Cancer mortality after low dose exposure to ionising radiation in workers in France, the United Kingdom, and the United States (INWORKS): cohort study

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ABSTRACT

OBJECTIVE

To evaluate the effect of protracted low dose, low dose rate exposure to ionising radiation on the risk of cancer.

DESIGN

Multinational cohort study.

SETTING

Cohorts of workers in the nuclear industry in France, the UK, and the US included in a major update to the International Nuclear Workers Study (INWORKS).

PARTICIPANTS

309 932 workers with individual monitoring data for external exposure to ionising radiation and a total follow-up of 10.7 million person years.

MAIN OUTCOME MEASURES

Estimates of excess relative rate per gray (Gy) of radiation dose for mortality from cancer.

RESULTS

The study included 103 553 deaths, of which 28 089 were due to solid cancers. The estimated rate of mortality due to solid cancer increased with cumulative dose by 52% (90% confidence interval 27% to 77%) per Gy, lagged by 10 years. Restricting the analysis to the low cumulative dose range (0-100 mGy) approximately doubled the estimate of association (and increased the width of its confidence interval), as did restricting the analysis to workers hired in the more recent years of operations when estimates of occupational external penetrating radiation dose were recorded more accurately. Exclusion of deaths from lung cancer and pleural cancer had a modest effect on the estimated magnitude of association, providing indirect evidence that the association was not substantially confounded by smoking or occupational exposure to asbestos.

CONCLUSIONS

This major update to INWORKS provides a direct estimate of the association between protracted low dose exposure to ionising radiation and solid cancer mortality based on some of the world's most informative cohorts of radiation workers. The summary estimate of excess relative rate solid cancer mortality per Gy is larger than estimates currently informing radiation protection, and some evidence suggests a steeper slope for the dose-response association in the low dose range than over the full dose range. These results can help to strengthen radiation protection, especially for low dose exposures that are of primary interest in contemporary medical, occupational, and environmental settings.

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

The results of an updated study of nuclear workers in France, the UK, and the US suggest a linear increase in the relative rate of cancer with increasing exposure to radiation

Some evidence suggested a steeper slope for the dose-response association at lower doses than over the full dose range

The risk per unit of radiation dose for solid cancer was larger in analyses restricted to the low dose range (0-100 mGy) and to workers hired in the more recent years of operations

Introduction

Unlike many carcinogens, which have been reduced or removed once recognised, the public's exposure to ionising radiation has increased in recent decades.[1-3] In the US, for example, the average person's annual effective dose doubled between 1985 and 2006 and has remained elevated since,[4] primarily owing to increases in exposure to ionising radiation from medical imaging procedures (whereas the average radiation worker's annual occupational dose remained relatively constant over that period).[5-7] Understanding of associations between low dose and low dose rate radiation exposures and cancer informs decisions about medical and commercial uses of ionising radiation, as well as decisions about exposure limits for members of the public and people working with ionising radiation.

The study of Japanese survivors of the atomic bombs serves as the primary basis for the quantitative risk estimates used in radiation protection.[8 9] Although that study concerns a high dose rate setting, findings from it inform contemporary assessments for low dose and low dose rate radiation exposures.[10-12] The International Nuclear Workers Study (INWORKS) was undertaken to provide a large scale international assessment of mortality risks from protracted low dose, low dose rate ionising radiation exposures.[13] INWORKS pools cohorts of nuclear workers monitored with radiation badges in France, the UK, and the US, countries that have assembled some of the largest and most informative cohorts of nuclear workers in the world.[14-18] Here, we report on a major update of analyses of associations

between radiation dose and mortality due to solid cancers in INWORKS, with follow-up extended by 10 or more years in each country.

Methods

INWORKS was established to provide a basis for deriving quantitative estimates of the association between protracted low dose, low dose rate exposure to ionising radiation and mortality. INWORKS builds on the work done for the International Collaborative Study of Cancer Risk among Radiation Workers in the Nuclear Industry by taking advantage of data from the most informative cohorts involved in that study.[19] Criteria for selection of the study cohorts included completeness and quality of data, start of facility operations, and exposure primarily to high energy, low linear energy transfer penetrating radiations.[13] Data came from three major French employers (Commissariat à l'Energie Atomique et aux énergies alternatives, Orano, and Electricité de France), from the UK 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), and 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. To be included, workers must have the information needed for linkages with vital records (that is, individual identifiers and date of birth) and must have been employed in the nuclear industry for at least one year and monitored for external radiation with personal dosimeters.[13]

In all countries, institutional review boards determined that documentation of informed consent was not necessary for this records based study. In France, information on workers came from existing records, with no direct contact with participants, and the institutional review board waived requirements for individual informed consent. In the UK, workers could refuse to participate in the National Registry for Radiation Workers, although less than 1% did. In the US, information on workers came from existing records, with no direct contact with participants, and the institutional review board waived requirements for informed consent.

We derived individual annual estimates of whole body dose primarily due to external exposure to penetrating radiation in the form of photons from personal occupational exposure monitoring data.[20-22] Unless otherwise stated, any reference to dose in this paper implies absorbed dose to the colon expressed in gray (Gy). We derived the estimated colon dose to facilitate comparison with analyses of associations between radiation dose and solid cancer done in other major cohorts.[23 24] Film dosimeters with one or two elements (that is, filters, often made of lead, tin, or cadmium) were commonly used for personal dosimetry beginning in the 1940s.[20] Multi-element dosimeters were implemented in most mixed activity facilities by the late 1950s to account for mixed field irradiation and allow for better estimation of dose over a wider range of photon energies.[20] Thermoluminescent dosimeters largely replaced the film badge beginning in the 1970s.[20] Administrative practices also changed over time; the frequency of dosimeter exchange was greater (for example, weekly or biweekly) before around 1965 and lesser (for example, monthly or quarterly) thereafter.[20] Portsmouth Naval Shipyard's dose information was not available after 1996; however, few people in that study cohort were still working after 1996. We did not add recorded estimates of doses from tritium intakes or neutron exposures to recorded dose from exposure to external photon radiation.[22] 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.[20 22 25]

Available measures of incorporated radionuclides included bioassay results, indication of confirmed uptake (for example, fraction of a body burden or annual limit on intake), or an assigned committed dose. We used available records or workstation-exposure matrix information (for France) to categorise workers on the basis of indication of a known or suspected internal contamination (we identified French and US workers with a known or suspected uptake, as well as UK workers who were known to have been monitored for internal exposure).[20 22]

We ascertained vital status through 2012, 2014, and 2016 for the UK, French, and US cohorts, respectively, through linkage with national and regional death registries, employers' records, tax records, and social security administration records. We abstracted information on underlying cause of death from death certificates and coded it according to the ICD (international classification of diseases) revision in effect at the time of death. We examined all cancer related mortality (ICD-9 codes 140-208) because radiation induced cancers could occur at most, if not all, sites after 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 solid cancer (ICD-9 codes 140-199) as a primary outcome of interest and an outcome typically examined in studies of the effects of low dose radiation. We also examined the association between radiation dose and solid cancer excluding lung cancer (ICD-9 code 162), because the exclusion of lung cancer is an indirect method to evaluate concerns about confounding by smoking; solid cancer excluding cancers of the oral cavity and pharynx, oesophagus, stomach, colon, rectum, liver, gallbladder, pancreas, nasal cavity, larynx, lung, cervix, ovary, bladder, kidney, and ureter (ICD-9 codes 140-151, 153-154.1, 154.8-157, 160-162, 180, 183, and 188-189), which constitute

a larger group of smoking related cancers[26]; chronic obstructive pulmonary disease (ICD-9 codes 490-492, and 496), because this outcome is strongly associated with tobacco smoking but not known to be associated with low dose ionising radiation, providing an indirect method to assess concerns about confounding by smoking[27]; solid cancer excluding cancers of the lung, liver, and bone (ICD-9 codes 155, 162, and 170), which are three organs that may receive substantial doses in cases of incorporated plutonium[24 28 29]; and solid cancer excluding cancers of the lung and pleura (ICD-9 codes 162 and 163), to assess concerns about potential bias due to occupational exposure to asbestos. Supplementary table A provides additional details on the ICD codes that define each outcome category.

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, so French workers entered follow-up on 1 January 1968 or later. For the UK cohort, start of follow-up for workers first employed before 1955 was defined as 1 January 1955 owing to indications that follow-up information before that date may not be complete.[30 31] A person exited the study on the earliest of the date of death, date lost to follow-up, or end of follow-up for vital status ascertainment.

Statistical methods

The statistical methods used were similar to those used in previous international studies of nuclear workers.[18] We quantified radiation dose-mortality associations by using a stratum specific model for mortality rates, I_k, of the form $I_k=\exp(\alpha_k)(1+\beta Z)$, where k indexes strata, Z is the cumulative dose in Gy, and β is excess relative rate (the relative rate minus 1) per Gy.[32-34] The excess relative rate is expressed as a proportional increase in the rate over baseline, per unit dose, where a value of 0 indicates no radiation associated increase in the mortality rate. Models were fitted using Poisson regression methods for analysis of mortality rates, incorporating person time at risk as the rate denominator.[35] We adjusted estimates of excess relative rate per Gy, through stratification, for the effects of country, attained age (in 5 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 on the basis of 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), and neutron monitoring status. Information on country, age, sex, and year of birth was complete; we included workers with missing information on job classification (<1% of workers were missing such information) in the category of uncertain socioeconomic status. We identified our adjustment set of covariates on the basis of substantive knowledge and consideration of causal structures facilitated by reference to directed acyclic graphs (supplementary figure A).[36-38] To allow for a minimal induction and latency period between exposure and death, cumulative doses were lagged by 10 years; we chose a 10 year lag a priori, and it facilitates comparison of results with our previous analysis of these data as well as with some other studies of solid cancer mortality among nuclear workers.[18 19 39 40]

We did sensitivity analyses in which cumulative doses were lagged five years, 15 years, or 20 years, cumulative doses were restricted to the lower dose range, workers with a positive neutron dose were excluded, workers flagged for internal contamination or monitoring were excluded, and regression model adjustment was made for workers flagged for internal contamination or monitoring. We compared results obtained under alternative lags with respect to goodness of model fit.[41] We examined the dose-response association visually by fitting a regression model with indicator variables for categories of cumulative dose (that is, a piecewise constant model for the association) and plotting the resultant relative rate estimates against category specific mean dose values (noting that reported estimates of excess relative rate per Gy were derived from regression models fitted to the full data tabulation). To formally assess departure from linearity in the effect of cumulative dose, we fitted a model that also included a quadratic function of cumulative dose, and we also fitted a linear exponential model of the form $I_k=\exp(\alpha_k)(1+\beta Z)\exp(\delta Z)$; we evaluated the improvement in model goodness of fit by using a likelihood ratio test statistic. To evaluate the influence of a single country on overall results, analyses excluded one country at a time, and we fitted a model with a product term between country and dose, allowing heterogeneity to be assessed on the basis of the likelihood ratio test. We derived an estimate of between country heterogeneity in association by using the method of DerSimonian and Laird for random effects.[42 43] To assess the effect of inaccuracies in dose estimates for workers employed in the early years of nuclear industry operations, we excluded workers hired before 1958 and before 1965; we chose these dates because they represent the years at various facilities when dosimetry improved owing to changes in dosimeter technology and administrative practice.[22 25]

We report likelihood based 90% confidence intervals for estimates of the excess relative rate per Gy, a common approach in radiation epidemiological studies in which the objective is to evaluate whether an increased risk of cancer exists after exposure to radiation; this facilitates comparison of the precision of our estimated associations with findings reported in other important epidemiological studies of populations exposed to radiation.[19 39 40 44-47] We report the change in deviance on inclusion of a term in the regression model as a likelihood ratio test statistic

along with its associated P value, which provides a continuous measure of the fit of the model to the data (that is, compatibility between the observed data and the model used to compute the statistic).[48] We interpret the P value as a continuous measure rather than limiting interpretation to dichotomisation of the P value at a threshold for declaring significance (such as 0.05). We fitted models by using conditional Poisson regression with primary control for confounding obtained by stratification, implemented in the SAS software package (version 9.4).[49]

Patient and public involvement statement

No patients were involved in setting the research question, the outcome measures, or the design and implementation of the study. The nuclear sites at which workers were employed were restricted, we lacked permissions to engage directly with employees, and the study involves large number of workers employed in the past. However, discussions with workers helped to motivate our study analyses and consideration of study limitations.

Results

The study included 309 932 workers and encompassed 10.7 million person years of follow-up (table 1). The study cohort included 40 445 women. We followed the average worker to nearly 70 years of age; among these workers we observed 103 553 deaths by the end of follow-up, of which 31 009 deaths were due to cancer and 28 089 deaths were due to solid cancer. Less than 2% of decedents had a missing or unknown underlying cause of death, and less than 2% of workers emigrated or were otherwise lost to follow-up for vital status ascertainment.

The excess relative rate was 0.53 (90% confidence interval 0.30 to 0.77) per Gy for all cancer mortality and 0.52 (0.27 to 0.77) per Gy for solid cancer mortality (table 2). Our a priori 10 year lag assumption was reasonably well supported by the data (supplementary table B). The estimated association between radiation dose and solid cancer was slightly smaller in magnitude and poorer in model goodness of fit under a five year lag assumption than under a 10 year lag assumption. The estimated association between radiation dose and solid cancer was similar in magnitude and poorer in model goodness of fit under a 20 year lag assumption than under a 10 year lag assumption (supplementary table B). Under a 15 year lag assumption, the estimated association between radiation dose and solid cancer was slightly larger in magnitude and had slightly better model goodness of fit than under a 10 year lag assumption (supplementary table B).

To evaluate the impact of data from each country on the summary estimate for the pooled data, we excluded countries from the INWORKS cohort one at a time. The estimate for the association between cumulative dose under a 10 year lag and solid cancer mortality was 0.47 (0.22 to 0.73) per Gy when we excluded France, 0.41 (0.04 to 0.80) per Gy when we excluded the UK, and 0.66 (0.35 to 1.00) per Gy when we excluded the US from INWORKS. We observed minimal evidence of heterogeneity in the estimated associations by country on the basis of a statistical test (likelihood ratio test=2.3, df=2; P=0.31). A random effects model suggested modest between country variance (τ^2=0.01; Q statistic for heterogeneity=2.3, df=2; P=0.31), with 16% of the overall variation in study results being due to between study heterogeneity.

The association between cumulative dose, lagged 10 years, and solid cancer mortality was reasonably well described by a linear model (fig 1); inclusion of a parameter describing the linear association between cumulative dose and solid cancer contributed substantially to model goodness of fit (supplementary table B). The addition of a parameter for the square of cumulative dose led to only a modest improvement in model goodness of fit compared with the linear model (likelihood ratio test =2.51, df=1; P=0.11), suggesting some downward curvature (that is, a negative estimated coefficient for the quadratic term). The addition of a parameter for an exponential term in the model led to a modest improvement in model goodness of fit for a linear-exponential model compared with the linear model (likelihood ratio test =3.17, df=1; P=0.08), again suggesting some downward curvature. To assess the trend over the lower cumulative dose range, we estimated associations between cumulative dose and solid cancer mortality over restricted ranges of 0-400 mGy cumulative dose (excess relative rate 0.63 (0.34 to 0.92) per Gy), 0-200 mGy cumulative dose (0.97 (0.55 to 1.39) per Gy), 0-100 mGy cumulative dose (1.12 (0.45 to 1.80) per Gy), 0-50 mGy cumulative dose (1.38 (0.20 to 2.60) per Gy), and 0-20 mGy cumulative dose (1.30 (−1.33 to 4.06) per Gy) (supplementary table C). Over the restricted range of 0-200 mGy cumulative dose, the association between cumulative dose and solid cancer mortality was well described by a linear model, and the addition of a parameter for the square of cumulative dose led to minimal improvement in model goodness of fit compared with the linear model (likelihood ratio test=0.54, df=1; P=0.46).

To indirectly assess potential confounding by smoking, we estimated the association between cumulative radiation dose and solid cancers other than lung cancer (excess relative rate 0.46 (0.18 to 0.76) per Gy) (table 2). The association between cumulative radiation dose and solid cancers other than lung cancer was reasonably well described by a linear model (supplementary figure B); neither the addition of a parameter for the square of cumulative dose (likelihood ratio test=0.24, df=1; P=0.62) nor the addition of a parameter in a linear-exponential model led to substantial improvement in model goodness of fit compared with the linear model (likelihood ratio test=0.26, df=1; P=0.61). We also estimated the association between cumulative radiation dose and solid cancer excluding a broader group of smoking related cancers (excess relative rate 0.52 (0.10 to 0.99) per Gy, based on 8889 deaths). We examined the association between cumulative radiation dose and chronic obstructive pulmonary disease, an

Table 1 | Characteristics of cohorts included in INWORKS: nuclear workers in France, UK, and US, 1944-2016

Characteristic	France	UK	US	INWORKS
Calendar years of follow-up	1968-2014	1955-2012	1944-2016	1944-2016
Workers	60 697	147 872	101 363	309 932
Person years (millions):	2.08	4.67	3.98	10.72
Men	1.80	4.27	3.17	9.24
Women	0.28	0.40	0.81	1.48
Deaths (all causes):	12 270	39 933	51 350	103 553
All cancer	4885	12 556	13 568	31 009
Solid cancer	4446	11 574	12 069	28 089
Solid cancer other than lung	3317	8308	8198	19 823
Chronic obstructive pulmonary disease	133	1545	2527	4205
Average duration of follow-up (years)	34.2	31.6	39.3	34.6
Average age at end of follow-up (years)	64.8	62.5	71.4	65.9
Average individual cumulative dose (mGy)	12.9	20.19	16.8	17.7
Average individual cumulative dose to colon* (mGy)	17.8	22.75	20.1	20.9

*Among workers whose estimated dose was >0.

outcome strongly associated with tobacco smoking but not known to be associated with low dose ionising radiation; we observed minimal evidence of association between cumulative radiation dose and chronic obstructive pulmonary disease (excess relative rate 0.12 (−0.43 to 0.68) per Gy) (table 2). To indirectly assess potential confounding by asbestos, we estimated the association between radiation dose and solid cancers other than lung cancer and pleural cancer (excess relative rate 0.43 (0.15 to 0.73) per Gy, based on 19 550 deaths).

To address concerns about potential inaccuracies in dose estimation in the early years of operations, we examined the association between cumulative radiation dose and solid cancer mortality restricted to the 238 639 workers hired in 1958 or later (excess relative rate 1.22 (0.74 to 1.72) per Gy) and restricted to the 189 386 workers hired in 1965 or later (1.44 (0.65 to 2.32) per Gy) (supplementary table D). For comparison, we examined the association among workers who were hired before 1958 (excess relative rate 0.20 (−0.07 to 0.49) per Gy). Similarly to analyses of the full cohort, we observed evidence of downward curvature in the association between cumulative dose and solid cancer mortality in the analyses restricted to workers hired in 1965 or later (change in deviance on addition of a parameter for the square of cumulative dose was 2.68, df=1; P=0.10, and change in deviance on addition of a parameter for an exponential term in the model was 5.39, df=1; P=0.02). In analyses restricted to workers hired in these more contemporary periods, estimated associations between cumulative radiation dose and solid cancers other than lung cancer were similar in magnitude to estimates of association for solid cancer; neither the addition of a parameter for the square of cumulative dose (likelihood ratio test=0.08, df=1; P=0.78) nor the addition of a parameter in a linear-exponential model led to substantial improvement in model goodness of fit compared to the linear model (likelihood ratio test=0.17, df=1; P=0.68). In analyses restricted to workers hired in these more contemporary periods, we observed minimal evidence of association between radiation dose and chronic obstructive pulmonary disease (supplementary table D).

Because our primary interest is in the effect of external exposure to penetrating photons, we examined results in analyses restricted to the 84% of workers (9.05 million person years and 23 410 deaths due to solid cancer) who were never flagged for incorporated radionuclides or internal monitoring (excess relative rate 0.82 (0.46 to 1.22) per Gy). For comparison, we examined results among workers who were flagged for incorporated radionuclides or internal monitoring (excess relative rate 0.21 (−0.11 to 0.56) per Gy) (supplementary table E). We found negligible evidence of curvature in the association between cumulative dose and solid cancer mortality in analyses restricted to workers who were never flagged for incorporated radionuclides or internal monitoring (change in deviance on addition of a parameter for the square of cumulative dose=0.39, df=1; P=0.53), nor in analyses restricted to workers who were flagged for incorporated radionuclides or internal monitoring (change in deviance on addition of a parameter for the square of cumulative dose=1.02, df=1; P=0.31). We also estimated the association between cumulative radiation dose and solid cancers other than lung, liver, and bone cancer among workers who had no reported internal deposition (excess relative rate 0.81 (0.36 to 1.28) per Gy, based on 15 943 deaths). In addition, in the full cohort, we estimated the association between cumulative radiation dose and solid cancer after further adjusting for indication of incorporated radionuclides or internal monitoring (excess relative rate 0.52 (0.26 to 0.78) per Gy).

Table 2 | Estimates of excess relative rate (ERR) per Gy for death due to specific outcome categories in INWORKS

Category	Deaths	ERR per Gy* (90% CI)
All cancer	31 009	0.53 (0.30 to 0.77)
Solid cancer	28 089	0.52 (0.27 to 0.77)
Solid cancer other than lung	19 823	0.46 (0.18 to 0.76)
Chronic obstructive pulmonary disease	4205	0.12 (−0.43 to 0.68)

10 year lag assumption.
CI: confidence interval.
*Strata: country, age, sex, birth cohort, socioeconomic status, duration employed, neutron monitoring status.

Because of concerns about measurement of exposure to neutrons, we examined results in analyses restricted to the 9.45 million person years and 24 213 deaths due to solid cancer observed among workers who had no reported neutron dose (excess relative rate 0.55 (0.23 to 0.90) per Gy). For comparison, we examined results among workers who had recorded neutron dose (supplementary table F).

We assessed the sensitivity of results to adjustment for socioeconomic status, duration of employment, and neutron monitoring, by fitting a simpler model that adjusted only for country, age, sex, and birth cohort. The estimated association between cumulative radiation dose and deaths due to solid cancer (excess relative rate 0.49 (0.30 to 0.69) per Gy) was similar in magnitude to that obtained from the fully adjusted model, with somewhat greater precision in analyses using the simpler adjustment set of covariates. In a separate sensitivity analysis, we restricted the analysis to men, among whom most of the collective dose and cancer deaths were accrued; the estimated association between cumulative dose under a 10 year lag and solid cancer was 0.52 (0.28 to 0.77) per Gy, based on 27 115 deaths).

Discussion

This study, which involved a major update to an international cohort mortality study of radiation dosimeter monitored workers, reports evidence of an increase in the excess relative rate of solid cancer mortality with increasing cumulative exposure to ionising radiation at the low dose rates typically encountered by French, UK, and US nuclear workers. The study provides evidence in support of a linear association between protracted low dose external exposure to ionising radiation and solid cancer mortality. Although some evidence suggests a steeper slope for the dose-response association at lower doses than over the full dose range (supplementary table C), a linear model offers a simple summarisation of the association with reasonable fit to the observed data (fig 1).

INWORKS draws on a large international collaboration to assemble records for radiation monitored workers and follow them over time to study cause specific mortality in relation to dose. With this updated follow-up, the magnitudes of estimates of association are similar to the values reported in the previous analysis (supplementary table G).[18] However, this analysis encompasses a more than 50% increase in the number of solid cancer deaths compared with the previous analysis,[18] and it consequently affords improved precision in these estimates of association (supplementary table G). Notably, the study provides one of the most informative assessments to date on the magnitude of the radiation dose-solid cancer association in the low dose region, a key concern for contemporary radiation protection. The study provides evidence for a positive association between radiation dose and solid cancer mortality in the 0-100 mGy and 0-50 mGy cumulative dose ranges (supplementary table C). For comparison, previous analyses of the Life Span Study of Japanese atomic bomb survivors have explored the minimal dose level at which a significant association is observed between radiation dose and solid cancer mortality and reported a range of approximately 0-150 mGy (based on follow-up information for that study through 2003).[50] Of course, estimates of association obtained in analyses restricted to these lower dose ranges are less precise than those obtained in an unrestricted analysis (supplementary table C); however, analyses restricted to these lower dose ranges directly relate to the radiation protection community's interest in epidemiological evidence of a radiation dose-cancer association at low doses (for example, ≤100 mGy).[51] Restricting analyses to information at these lower dose ranges showed that the estimated excess relative rate per Gy for solid cancer mortality in the unrestricted analysis (table 2) was smaller in magnitude than the estimate obtained on restricting the analysis to the lower dose ranges, indicative of attenuation of the association at the highest cumulative exposure levels. For people interested only in the exposure-response relation in the low cumulative exposure range, a linear trend estimate obtained in analyses restricted to a lower cumulative exposure range may be appealing as it is not influenced by any attenuation at higher exposure levels.

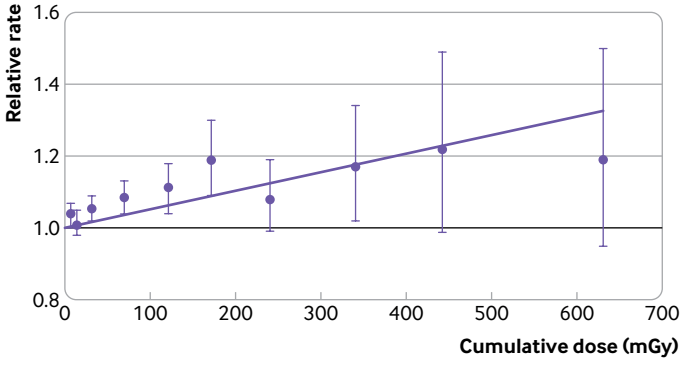

Fig 1 | Relative rate of mortality due to solid cancer by categories of cumulative colon dose, lagged 10 years in INWORKS. Bars indicate 90% confidence intervals, and purple line depicts fitted linear model for change in excess relative rate of solid cancer mortality with dose. Strata: country, age, sex, birth cohort, socioeconomic status, duration employed, neutron monitoring status

Comparison with other studies

Analyses of cancer in the Life Span Study of the Japanese atomic bomb survivors serve as the primary quantitative basis for the calculation of radiation detriment in systems of radiological protection.[52] The study of Japanese atomic bomb survivors is challenging as a basis for assessing contemporary concerns about radiation protection because many atomic bomb survivors were exposed to acute high doses of radiation, and selective survival after the atomic bombings, as well as wartime conscription of healthy adults out of the cities before the bombings, mean that the study members are a select subset of the pre-war population. For the purposes of radiation protection, people often assume that low dose rate

exposures pose less carcinogenic hazard than the high dose rate exposures experienced by the Japanese atomic bomb survivors.[9] However, persistent concerns about effects of low dose radiation exposures have motivated a wide range of research activities, including epidemiological studies of workers in the nuclear industry.[51 53] Our study does not find evidence of reduced risk per unit dose for solid cancer among workers typically exposed to radiation at low dose rates. The estimated association between radiation and solid cancer mortality in INWORKS (excess relative rate 0.52 (90% confidence interval 0.27 to 0.77) per Gy) is larger than, albeit statistically compatible with, an estimate from a mortality analysis of male survivors of the Japanese atomic bomb exposed at ages 20-60 years (excess relative rate 0.32 (95% confidence interval 0.01 to 0.50) per Sv).[19 53]

The coherence of findings from INWORKS with those derived from other contemporary epidemiological studies of low dose radiation (mean doses <100 mGy) also contributes to an overall evaluation of the study findings.[54-57] A recent meta-analysis of studies of mortality in populations exposed to low doses of radiation, including the previous INWORKS analysis, found that the meta-analytic summary estimate of excess relative rate per Gy for solid cancer mortality was very close to the INWORKS study summary estimate, and also compatible with estimates derived from the Japanese Life Span Study.[57] However, when considering studies of higher doses, an important exception was the study of workers employed in the Soviet programme for plutonium production at the Mayak facilities in the southern Urals, which reported an excess relative rate for solid cancer per Gy that was three to four times lower than the our INWORKS summary estimate and the summary estimate derived from the Life Span Study of the Japanese atomic bomb survivors.[57] Given its size and the high magnitude of doses, the Mayak study exerted substantial influence on meta-analytic estimates of the excess relative rate for solid cancer per Gy that included higher dose studies.[57] The reasons for differences between the Mayak study and INWORKS are unclear, but in the early years of operation at the Mayak facilities many workers were highly exposed with substantial uncertainty about their internal and external radiation doses.[28 57] Analyses of mortality among French nuclear workers showed a positive association between estimated colon dose and solid cancer mortality (excess relative rate 0.69 (95% confidence interval −0.28 to 1.77) per Gy)[58]; we note that INWORKS includes a sizable fraction of this cohort. Analyses of mortality among US nuclear workers showed a positive association between cumulative dose and solid cancer mortality (excess relative rate 0.19 (95% confidence interval −0.10 to 0.52) per Gy), which was of larger magnitude among workers first hired after 1960[59]; again, we note the overlap between this cohort and INWORKS. Analyses of cancer incidence among workers in the UK National Registry for Radiation Workers (UK NRRW) showed a positive association between external dose and solid cancer incidence (excess relative rate 0.20 (95% confidence interval −0.00 to 0.43) per Sv), although a linear model seemed to overestimate risk at higher doses, such that a linear-exponential model fitted the data better than a linear model, with the linear component of the model yielding an excess relative rate per Sv of 1.14 (0.30 to 2.36).[60] Among workers in that cohort exposed to only external radiation, the estimated excess relative rate per Sv (0.52, 0.11 to 0.96) was more clearly linear, and in analyses of solid cancer incidence other than lung the estimated excess relative rate per Sv was also more clearly linear (noting that INWORKS includes a sizable fraction of the workers in the UKNRRW cohort). In contrast to analyses of the UK NRRW, our analyses of INWORKS adjusted the recorded dose to account for bias in historical dosimeter response and attenuation, taking the estimated colon dose as the quantity of interest, but we still observed some downward curvature. Analyses of radiation-mortality associations in INWORKS using recorded photon dose as the dose metric, rather than adjusted estimates of colon dose, yielded estimates of association of somewhat lower magnitude but similar goodness of model fit to estimates obtained in analyses using the estimated colon dose (supplementary table H). As this study shows, large scale studies of nuclear worker such as INWORKS, as well as studies of Mayak workers and the US Million Person Study,[28 61] provide important information to support the radiological protection system.

Strengths and limitations of study

This study draws on the previous work done to characterise the performance of the various radiation dosimeters used in France, the UK, and the US over the study period and to account for differences between countries and over time in dosimeter performance. The performances of a variety of types of dosimeters were evaluated,[21] and panels of experts were convened to characterise workplace conditions, monitoring routines, photon energies, and exposure geometries over the study period. A database of correction factors was developed to account for the influence of geometries of exposure, energies of photons, and other sources of bias and uncertainty in radiation dose estimates.[20 22] For these INWORKS analyses, 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.[22] Despite those efforts, concerns have been expressed that errors in radiation dose estimates for workers employed in the early years of the industry's operations could lead to biased estimates of radiation dose-cancer mortality associations.[62-64] Workers employed in the earliest years of the industry were often monitored with open window or single element personal film badge dosimeters, and film badges were exchanged on a relatively frequent basis.[20 22 65] Consequently, exposure measurement error related to personal dosimeter technology, monitoring practices,

and historical records, particularly in the early years of operation, has received attention.[20 63 65]

We report analyses restricted to workers hired in more recent periods, showing that our overall results were not driven solely by information contributed by workers employed in the earliest years of the industry. To the contrary, after exclusion of workers hired in the earliest years of operations our estimate of the excess relative rate per Gy for solid cancer was larger than the estimate derived from analysis of the full cohort (supplementary table D). The results obtained in analyses of the full INWORKS cohort are of interest in comparison with our early report (supplementary table G); however, among contemporary workers with presumably higher quality dosimetry information, the linear estimate of the radiation dose-solid cancer mortality association was larger than the overall summary estimate of association (supplementary table D). Improvements over time in radiation dosimetry should lead to more accurate dose estimates and to estimates of radiation risk that are less susceptible to bias due to exposure measurement error in analyses restricted to workers employed in more contemporary periods. Of course, comparisons of the magnitudes of summary radiation risk estimates between subgroups should be viewed with caution because subgroups may have different distributions of modifying factors (such as time since exposure)[17]; in this paper, we have not focused on assessment of such modifiers. Nevertheless, our estimates of radiation risks among the more contemporary workers (supplementary table D) should be of interest because exposures and work conditions among these workers are more indicative of the current experience. Interestingly, although downward curvature in a radiation dose-response model may be induced when highly exposed workers are subject to more measurement error than those with lower exposure,[66-68] evidence of downward curvature in our study persisted in analyses restricted to more recent hires. This suggests that errors in external dose estimates are unlikely to fully explain the attenuation of the dose-response association at the highest doses. Of course, some measurement error persists in contemporary dose estimates; however, modern dosimetry systems tend to produce individual dose estimates with markedly less error than earlier dosimetry systems, and our assessment of the dosimeters used in this more contemporary period indicate high levels of accuracy and comparability in performance of dosimeters used in all three countries.[20 22]

The workplace spectra encountered by nuclear workers (predominantly photons of energies between 100 and 3000 kiloelectron volt) have been suggested to be more effective at causing cancer than the spectra encountered by survivors of the nuclear bomb (predominantly in the 2000-5000 kiloelectron volt range).[20 22 69] Although attention to the adequacy of radiation protection standards in settings involving low energy photons is warranted,[70] a relatively small fraction of absorbed doses from external exposures in INWORKS was due to lower energy (<250 kiloelectron volt) photons,[20] which is the range at which the evidence of increased biological effectiveness is greatest.[70 71] Moreover, the spectra encountered by workers in our study is presumably directly relevant for contemporary radiation protection in occupational, and many medical, settings.

Although INWORKS lacks individual level data on several potentially important confounding factors, including cigarette smoking, we were able to indirectly assess confounding by smoking. For example, after exclusion of lung cancers from the group of solid cancers we observed evidence of a positive dose-response association similar in magnitude to that observed for all solid cancers (table 2). Such a pattern is contrary to what would be expected if substantial confounding by smoking existed, as is the minimal evidence of association between radiation dose and chronic obstructive pulmonary disease, an outcome strongly associated with smoking (table 2).[72] Figure 1 and supplementary figure B help to inform interpretation of the effect of lung cancer on the association between cumulative dose and solid cancer. At the highest category of cumulative dose, a linear model for the association fits somewhat better after exclusion of lung cancers from the group of solid cancers. Such attenuation at high exposure levels, not unusual in mortality studies in industrial cohorts, could suggest negative confounding (at the highest cumulative dose levels) by a lung carcinogen, exposure dependent effect modification, or selection bias.[66-68] Because we do not have individual level data on smoking, we cannot empirically answer questions about modification of the effect of radiation by smoking. Similarly, we observed little evidence that exposure to asbestos substantially confounds the association between cumulative radiation dose and solid cancer mortality in this study population: after exclusion of lung and pleural cancers from the group of solid cancers, we observed a dose-response association similar in magnitude to that for all solid cancers. Exclusion of workers flagged for internal radionuclide monitoring resulted in a larger estimate of excess relative rate per Gy of solid cancer than an analysis without such exclusion and reduced evidence of downward curvature in the association between cumulative dose and solid cancer mortality, suggesting that attenuation of the dose-response association at higher doses may be associated with factors related to internal radionuclide monitoring status. After exclusion of deaths due to lung, liver, and bone cancers (sites that may receive substantial doses in cases of incorporated plutonium), the estimate of excess relative rate per Gy remained similar in magnitude. Further investigation of the influence of internal monitoring, period of hire, and dose range is warranted. A relatively small proportion of workers were judged to be substantially exposed to neutrons[20]; our primary analyses adjusted for an indicator of potential for substantial exposure to neutrons, while acknowledging the potential for underestimated or missed doses from neutrons of some energies,

particularly in early period of operations. An expert group of dosimetrists recommended flagging workers with substantial neutron doses but not incorporating these into organ dose estimates owing to limitations of historical neutron dosimetry and between country differences in methods.[22] In a sensitivity analysis, we observed that among workers who had no reported neutron dose, the estimated association between colon dose and mortality due to solid cancer was similar to the estimate obtained for the whole cohort after adjustment for neutron monitoring status.

This analysis focused on the broad category of mortality due to all solid cancers, a commonly examined outcome of interest for assessment of radiation risk. The results provide one simple summarisation of radiation associated excess cancer mortality. Of course, site specific cancer risk estimates also are of interest and inform understanding of variation in radiation-cancer associations between cancer sites[14]; however, in studies that rely on death certificate information, the specificity of the death certificate as a tool for ascertaining cancer occurrence is often better for a broad category (such as solid cancer) than for narrow disease specific categories. Moreover, in epidemiological studies of low dose radiation, regression model estimates for cancer site specific outcomes are often unstable (reflecting small numbers of radiation related excess cases). In the past, we have illustrated the use of a hierarchical regression approach to stabilise site specific estimates,[14] but this paper focuses on all solid cancers combined. Further examination of the association between radiation dose and lung cancer mortality in future site specific analyses should help to further inform interpretation of the overall solid cancer mortality associations. Although our results directly relate to relatively contemporary French, UK, and US nuclear workers, variation over time and between populations in the distribution of cancers by site may influence a population summary estimate of excess relative rate per Gy for all solid cancers, as discussed, for example, with regards to interpretation of findings from the Japanese Life Span Study.[73]

Studies of worker include a group of people who tend to be healthier than the general population (that is, they must be fit enough to secure employment),[74 75] and long term workers tend to be healthier than short term workers, which can lead to a "healthy worker survivor" bias that may obscure or distort estimates of the harmful effects of protracted occupational exposures.[36 76-78] Attenuation of the slope of an occupational exposure-response association at high cumulative exposure levels could arise because long term workers tend to have lower disease rates than short term workers and their cumulative exposures tend to be higher than the cumulative exposures accrued by short term workers. Interestingly, we observed less evidence of such attenuation in analyses that excluded lung cancer from the group of solid cancers, which could suggest bias that disproportionately masks the effect of exposure to radiation on lung cancer mortality at the highest cumulative doses (thereby leading to evidence of downward curvature). Despite such limitations, our study provides direct estimates of radiation risks among relatively contemporary working age adults in the French, UK, and US nuclear industries; as such, the results of INWORKS offer a useful complement to findings derived from the study of Japanese atomic bomb survivors.

Conclusions

INWORKS is unusual in its international scope, and the study benefits from decades of work by researchers in France,[46 79] the UK,[31 80 81] and the US,[82-85] as well as in international collaborations,[20-22 39 65 86] to assemble these data, achieve the high level of completeness of information, and support these analyses by critical assessments of the quality of information and methods supporting this study. The results of this major update of INWORKS should help to inform deliberations of radiation protection organisations, such as the International Commission on Radiological Protection, regarding risk assessment in settings of low dose and low dose rate radiation exposures, particularly with regards to evidence supportive of assumptions about the magnitude of the excess relative rate per Gy and linearity of the association between protracted relatively low dose and low dose rate exposures and solid cancer mortality.[9]

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Contributors: DBR conceived the study. DBR, KL, DL, MG, RH, KKR, SB, AK, MKSB, and ITC developed the research questions and designed the study. KL and DL worked on provision of the French data; KKR, SB, and RDD worked on provision of the US data; MG and RH worked on provision of the UK data. MM was responsible for data management and processing as well as some analyses. ITC 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. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

The findings and conclusions in this report are those of the authors and do not necessarily represent the views of the National Institute for Occupational Safety and Health. Where authors are identified as personnel of the International Agency for Research on Cancer/World Health Organization, the authors alone are responsible for the views expressed in this article and they do not necessarily represent the decisions, policy, or views of the International Agency for Research on Cancer/World Health Organization.

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Ethical approval: The study was approved by the International Agency for Research on Cancer's ethical review committee (No 11-09 and later amendments), relevant ethical committees of the participating countries, and the ethical review committee of the University of North Carolina at Chapel Hill.

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) and cannot be made available 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.

Dissemination to participants and related patient and public communities: Plain language messages about the results will be shared with the appropriate offices at the US National Institute for Occupational Safety and Health, the French Institut de Radioprotection et de Sûreté Nucléaire, the UK Health Security Agency, and the International Agency for Research on Cancer; these organisations engage with employers, workers' representatives, members of the public (for example, via social media feeds), and advocacy groups. Some of the lead researchers (DBR, DL) will also contact expert and advisory bodies (International Commission on Radiological Protection, National Council on Radiation Protection and Measurements, United Nations Scientific Committee on the Effects of Atomic Radiation), of which they are already part. Organisations such as the International Agency for Research on Cancer rely on publications such as this one to inform their patient and public facing materials on websites such as iarc.who.int.

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Web appendix: Supplementary materials