workers flagged for internal contamination or monitoring were excluded. Results obtained under alternative lags were compared with respect to goodness of model fit.[23]

To evaluate the influence of a single country on overall results, analyses excluded one country at a time; and, a model with a product term between country and dose was fitted, allowing heterogeneity to be assessed based on the likelihood ratio test. To assess departures from linearity in the effect of cumulative dose, we fitted a model that included a higher order polynomial function of cumulative dose and evaluated the improvement in model goodness of fit. We examined the dose-response association visually by fitting a regression model with indicator variables for categories of cumulative dose and plotting the resultant relative rate estimates against category specific, mean dose values.

We examined results after further stratifying the data according to whether a worker was flagged for internal contamination or monitoring, and after adjusting for mortality differences between the major employers in each country. We estimated the excess number of deaths associated with radiation exposure by calculating the difference between the fitted number of deaths within a stratum defined by levels of the stratification variables and the background number of deaths (obtained by multiplying the stratum specific rate of mortality at baseline by the person time in that stratum).

The objective of radiation epidemiological studies is generally to evaluate whether there is an increased cancer risk following radiation exposure; therefore, one sided P values and corresponding 90% confidence intervals are often reported.[2-5 24-26] Following this logic, we report 90% likelihood based confidence intervals for estimates of the excess relative rate per Gy. This also facilitates comparison of the precision of our estimated associations with findings reported in other important epidemiological studies of radiation exposed populations.[2-5 24-26] All models were fit using the EPICURE software package.

Patient involvement

No patients were involved in setting the research question or the outcome measures, nor were they involved in the design and implementation of the study. There are no plans to involve patients in the dissemination of results.

Results

The study population included 308 297 workers (table 1). Of 66 632 (22%) known deaths at the end of follow-up, 19 748 were identified to be due to cancer (n=684, leukaemia; n=5802, lung cancer). The follow-up of this cohort encompasses 8.2 million person years, with median follow-up of 26 years per worker, and median length of employment of 12 years. The median attained age at the end of follow-up was 58 years. Most workers were men (87%, n=268 262), and 97% of the collective colon dose was accrued by men. Among the 257 166 workers who had a positive recorded dose, the distribution of cumulative colon dose estimates was skewed (median 4.1 mGy, mean 20.9 mGy, 90th percentile 53.4 mGy, maximum 1331.7 mGy). The total collective colon dose was 5370.3 person Gy.

Table 1 | Characteristics of cohorts included in the INWORKS consortium (nuclear workers in France, UK, and USA, 1944-2005)

	France	UK	US	INWORKS
Calendar years of follow-up	1968-2004	1946-2001	1944-2005	1944-2005
Workers (no)	59 003	147 866	101 428	308 297
Person years (millions)	1.5	3.4	3.3	8.2
Causes of death (no)				
All causes	6310	25 307	35 015	66 632
All cancer	2552	7558	9638	19 748
All cancer other than leukaemia	2473	7350	9241	19 064
Solid cancer	2356	6994	8607	17 957
Solid cancer other than lung cancer	1761	4750	5644	12 155
Exposed workers (no)*	42 206	130 373	84 587	257 166
Collective dose (person Gy)	742.0	2936.1	1692.2	5370.3
Average individual cumulative dose (mGy)†	17.6	22.5	20.0	20.9

*Workers with cumulative dose greater than zero.
†Average estimated cumulative dose to the colon, among exposed workers.

For all cancers, the excess relative rate was 0.51 per Gy (90% confidence interval 0.23 to 0.82); table 2). The excess relative rate was 0.48 per Gy (0.20 to 0.79) for all cancers other than leukaemia, and 0.47 per Gy (0.18 to 0.79) for solid cancers. To indirectly assess confounding by smoking, we estimated the association between radiation dose and solid cancers other than lung cancer (excess relative rate 0.46 per Gy (0.11 to 0.85)), and observed that the point estimate was similar that obtained for all solid cancers. To assess potential bias due to asbestos exposure, we estimated the association between radiation dose and solid cancers other than lung and pleural cancer (0.43 per Gy (0.08 to 0.82)), again similar in magnitude to the point estimate obtained for all solid cancers.

Excluded cancers from the category of solid cancer (of the oral cavity and pharynx, oesophagus, stomach, colon, rectum, liver, gallbladder, pancreas, nasal cavity, larynx, lung, cervix, ovary, bladder, kidney, and ureter) yielded an estimated excess relative rate of 0.37 per Gy (90% confidence interval −0.14 to 0.95). The exclusion of this larger group of smoking related cancers, which constituted 70% of solid cancer deaths, thus resulted in a reduced magnitude and precision of the estimated excess relative rate per Gy.

Sensitivity analyses were conducted under five and 15 year lag assumptions (web table A1). Associations were slightly smaller in magnitude under a five year lag, and model goodness of fit was poorer than that obtained under our a priori 10 year lag assumption. Associations were slightly larger in magnitude under a 15 year lag with similar goodness of model fit than that obtained under a 10 year lag assumption.

Table 2 | Estimates of excess relative rate per Gy for death due to specific cancer categories in INWORKS*

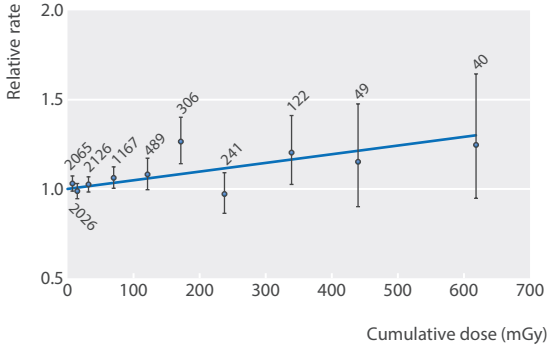
Causes of death	No of deaths	Excess relative rate per Gy (90% CI)
All cancer	19 748	0.51 (0.23 to 0.82)
All cancer other than leukaemia	19 064	0.48 (0.20 to 0.79)
Solid cancer	17 957	0.47 (0.18 to 0.79)
Solid cancer other than lung cancer	12 155	0.46 (0.11 to 0.85)

*10 year lag assumption.

A model describing a linear increase in the excess relative rate with dose appeared to provide a reasonable description of the data for all cancer other than leukaemia on visual examination (fig). Based on our fitted model, we estimated that about 209 of the 19 064 observed deaths due to cancer other than leukaemia were excess deaths associated with external radiation exposure (web table A2). To formally assess departure from linearity, we fitted a model that also included a parameter for the square of cumulative dose; this inclusion led to little improvement in the model goodness of fit (likelihood ratio test=0.58, df=1, P=0.44). To assess the trend over the lower cumulative dose range, we estimated associations over restricted ranges of 0-200 mGy cumulative dose (excess relative rate 1.04 per Gy; 90% confidence interval 0.55 to 1.56), 0-150 mGy cumulative dose (0.69 per Gy; 0.10 to 1.30), and 0-100 mGy cumulative dose (0.81 per Gy; 0.01 to 1.64; web fig S1).

To evaluate the effect of data from each country on the summary estimate for the pooled data, we excluded countries from the INWORKS cohort one at a time. Estimates for the association between cumulative dose under a 10 year lag and all cancer mortality other than leukaemia was 0.48 per Gy (90% confidence interval 0.19 to 0.80) after we excluded France, 0.39 per Gy (−0.03 to 0.85) after we excluded the UK, and 0.56 per Gy (0.19 to 0.97) after we excluded the USA from INWORKS. We saw no evidence of heterogeneity in the estimated associations by country based on a statistical test (likelihood ratio test=0.24, df=2, P=0.89) and visual examination of country specific estimates of association further supports such a conclusion (web fig S2).

To assess potential bias due to differences (other than external radiation doses) between the major employers in each country, we fitted a model that adjusted for each of the main facilities included in INWORKS. We saw



Relative rate of mortality due to all cancer other than leukaemia by categories of cumulative colon dose, lagged 10 years in INWORKS. Vertical lines=90% confidence intervals; dashed line=fitted linear model for the change in the excess relative rate of mortality due to all cancer other than leukaemia with dose; numbers above vertical lines=number of deaths due to cancer other than leukaemia in that dose category. The number of cancers in the lowest dose category (n=10 433) has not been annotated on this figure for reasons of legibility

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little change in the magnitude of the estimated association on further adjustment for facility (excess relative rate of cancer other than leukaemia 0.43 per Gy; 90% confidence interval 0.13 to 0.75). We examined results after further stratifying the data according to whether a worker was identified based on a known or suspected uptake or monitoring for any radionuclide (excess relative rate of cancer other than leukaemia 0.46 per Gy; 0.17 to 0.78); similarly, the estimated association was 0.45 per Gy (0.16 to 0.78) on stratification according to whether a worker was identified based on a known or suspected uptake or monitoring for any radionuclide other than tritium. We estimated the association between radiation dose and solid cancers other than lung, liver, and bone cancer (excess relative rate 0.51 per Gy; 0.15 to 0.91), and observed that the point estimate was similar to that obtained for all solid cancers.

Because most deaths from cancer occurred among men, and 97% of the collective dose was accrued by men, we examined results in analyses restricted to men. The estimated excess relative rate for all cancer other than leukaemia was slightly larger after the exclusion of women (0.51 per Gy; 90% confidence interval 0.22 to 0.82). Eighty seven per cent (n=268 523) of the workers in the INWORKS cohort had no reported dose from neutron exposure. Because our primary interest was in the effect of protracted external exposure to penetrating radiation in the form of photons, we examined results in analyses restricted to workers with no reported neutron dose (0.55 per Gy; 0.17 to 0.95). Similarly, because 83% (n=256 772) of workers were never flagged for incorporated radionuclides or internal monitoring, we examined results in analyses restricted to these workers (0.72 per Gy; 0.29 to 1.19).

Discussion

Principal findings

This study provides evidence of a linear increase in the excess relative rate of cancer mortality with increasing exposure to ionising radiation at the low dose rates typically encountered in the nuclear industries in France, the UK, and the USA. Restricting analyses to information regarding doses below 200, 150, and 100 mGy showed that the estimated excess relative rate per Gy for all cancers other than leukaemia were not driven by the highest dose categories. Analyses restricted to these lower doses also address the radiation protection community's interest in epidemiological evidence of a radiation dose-cancer association in these low dose ranges. INWORKS thus provides supportive evidence for a positive association between radiation dose and all cancer other than leukaemia, even if less precise when analyses are restricted to data for the 0-100 mGy dose range.

Comparison with other studies

The primary basis for the radiation risk estimates used to establish contemporary radiation protection standards comes from analyses of cancer in the Life Span Study of the Japanese atomic bomb survivors. Historically, it has been assumed that radiation-solid cancer associations diminish with falling dose rate. For example, the International Commission on Radiological Protection (2007) recommended that regulators divide the radiation risk coefficients obtained from the study of Japanese atomic bomb survivors in half when estimating risks for cancers other than leukaemia in settings with exposures of low dose and low dose rate radiation.[27] This was recommended because the high dose rate exposures from the atomic bombings were assumed to be more dangerous than the low dose rate exposures typically encountered by workers and members of the public.[27] Questions about the effects of such low dose exposure have, in part, motivated studies of nuclear workers since the 1970s.[28-33]

Our estimated association between radiation and solid cancer (excess relative rate 0.47 per Gy; 90% confidence interval 0.18 to 0.79) is larger than but statistically compatible with the estimate from a mortality analysis of male survivors of the Japanese atomic bomb exposed at ages 20-60 years (excess relative rate 0.32 per Sv; 95% confidence interval 0.01 to 0.50).[3] Statistical compatibility of risk estimates between studies may suggest some degree of coherence in the evidence derived from these large studies. However, in observational cohort studies, such as INWORKS and the Life Span Study of Japanese atomic bomb survivors,[15 24 25] large sample sizes and statistical precision are no protection against bias. We have attempted to deal with some concerns regarding bias through decisions in study design. To this end, INWORKS was not intended to assemble the largest number of nuclear workers possible, but rather to assemble those cohorts that were most informative with regard to quality and completeness of exposure and follow-up data.

The parent study of the INWORKS collaboration included 407 391 workers from 15 countries.[3] Although INWORKS included fewer nuclear workers than the earlier study, dose-response analyses in INWORKS encompassed substantially more cancer deaths than the parent study (17 957 *v* 4770 solid cancers), reflecting the extended follow-up of the INWORKS cohorts. INWORKS did not include data from Canada, a cohort for which the excess relative rate per Gy estimate was considerably larger than that observed in most other countries in the parent study, and for which concerns have been raised regarding data quality and completeness.[3 34 35] In our analysis, no single country's data exerted a large impact on the magnitude of the summary risk estimate. Rather, a statistical test of heterogeneity by country rejected the conclusion of significant variation in the radiation-cancer association between the three countries.

The summary risk estimates in the current analysis are more precise and are larger in magnitude than those obtained from previous country specific analyses.[4-6] For example, a previous analysis of data from France reported an estimated excess relative rate for solid cancers of 0.34 per Gy (90% confidence interval −0.56 to 1.38).[4] Data from the UK National Registry for Radiation Workers had an estimated excess relative rate for death due to cancers other than leukaemia of 0.28 per Gy (0.02 to 0.56).[5] Finally, data from the US showed an estimated

excess relative rate for cancers other than leukaemia of 0.14 per Gy (−0.17 to 0.48).[6]

Our estimated radiation risk coefficients could be somewhat larger than those in previous analyses of the constituent cohorts because we adjusted the recorded dose to account for bias in historical dosimeter response and attenuation, taking the estimated colon dose as the quantity of interest.[14] Analysis of the INWORKS data using recorded photon dose as the dose metric, rather than adjusted estimates of colon dose, yielded somewhat lower estimates of association, although use of adjusted colon dose estimates resulted in no significant improvement in model goodness of fit (web table A3). This finding accords with the general principle that it is possible to use assumptions about patterns of exposure misclassification (for example, different exposure periods or conditions) to reduce bias, but it is much more difficult to recover the precision that would be obtained if one knew each person's true exposure.[36]

Strengths and limitations of study

Our adjusted dose estimates drew on the substantial work done to characterise the performance of the various radiation dosimeters used in France, the UK, and the USA over the study period and account for differences between countries and over time in dosimeter performance.[37 38] Use of colon dose estimates facilitated comparison of our radiation risk estimates with those reported in mortality analyses of Japanese atomic bomb survivors that also related to estimated colon dose.[39] However, exposure measurement errors related to personal dosimeters, monitoring practices, and historical records, particularly in the early years of operation, remain a study limitation.[37 38] Radiation exposures might also have occurred outside of employment at facilities for which we have dosimetry records, and some workers could have had occupational radiation exposures that were not identified in the records available for this study.

In view of our focus on mortality due to cancer, a reasonable concern is potential confounding by cigarette smoking, which was unmeasured in our study.[40] Contrary to the pattern that would be expected if there was confounding by smoking, the magnitude of the estimated excess relative rate per Gy under a 10 year lag was essentially unchanged after excluding lung cancer. A separate paper on non-cancer disease further supports the conclusion of no significant confounding by smoking as evidenced by the lack of association between radiation dose and chronic obstructive pulmonary disease, an outcome strongly associated with smoking.[40] Although there has been interest in the joint effects of radiation and smoking on cancer risk,[41] this could not be evaluated in our study.

Similarly, we could not directly adjust for the effects of exposure to other known occupational lung carcinogens, such as asbestos. However, the magnitude of the estimated association between radiation dose and solid cancer mortality remained unchanged after the exclusion of lung cancer (and further exclusion of pleural cancer). Therefore, occupational lung carcinogens may not be an important confounder in the overall analysis of the association between radiation and solid cancer.

In INWORKS, adjustment for socioeconomic status reduced the magnitude of dose-response estimates, suggesting positive confounding by socioeconomic status. This variable, which is primarily based on job title, is likely to be a poor proxy for factors that relate social class to mortality differences, and suggests the possibility of residual confounding of radiation-cancer associations by socioeconomic status. We adjusted for duration of work owing to evidence of a modest deficit in relative mortality among workers who had at least 10 years of radiation work, and a larger deficit in relative mortality among workers who had at least 30 years of radiation work.[5] Stratification by duration of radiation work slightly increased estimates of association, suggesting negative confounding due to preferential retention of workers in better health (sometimes termed healthy worker survivor bias).[42] We assessed the sensitivity to adjustment for these variables by fitting a simpler model that adjusted only for country, age, sex, and birth cohort. The estimated association between dose and cancer mortality other than leukaemia was similar in magnitude and precision to that obtained from the fully adjusted model, suggesting that the net effect of adjustment for these variables was small (web table A4).

In the international collaborative study of cancer risk among radiation workers in the nuclear industry,[3] people with potential exposure to neutrons, which was difficult to reliably quantify using the historical personnel dosimeters, were excluded from analyses to focus on workers with well-measured photon doses.[43] A concern raised regarding this exclusion was that it excluded a large number of workers with high cumulative external photon doses.[44]

In the current analysis, we included workers with potential exposure to neutrons and adjusted where possible for neutron monitoring status. In sensitivity analyses, we excluded the 13% of the cohort that ever had a recorded neutron dose. The resulting estimated association between colon dose and mortality due to cancer other than leukaemia (excess relative rate 0.55 per Gy; 90% confidence interval 0.17 to 0.95) was similar to that obtained for the whole cohort after adjustment for neutron monitoring status (0.48 per Gy; 0.20 to 0.79). However, owing to the limitations of historical neutron dosimetry information, an analysis restricted to workers with no recorded neutron dose is likely to have included workers who had unrecorded neutron exposures, particularly among those employed in the early years of operations.[45]

The estimated association among workers with a positive recorded neutron dose (excess relative rate 0.36 per Gy; 90% confidence interval −0.08 to 0.88) and those with a recorded neutron dose exceeding 10% of total dose (0.62 per Gy; −0.50 to 2.09) were also similar in magnitude to, but less precise than, the whole cohort estimate after adjustment for neutron monitoring status. Therefore, the summary adjusted estimate does not appear to have obscured any meaningful heterogeneity

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in the excess relative rate per Gy by neutron monitoring status (web table A5).

Employees who had recorded neutron doses—which reflects work in radiologically controlled areas where neutron dosimeters were issued—tended to have lower baseline rates of cancer mortality than those who did not. Reduced mortality rates among workers in radiologically controlled areas has been attributed to factors such as restrictions on smoking in such areas, and additional medical screening for work in areas where additional hazards might occur.[46 47] Adjustment for neutron monitoring status accounts for such differences in baseline rates between groups, yielding a summary adjusted estimate comparable to the stratum specific estimates of excess relative rate per Gy. However, an unadjusted estimate produced a smaller value (0.20 per Gy; 90% confidence interval −0.03 to 0.46; web table A5). Adjustment for neutron monitoring status, however, might be inadequate to fully control for differences in baseline rates between these groups, owing to limitations of historical neutron dosimetry information. Furthermore, bias could persist in adjusted analyses if health related selection out of employment affects a worker's future monitoring status and exposure history, and is itself affected by previous radiation exposure.[42]

INWORKS included workers with potential for committed doses from incorporated radionuclides. As a sensitivity analysis, we excluded the 17% (n=51 525) of the cohort who had been identified on the basis of internal contamination or monitoring. This exclusion had a much larger effect for the UK cohort than for those in the USA or France. The UK had identified anyone monitored for internal exposure, whereas the US and France identified anyone with a confirmed uptake.

In the present study, after the exclusion of workers flagged for internal contamination or monitoring, the estimated association between colon dose and mortality due to cancer other than leukaemia was larger in magnitude than the estimate for the whole cohort. This difference was consistent with a previous observation that among UK nuclear workers, radiation dose-cancer associations were smaller for workers who were potentially exposed to internal radiation than for those not exposed.[48] After excluding cancers of the lung, liver, and bone, we observed that the magnitude of the estimated excess relative rate (0.51 per Gy; 90% confidence interval 0.15 to 0.91) was similar for all solid cancers. This estimate was larger than the estimated association between colon dose from external ionising radiation exposure and mortality due to solid cancers other than lung, liver, and bone among workers employed at the Mayak Production Association in Ozyorsk, Russia (0.16 per Gy; 0.08 to 0.24).[20] Further work on internal doses is ongoing and could allow for increased attention to effects of incorporated radionuclides in future analyses.

Conclusions and implications for future research

Follow-up of large cohorts of nuclear industry workers has been ongoing for over 30 years; our data now yield sufficient statistical information to permit relatively precise estimates of cancer mortality risk in a population for whom average cumulative doses are about 20 mGy. These findings represent a substantial addition to the scientific basis for understanding the risks of cancer from protracted, low dose rate, exposure to ionising radiation; and underscore the value of the substantial efforts being made in France, the UK, and the USA to continue gathering data for these worker studies.

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Contributors: DBR and AK conceived the study. DBR, AK, EC, RDD, MG, JAO'H, RH, DL, KL, MKS-B, and IT-C developed the research questions and designed the study. KL and DL worked on provision of the French data, MKS-B and RDD worked on provision of the US data; MG, JAO'H, and RH worked on provision of the UK data. MM and GBH were responsible for data management and processing as well as some analyses. IT-C was responsible for the dosimetry. DBR did the statistical analysis and produced the initial draft of the manuscript, which was revised and approved by all authors. DBR is the guarantor.

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Data sharing: For reasons of ethics and permissions from different agencies, the data are maintained at the International Agency for Research on Cancer (Lyon, France); it is not possible to send the data outside of the agency.

The lead author (the manuscript's guarantor) affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

1 Rhodes R. The Making of the Atomic Bomb. Simon & Schuster, 1986.
2 Cardis E, Gilbert ES, Carpenter L, et al. Effects of low doses and low dose rates of external ionizing radiation: cancer mortality among nuclear industry workers in three countries. *Radiat Res* 1995;142:117-32.

3 Cardis E, Vrijheid M, Blettner M, et al. Risk of cancer after low doses of ionising radiation—retrospective cohort study in 15 countries. *BMJ* 2005;331:77.
4 Metz-Flamant C, Laurent O, Samson E, et al. Mortality associated with chronic external radiation exposure in the French combined cohort of nuclear workers. *Occup Environ Med* 2013;70:630-8.
5 Muirhead CR, O'Hagan JA, Haylock RG, et al. Mortality and cancer incidence following occupational radiation exposure: third analysis of the National Registry for Radiation Workers. *Br J Cancer* 2009;100:206-12.
6 Schubauer-Berigan MK, Daniels RD, Bertke SJ, et al. Cancer mortality through 2005 among a pooled cohort of U.S. nuclear workers exposed to external ionizing radiation. *Radiat Res* 2015;183:620-31.
7 Leuraud K, Richardson DB, Cardis E, et al. Ionizing radiation and risk of death from leukaemia and lymphoma in radiation-monitored workers (INWORKS): an international cohort study. *Lancet Haematol* 2015;2:e276-81.
8 Bithell JF, Stewart AM. Pre-natal irradiation and childhood malignancy: a review of British data from the Oxford Survey. *Br J Cancer* 1975;31:271-27.
9 Doll R, Wakeford R. Risk of childhood cancer from fetal irradiation. *Br J Radiol* 1997;70:130-9.
10 International Agency for Research on Cancer. A review of human carcinogens. Part D: Radiation. IARC, 2012.
11 Pearce MS, Salotti JA, Little MP, et al. Radiation exposure from CT scans in childhood and subsequent risk of leukaemia and brain tumours: a retrospective cohort study. *Lancet* 2012;380:499-505.
12 Mathews JD, Forsythe AV, Brady Z, et al. Cancer risk in 680 000 people exposed to computed tomography scans in childhood or adolescence: data linkage study of 11 million Australians. *BMJ* 2013;346:f2360.
13 Institute of Medicine of the US National Academies, National Research Council. Research on Health Effects of Low-Level Ionizing Radiation Exposure: Opportunities for the Armed Forces Radiobiology Research Institute. National Academies Press, 2014.
14 Thierry-Chef I, Richardson DB, Daniels RD, et al. Dose estimation for a study of nuclear workers in France, the United Kingdom and the United States of America: methods for the International Nuclear Workers Study (INWORKS). *Radiat Res* 2015;183:632-42.
15 Preston DL, Shimizu Y, Pierce DA, et al. Studies of mortality of atomic bomb survivors. Report 13: solid cancer and noncancer disease mortality: 1950-1997. *Radiat Res* 2003;160:381-407.
16 Hamra GB, Richardson DB, Cardis E, et al. Cohort profile: the international nuclear workers study (INWORKS). *Int J Epidemiol* 2015, doi:10.1093/ije/dyv122.
17 Gilbert ES. Mortality of workers at the Oak Ridge National Laboratory [letter] [see comments]. *Health Phys* 1992;62:260-4.
18 Wakeford R. Cancer risk among nuclear workers. *J Radiol Prot* 2005;25:225-8.
19 International Agency for Research on Cancer. A review of human carcinogens. E. Personal habits and indoor combustions. IARC, 2012.
20 Sokolnikov M, Preston D, Gilbert E, et al. Radiation effects on mortality from solid cancers other than lung, liver, and bone cancer in the Mayak worker cohort: 1948-2008. *PLoS ONE* 2015;10:e0117784.
21 Frome EL. The analysis of rates using Poisson regression models. *Biometrics* 1983;39:665-74.
22 Rothman KJ. Induction and latent periods. *Am J Epidemiol* 1981;114:253-9.
23 Richardson DB, Cole SR, Chu H, et al. Lagging exposure information in cumulative exposure-response analyses. *Am J Epidemiol* 2011;174:1416-22.
24 Preston DL, Kato H, Kopecky KJ, et al. Studies of the mortality of A-bomb survivors, report 8. Cancer mortality, 1950-1982. *Radiat Res* 1987;111:151-78.
25 Preston DL, Ron E, Tokuoka S, et al. Solid cancer incidence in atomic bomb survivors: 1958-1998. *Radiat Res* 2007;168:1-64.
26 Gilbert ES, Cragle DL, Wiggs LD. Updated analyses of combined mortality data for workers at the Hanford Site, Oak Ridge National Laboratory, and Rocky Flats Weapons Plant. *Radiat Res* 1993;136:408-21.
27 International Commission on Radiological Protection. The 2007 recommendations of the International Commission on Radiological Protection. ICRP publication 103. *Ann ICRP* 2007;37:1-332.
28 Mancuso TF, Stewart A, Kneale G. Radiation exposures of Hanford workers dying from cancer and other causes. *Health Phys* 1977;33:369-85.
29 Gilbert ES. Methods of analyzing mortality of workers exposed to low levels of ionizing radiation. Pacific Northwest Laboratories, Battelle Memorial Institute, 1977.
30 Gilbert ES, Fry SA, Wiggs LD, et al. Analyses of combined mortality data on workers at the Hanford Site, Oak Ridge National Laboratory, and Rocky Flats Nuclear Weapons Plant. *Radiat Res* 1989;120:19-35.
31 Beral V, Inskip H, Fraser P, et al. Mortality of employees of the United Kingdom Atomic Energy Authority, 1946-1979. *BMJ (Clinical research ed)* 1985;291:440-7.
32 Kendall GM, Muirhead CR, MacGibbon BH, et al. Mortality and occupational exposure to radiation: first analysis of the National Registry for Radiation Workers. *BMJ* 1992;304:220-5.
33 International Agency for Research on Cancer. Direct estimates of cancer mortality due to low doses of ionising radiation: an international study. IARC study group on cancer risk among nuclear industry workers. *Lancet* 1994;344:1039-43.
34 Zablotska LB, Lane RS, Thompson PA. A reanalysis of cancer mortality in Canadian nuclear workers (1956-1994) based on revised exposure and cohort data. *Br J Cancer* 2014;110:214-23.
35 Wakeford R. Nuclear worker studies: promise and pitfalls. *Br J Cancer* 2014;110:1-3.
36 Armstrong BG. Effect of measurement error on epidemiological studies of environmental and occupational exposures. *Occup Environ Med* 1998;55:651-6.
37 Thierry-Chef I, Marshall M, Fix JJ, et al. The 15-country collaborative study of cancer risk among radiation workers in the nuclear industry: study of errors in dosimetry. *Radiat Res* 2007;167:380-95.
38 Thierry-Chef I, Pernicka F, Marshall M, et al. Study of a selection of 10 historical types of dosemeter: variation of the response to Hp(10) with photon energy and geometry of exposure. *Radiat Prot Dosimetry* 2002;102:101-13.
39 Ozasa K, Shimizu Y, Suyama A, et al. Studies of the mortality of atomic bomb survivors, Report 14, 1950-2003: an overview of cancer and noncancer diseases. *Radiat Res* 2012;177:229-43.
40 Richardson DB, Laurier D, Schubauer-Berigan MK, et al. Assessment and indirect adjustment for confounding by smoking in cohort studies using relative hazards models. *Am J Epidemiol* 2014;180:933-40.
41 Pierce DA, Sharp GB, Mabuchi K. Joint effects of radiation and smoking on lung cancer risk among atomic bomb survivors. *Radiat Res* 2003;159:511-20.
42 Buckley JP, Keil AP, McGrath LJ, et al. Evolving methods for inference in the presence of healthy worker survivor bias. *Epidemiology* 2014;26:204-12.
43 Fix JJ, Salmon L, Cowper G, et al. A retrospective evaluation of the dosimetry employed in an international combined epidemiological study. *Radiat Prot Dosimetry* 1997;74:39-53.
44 Wakeford R. More on the risk of cancer among nuclear workers. *J Radiol Prot* 2009;29:1-4.
45 Kite AV, Anderson RW. An overview of retrospective occupational dosimetry at BNFL [3-102 to 3-104]. Proceedings of the international congress on radiation protection and general assembly of the International Radiation Protection Association, Vienna (Austria); 1996 April. Austrian Radiation Protection Association, International Radiation Protection Association, 1996.
46 McGeoghegan D, Binks K, Gillies M, et al. The non-cancer mortality experience of male workers at British Nuclear Fuels plc, 1946-2005. *Int J Epidemiol* 2008;37:506-18.
47 Wing S, Richardson D, Wolf S, et al. Plutonium-related work and cause-specific mortality at the United States Department of Energy Hanford Site. *Am J Indust Med* 2004;45:153-64.
48 Gillies M, Haylock R. The cancer mortality and incidence experience of workers at British Nuclear Fuels plc, 1946-2005. *J Radiol Prot* 2014;34:595-623.

Web appendix: Supplementary analyses