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Title: Site-specific cancer mortality after low level exposure to ionizing radiation: Findings from an update of the International Nuclear Workers Study (INWORKS)

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Key words: Ionizing radiation; cohort studies; mortality study; occupational exposures; nuclear workers, cancer

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ABSTRACT

A major update to the International Nuclear Workers Study was undertaken that allows us to report updated estimates of associations between radiation and site-specific solid cancer mortality. A cohort of 309,932 nuclear workers employed in France, the United Kingdom, and United States were monitored for external radiation exposure and associations with cancer mortality were quantified as the excess relative rate (ERR) per gray (Gy) using a maximum likelihood and a Markov chain Monte Carlo method (to stabilize estimates via a hierarchical regression). The analysis included 28,089 deaths due to solid cancer, the most common being lung, prostate, and colon cancer. Using maximum likelihood, positive estimates of ERR per Gy were obtained for stomach, colon, rectum, pancreas, peritoneum, larynx, lung, pleura/mesothelioma, bone and connective tissue, skin, prostate, testis, bladder, kidney, thyroid, and residual cancers; negative estimates of ERR per Gy were found cancers of oral cavity and pharynx, esophagus, and ovary. A hierarchical model stabilized site-specific estimates of association, including for lung (ERR per Gy=0.65; 95% credible interval [CrI]: 0.24, 1.07), prostate (ERR per Gy=0.44; 95% CrI: -0.06, 0.91), and colon cancer (ERR per Gy=0.53; 95% CrI: -0.07, 1.11). The results contribute evidence regarding associations between low dose radiation and cancer.

KEYWORDS: Ionizing radiation; cohort studies; mortality study; occupational exposures; nuclear workers, cancer

The International Nuclear Workers Study (INWORKS) includes nuclear workers in France, the United Kingdom (UK), and the United States (US) who were monitored for external exposure to ionizing radiation using personal dosimeters and were subsequently followed to collect information on vital status and causes of death (1, 2). Findings from INWORKS have been influential on recent evaluations of radiation-related cancer risks, particularly with regards to low dose and low dose rate exposure settings (3-5). There has been substantial interest in findings from INWORKS regarding variation in estimates of association between radiation dose and different site-specific cancers (6). Such findings are relevant to discussions of etiology, compensation, and generalizability of radiation risk estimates across populations that differ in baseline site-specific cancer rates. They may also be useful in examining the adequacy of current radiation protection standards.

Recently, a major update of the INWORKS study was undertaken that strengthened evidence of positive association between radiation dose and mortality due to all cancers combined (7). Here, we report on estimates of associations between ionizing radiation and site-specific solid cancer mortality obtained using a maximum likelihood method and using a Markov chain Monte Carlo method, the latter to stabilize estimates by shrinkage towards the mean of the site-specific solid cancer estimates via a hierarchical regression (8, 9).

METHODS

INWORKS is a collaborative occupational cohort mortality study of workers from France, the UK, and the US who were employed in the nuclear industry for at least one year and monitored for external radiation exposure through the use of personal dosimeters (10-12). Annual

estimates of whole-body dose due to external exposure to ionizing radiation were available from company records for UK workers and government and company records for US and French workers; this information was used to derive estimates of absorbed dose to a specified organ expressed in grays (Gy), where target organ doses were derived by dividing recorded external penetrating radiation dose estimates by an organ-specific dose factor (13-15). Measures of incorporated radionuclides included positive bioassay results, indication of confirmed uptake, or an assigned committed dose; we used these measures as an indication of a known or suspected internal contamination. Estimates of doses from neutron exposure, when available, often lack documentation on measurement processes and values of radiation weighting factors; we used available records of estimated neutron doses 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. Vital status was ascertained through 2012, 2014, and 2016 for the UK, French, and US cohorts, respectively, through linkage with national and regional death registries, employer records, tax records, and Social Security Administration records. Information on underlying cause of death was abstracted from death certificates and generally was coded according to the revision of the International Classification of Diseases (ICD) in effect at the time of death. We use the term cancer types to refer to deaths due to the specific types of solid cancer; the range of ICD codes associated with each cancer type, and the target organs selected for each cancer type, are reported in Table S1.

Statistical methods.

Person-years at risk and deaths by cancer type were tabulated in strata defined by 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, and cumulative dose (in categories < 5 / 10 / 20 / 50 / 100 / 150 / 200 / 300 / 400 / 500 > mGy). For each cell of this person-time table, we calculated the person-time weighted cell-specific mean dose to each of the target organs of interest. We quantified radiation dose-cancer mortality associations using a Poisson regression model for cancer type-specific rates,

$$\lambda^j(\alpha_s^j, \beta^j) = exp(\alpha_s^j)(1 + \beta^j Z^j),\ j=1, 2, \ldots, J,$$

letting j denote cancer type, λ^j cancer type specific rates, s index levels defined by the cross-classification of covariates, α_s^j denote cancer type-specific effects of covariates, Z^j denote target organ-specific cumulative dose (in Gy), and β^j quantifies the association between Z^j and the j^{th} cancer type as the excess relative rate (the relative rate minus 1) per Gy. Maximum likelihood estimates of β^j were obtained with background stratification on strata, s, defined by country, attained age, sex, year of birth, socioeconomic status, duration of employment or radiation work, and neutron monitoring status (16). Background stratified Poisson regression is an approach that has been used in the analyses of data derived from a variety of studies of radiation-exposed populations (11, 17-21). The coefficients for the stratum-specific effects, α_s^j, are not part of the expression for the likelihood that is maximized to obtain estimates of β^j (16). Cumulative doses were lagged by 10 years to allow for an induction and latency period between exposure and death (22). We undertook sensitivity analyses in which cumulative doses were lagged 5 years or 15 years; and, for each cancer type, results obtained under alternative lags were compared with

respect to goodness of model fit (23). For the three most frequent cancer types (lung, prostate, and colon), dose-response associations were examined 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. For the same three cancer types, we formally assessed departure from linearity by fitting a model that also included a parameter for the square of cumulative dose; models that included a higher order polynomial function of cumulative dose were evaluated with respect to improvement in model goodness of fit. We report maximum likelihood estimates of excess relative rate per Gy and associated 90% profile likelihood-based confidence intervals (CI). An excess relative rate model is commonly used in radiation epidemiology (24); the model has computational restrictions because the relative rate cannot be negative and hence the parameter β^j is constrained to be larger than $\frac{-1}{max[Z^j]}$, where $max[Z^j]$ is the maximum value for the organ-specific cumulative dose associated with cancer type *j* (25). In some cases, point estimates could not be obtained and we indicate this in the results. When a profile likelihood-based confidence bound could not be obtained, we report a Wald-type confidence bound. Sensitivity analyses examined radiation dose-site specific cancer mortality associations in the restricted dose range 0-400 mGy. To assess concerns about the impact of workers employed in the early years of nuclear industry operations (7), we excluded workers hired prior to 1958. To assess potential impact of incorporated radionuclides on site-specific dose-response estimates, sensitivity analyses examined radiation dose-site specific cancer mortality associations in analyses restricted to workers never flagged for incorporated radionuclides; and, to assess potential impact of neutron exposures on site-specific dose-response estimates, sensitivity analyses examined radiation dose-site specific cancer mortality associations in analyses restricted to workers never flagged for neutrons.

We also obtained estimates of the β^j parameters using a hierarchical regression approach under which the distribution of the β^j parameters is modeled as a function of the overall mean of the effects of exposure on the *J* cancer types and residual variation in these associations:

$\beta^j \sim N(\delta, \tau^2)$, for j=1…J,

where δ is the mean of the effects of exposure on the *J* cancer types and τ^2 is the prior variance that allows for deviation of the cancer type-specific effects from a common mean effect (8, 9). The approach stabilizes the ensemble of the *J* parameters such that estimates are shrunk towards a common mean; as τ^2 approaches 0, the fitted exposure-response associations will be shrunk towards a common mean (8, 26). We specified a normal (0, 10) prior for δ, so that this prior was weakly informative, and specified that the prior for the variance parameter, τ^2, followed a uniform (0.01, 5) distribution, following recommendations regarding prior distributions for variance parameters in hierarchical models (27). We performed a sensitivity analysis in which we specified a normal (0.32, 5) prior for δ, illustrating a more informative prior with a smaller variance and mean informed by an estimate of the excess relative rate per Gy for solid cancer mortality in a prior analysis of male survivors of the Japanese atomic bomb (18). Cancer type-specific estimates of the excess relative rate per Gy were obtained as the mean of the posterior distribution, and estimates of associated 90% highest posterior density credible intervals (CrI) were obtained using a Markov chain Monte Carlo (MCMC) algorithm implemented in SAS PROC MCMC.

RESULTS

The study includes 309,932 workers who contributed 10.72 million person-years of follow-up to ascertain information on vital status and causes of death (table 1). The average age at the start of employment was 28 years. Among workers whose estimated cumulative doses were >0 mGy, the average estimated cumulative dose to the bladder (21.3 mGy), skin (21.0 mGy), colon (20.9 mGy), lung (20.8 mGy), and stomach (20.8 mGy) were similar in magnitude, whereas average estimated cumulative doses to the liver (19.5 mGy), pancreas (19.2 mGy), and brain (18.6 mGy) were slightly lower in magnitude. Among female workers whose estimated cumulative doses were >0 mGy, the average estimated cumulative doses to the uterus (6.6 mGy), breast (5.9 mGy), and ovary (4.6 mGy) were substantially lower in magnitude.

The analysis includes 28,089 deaths due to solid cancer, representing a substantial update from the previous analysis of INWORKS (Table S1). While the percentage increase in the number of cancers varies by cancer type, the distribution of solid cancer deaths by cancer type has not changed markedly (Table S1). The most common cancer types were lung, prostate, and colon cancer; the least common were testis and thyroid cancer (table 2).

Maximum likelihood estimates

Cumulative dose, lagged by 10 years, was positively associated with the following cancer types: stomach, colon, rectum, pancreas, peritoneum, larynx, lung, pleura/mesothelioma, bone/connective tissue, skin, prostate, testis, bladder, kidney, thyroid, and residual cancers (table 2). No estimate of association was obtained for cancer of the female breast, uterus, brain, or liver/gallbladder due to convergence problems for these outcomes. Cumulative dose, lagged by 10 years, was negatively associated with oral cavity and pharynx, esophagus, and ovary cancers

(table 2). The largest estimates of association were obtained for cancers of the testis and thyroid (the two cancer types with the smallest numbers of deaths). For the most common cancer types, lung, prostate, and colon cancer (collectively accounting for half of all solid cancers), estimates of the excess relative rate ranged in magnitude from 0.31 to 0.67 per Gy of cumulative dose, lagged by 10 years. Tests of heterogeneity by country indicated no significant variation in the dose-response for lung cancer (likelihood ratio test (LRT)=0.67, 2 d.f.), prostate (LRT=0.14, 2 d.f.), or colon cancer (LRT=1.13, 2 d.f.).

Under a five-year lag, model goodness of fit for all outcomes examined was similar to, or poorer than, that obtained under a 10-year lag assumption, with the exception of cancers of the stomach and testis for which the estimated radiation dose-mortality associations exhibited somewhat better goodness of fit under a 5- than 10-year lag assumption (Table S2). Under a 15-year lag, model goodness of fit was similar to, or poorer than, that obtained under a 10-year lag assumption, with the exception of cancer of the rectum for which the estimated radiation dose-mortality association exhibited somewhat better goodness of fit under a 15-year lag than under a 10-year lag assumption (Table S2).

We visually examined the fit of the linear ERR model to the data for lung, prostate, and colon cancer by plotting the relative rate in categories of cumulative exposure (Figure 1). There was minimal evidence of curvature in the dose-response association for cancer of the prostate (LRT=1.3, 1 degree of freedom (d.f.), p=0.25) or colon (LRT=0.0, 1 d.f., p=0.92), based on a comparison of the fit of a linear model to the fit of a linear-quadratic model; however, a quadratic term led to moderate improvement in the model goodness of fit for lung cancer

(LRT=4.4, 1 d.f., p=0.04), with a negative estimated quadratic coefficient indicative of downward curvature.

Analyses restricted to the dose range below 400 mGy included 99.5% of the solid cancer deaths in the full study (i.e., 27,960 deaths due to solid cancer) and 10.71 million person-years of follow-up. Cumulative dose, lagged by 10 years, was positively associated with oral cavity and pharynx, stomach, colon, rectum, peritoneum, larynx, lung, pleura, bone/connective tissue, skin, ovary, prostate, testis, bladder, kidney, thyroid, and residual cancers (Table S3). No estimate of association was obtained for cancer of the female breast or uterus due to convergence problems for these outcomes. Cumulative dose, lagged by 10 years, was negatively associated with the following cancer types: esophagus, liver/gallbladder, pancreas, and brain cancer (Table S3). In analyses restricted to the dose range below 400 mGy, there was minimal evidence of curvature in the dose-response association for cancer of the prostate (LRT=0.0, 1 d.f., p=0.89), colon (LRT=0.3, 1 d.f., p=0.58), or lung (LRT=3.0, 1 d.f., p=0.08) when comparing the fit of linear to linear-quadratic models.

To address concerns about impact of workers hired in the early years of operations, we examined associations between cumulative radiation dose and deaths due to solid cancer restricted to the 238,639 workers hired in 1958 or later (Table S4). No estimate of association was obtained for cancer of the esophagus, uterus, ovary, or brain due to convergence problems for these outcomes. Cumulative dose, lagged by 10 years, was negatively associated with liver/gallbladder, pancreas, and skin cancer (Table S4). All other cancer sites had positive estimated coefficients. The magnitude of the estimated ERR/Gy for lung cancer (ERR/Gy=1.28; 90%CI: 0.37, 2.32),

prostate (ERR/Gy=0.57; 90%CI: -0.55, 2.00), and colon cancer (ERR/Gy=1.40; 90%CI: -0.02, 3.27) were larger than the estimates obtained in the unrestricted analysis.

To address concerns about bias due to internal exposure to radiation, we conducted an analysis restricted to the 84% of workers who were never flagged for incorporated radionuclides or internal monitoring (Table S5). Cumulative dose, lagged by 10 years, was negatively associated with esophagus, skin, bladder, and brain cancer. Focusing on lung, liver, and bone cancer, sites that receive greatest doses from internal depositions of plutonium and uranium, the magnitude of the estimated ERR/Gy for lung cancer is larger in analyses restricted to those with no internal deposition flag than in analyses of the cohort overall, and, similarly, the magnitude of the estimated ERR/Gy for bone cancer is larger in analyses restricted to those with no internal deposition flag than in analyses of the cohort overall; no estimate of association was obtained between external dose and mortality due to liver/gallbladder cancer due to convergence problems.

To address concerns about bias due to neutron exposure, we conducted an analysis restricted to workers never flagged for neutrons (Table S6). No estimate of association was obtained for cancer of the female breast or uterus due to convergence problems for these outcomes. Cumulative dose, lagged by 10 years, was negatively associated with oral cavity and pharynx, esophagus, liver/gallbladder, pancreas, ovary, bladder, kidney, and brain cancers. All other cancer sites had positive estimated coefficients. The magnitude of the estimated ERR/Gy for lung cancer (ERR/Gy=0.81; 90%CI: 0.18, 1.49) was larger than the estimate obtained in the unrestricted analysis.

Hierarchical Poisson regression

Upon using a hierarchical model, none of the posterior mean estimates were negative (table 2). The estimated value of δ, the common mean effect of exposure on the cancer types, was 0.59 (90% CrI: 0.23, 0.94); the variance parameter, τ^2, was estimated as 0.27 (90% CrI: 0.01, 0.66). Estimates of radiation dose-mortality associations for specific cancer sites obtained using a hierarchical Poisson regression modelling approach showed less variability and tended to have less extreme values than those obtained by maximum likelihood regression methods (Figure 2). For lung cancer, the mean of the posterior distribution, and 90% CrI, obtained by this hierarchical regression method were similar to the point estimates and 90% CI for the association obtained by maximum likelihood methods (Table 2). In contrast, for many of the less common cancer types, posterior mean estimates of the excess relative rate per Gy tended to be shrunk substantially towards the common mean estimate of association, and the site-specific estimates of association were stabilized (as reflected by narrower 90% CrIs than the 90% CIs).

In a sensitivity analysis, we re-calculated the shrinkage estimates in analyses illustrating a more informative prior for δ (i.e., a N(0.32, 5) prior). Results were extremely similar to those obtained using a vague prior (i.e., N(0,10) prior) for δ (Table S7). In a separate sensitivity analysis we re-calculated the shrinkage estimators in analyses restricted to the 27,960 solid cancer deaths and 10.71 million person-years observed in the dose range <400 mGy (Table S3). Hierarchical regression model estimates for the cancer type-specific associations based on data restricted to the dose range <400 mGy were similar to those obtained in hierarchical regression analyses of the unrestricted data (Table 2), with somewhat larger estimates for cancer of the lung, stomach,

and pleura/mesothelioma; the estimated value of δ, the common mean effect of exposure on the cancer types, was 0.65 (90% CrI: 0.19, 1.11); the variance parameter, τ^2, was estimated as 0.59 (90% CrI: 0.03, 1.24). We also re-calculated the shrinkage estimators in analyses restricted to workers hired in 1958 or later (Table S4), yielding posterior cancer type-specific estimates of association that, with the exception of esophageal cancer, were larger than estimates obtained in hierarchical regressions using the unrestricted INWORKS data. The estimated value of δ, the common mean effect of exposure on the cancer types, was 1.40 (90% CrI: 0.63, 2.16); the variance parameter, τ^2, was estimated as 1.65 (90% CrI: 0.05, 3.51).

DISCUSSION

INWORKS pools information for some of the most informative cohorts of nuclear industry workers in the world; the updated study reported upon here extends follow-up to encompass 10.72 million person-years of observation. This updated follow-up of INWORKS was undertaken to provide a large-scale international assessment of mortality risks from protracted low-dose, low dose-rate ionizing radiation exposures; the findings of this study strengthen support for positive associations between low dose, low dose rate exposure to ionizing radiation and a variety of site-specific cancers.

Maximum likelihood estimates

Cancer type-specific estimates of ERR per Gy tended to take less extreme values and the 90% confidence intervals for estimates of ERR per Gy derived in the current analysis using maximum likelihood methods tend to be narrower than in our prior INWORKS analysis (9). However, for

many site-specific cancers, maximum likelihood estimates of association remain quite imprecise (Table 2). Considering cancer of the lung, which is the most common cancer in INWORKS, the updated maximum likelihood regression estimate (ERR per Gy=0.67; 90% CI: 0.21, 1.19) is similar in magnitude to that reported in the Life Span Study (LSS) of Japanese atomic bomb survivors (ERR per Gy=0.64; 95% CI: 0.38, 0.94 at age 65 after radiation exposure at age 25) (28). However, our estimate is substantially larger than an estimate of the association between gamma exposure and lung cancer mortality among Mayak workers (ERR per Gy=0.24; 95% CI: 0.08, 0.44) (28), and our estimate differs in direction from the inverse association between ionizing radiation dose and lung cancer mortality among US nuclear power plant workers reported as part of the Million Worker Study (ERR per Gy= -0.4; 95%CI: -1.1; 0.2) (29). Considering mortality due to cancer of prostate, our maximum likelihood regression estimate (ERR/Gy=0.31; 90%CI: -0.23, 0.96) is similar in magnitude to that reported in the LSS of atomic bomb survivors (ERR per Gy=0.33; 95% CI: <0, 1.25), while noting that in an analysis of prostate cancer incidence in the LSS a larger estimate of association was reported (ERR per Gy=0.57; 95% CI: 0.21, 1.00) (30). In prior environmental and occupational studies, few have reported a strong indication of a positive association between radiation dose and prostate cancer mortality (31),(32). Considering mortality due to cancer of colon, the maximum likelihood estimate (ERR/Gy=0.41; 90%CI: -0.32, 1.32) is consistent with an estimate from the LSS (ERR per Gy= 0.54; 95% CI: 0.23, 0.93), although the INWORKS estimate is extremely imprecise. A positive but imprecise estimate of association was found between colon cancer and external radiation dose among the Mayak plant workers (ERR per Gy=0.21; 95%CI: -0.06, 0.62) (32), and minimal evidence of association between radiation dose and colon cancer was reported in other occupational cohorts (31, 33). Negative maximum likelihood-based estimates of ERR per

Gy were reported in this INWORKS analysis for oral cavity and pharynx, esophagus, and ovary cancer. Cancers of oral cavity and pharynx, esophagus, and ovary have rarely been found to be associated with low linear energy transfer radiation exposure in occupational studies (31). However, positive associations between radiation dose and mortality due to oral cavity and pharynx, esophageal, and ovary cancer were observed in analyses of cancer mortality in the LSS cohort with follow-up from 1950–2003 (34, 35).

Hierarchical regression estimates

We stabilized cancer type-specific estimates of association through hierarchical modeling. There was minimal shrinkage of estimates of ERR/Gy for common outcomes, such as lung cancer; in contrast, substantial shrinkage occurred for some rare cancer types (Figure 2). Posterior estimates for all type-specific cancers were positive, and credible intervals tended to be narrower than profile likelihood-based confidence intervals for all cancer types (Figure 2). The updated follow-up of these cohorts, and our application of a hierarchical regression approach, has led to an ensemble of estimates of cancer site-specific ERR/Gy based on hierarchical regression that is more stable than previous maximum likelihood estimates and should have lower mean squared error (8).

The hierarchical modeling approach that we employed allows that radiation-cancer type associations may vary between cancer types, under a model that assumes that the parameters describing cancer-type specific associations follow a normal distribution. While the assumption of normality is an important one, it is supported by prior observations regarding variability in site-specific radiation dose-cancer associations in analyses of the Japanese A-bomb survivors, it

has been leveraged in previous analyses of radiation-exposed populations,(8, 34, 36) and simulations and theoretical work have shown that hierarchical models are robust to moderate violations of the assumption of normality of effects (37-39). The assumption that a group of parameters can be modeled as following a normal distribution represents prior knowledge incorporated into the analysis. Consequently, the hierarchical regression estimates tend to yield more precise credible intervals than would be obtained in the absence of such an assumption, and the full ensemble of estimates of association tend to have less extreme values that those obtained by standard regression. Of course, the point estimate for any given cancer site may suffer greater bias upon shrinkage, as the ensemble of parameters tends to be pulled towards the grand mean. If the normality assumption is wrong, or if a critic disagrees with it, then this may suggest how sensitivity analysis can be used to assess how different beliefs regarding this prior alter results.

Strengths and limitations

Most information in INWORKS pertains to male nuclear industry workers (Table 1); fewer females were hired at the study facilities than males, females tended to be assigned to jobs that accrued lower radiation doses than males, and the average dose to the breast was lower than for cancer sites such as lung or skin, reducing the statistical power of analyses for this cancer type. Consequently, the current study provides relatively little information regarding radiation-associated cancer risks for female workers and for cancers occurring at sites such as the breast, uterus, and ovary. Like most observational studies, INWORKS has potential for uncontrolled confounding. For example, we lack individual smoking histories for cohort members; however, we previously indirectly assessed evidence of whether radiation dose-cancer associations were confounded by cigarette smoking (7, 40) finding minimal evidence of association between

radiation dose and chronic obstructive pulmonary disease. In the current analysis we examined associations between radiation dose and cancer types not strongly related to smoking (41) and therefore unlikely to suffer confounding by smoking. We observed positive associations with many cancer sites not strongly associated with smoking; and, the cancer outcomes most strongly associated with smoking (e.g., lung and esophageal cancer) were not the cancer sites exhibiting the largest magnitudes of association with radiation dose. Potential confounding by occupational exposure to asbestos is another concern in INWORKS. Prior investigations of US nuclear cohorts have observed elevated standardized mortality ratios for cancer of pleura/mesothelioma, notably at the Portsmouth Naval Shipyard (42). We observed a positive association between radiation and cancer of pleura/mesothelioma (as well as cancer of the peritoneum which may include cases of peritoneal mesothelioma) which suggests that occupational asbestos exposure may confound radiation dose-mortality associations; however, prior work has suggested that the association between asbestos exposure and ionizing radiation is likely weak (42) and that the degree of confounding by asbestos of associations between external dose and site specific solid cancers such as lung cancer is likely quite small (43). We assessed departures from linearity for the leading cancer outcomes. For colon and prostate cancer there was minimal evidence of departure from linearity in the dose-response association; however, for lung cancer there was evidence of downward curvature. One way to address downward curvature at higher cumulative doses is to restrict analyses to a lower dose range over which the association is more linear. In analyses restricted to the dose range <400 mGy there was reasonable support for a linear model for each of the cancer sites examined. In hierarchical analyses posterior estimates remained similar in magnitude when we focused on this lower dose range where we observed relatively strong support for linearity in dose-response associations for the leading cancer sites. Such

attenuation at high exposure levels is often observed in industrial cohort mortality studies and could suggest confounding or selection bias.(44-46) Long-term workers tend to be healthier than short-term workers (and their cumulative exposures tend to be higher than those of short-term workers) which can lead to a "healthy worker survivor" bias that may obscure or distort estimates of the effects of protracted occupational exposures (43, 47-49). A strength of INWORKS is that this study focuses on cohorts for which exposures were primarily to high-energy low-linear energy transfer penetrating radiations. Relatively few workers in INWORKS were flagged for incorporated radionuclides, which differs, for example, from studies of workers employed at the Mayak nuclear plant in Russia (28), where workers often were exposed to relatively high levels of plutonium (50). Further, we undertook sensitivity analyses restricted to workers with no known or suspected internal contamination by radionuclides. Contrary to the pattern expected if there was substantial positive confounding by internal radionuclide depositions of associations between external radiation dose and site-specific cancer mortality, the magnitude of the estimated ERR/Gy for lung cancer, for example, was larger in analyses restricted those with no known or suspected internal contamination by radionuclides than in our overall unrestricted analysis of INWORKS. In the early years of the nuclear industry, workers were recruited en masse into a new industry (51, 52). Because large numbers of healthy males had been selected out of the workforce by WWII military conscription, there have been questions raised about differences in health-related selection between early and later hires (53, 54). There have also been concerns regarding radiation exposure measurement errors in the early years of the nuclear industry (55-57). Recent analyses of all solid cancer found that restricting analysis to workers hired in the more recent years of operations led to a larger magnitude estimate of association between cumulative radiation dose and solid cancer mortality (7). We examined

cancer site-specific estimates of associations upon restriction to workers hired in 1958 or later; estimates tend to be larger in magnitude than in the unrestricted analyses, with exception of liver and gallbladder, pancreas, skin, female breast, and testis, which were smaller in magnitude upon restriction to workers hired in 1958 or later.

Conclusions

Follow-up of large cohorts of nuclear industry workers has been ongoing for over 3 decades. Further work on the development of informative prior distributions could be useful in strengthening understanding of site-specific radiation dose-cancer associations; and, further analyses that focus on estimation of the excess absolute risk of select cancer outcomes, which requires a modeling approach that differs from the one used here, could also be useful for informing evaluation of radiation risks. In addition, as follow-up of cohorts included in INWORKS continue to be updated (42, 58), the information available from international pooling of these data should offer even more useful insights into the risks of cancer from protracted low dose rate exposure to ionizing radiation.

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Table 1. Characteristics of the cohorts included in INWORKS, 1944-2016.

Characteristic	Solid cancer deaths	Person-years (millions) number (%)
Country		
France	4446	2.08 (19)
United Kingdom	11574	4.67 (44)
United States	12069	3.98 (37)
Age		
<40	322	3.15 (29)
40-44	421	1.24 (12)
45-49	828	1.26 (12)
50-54	1558	1.21 (11)
55-59	2461	1.08 (10)
60-64	3581	0.91 (8)
65-69	4458	0.71 (7)
70-74	4600	0.52 (5)
75-79	4310	0.34 (3)
80-84	3171	0.19 (2)
85+	2379	0.11 (1)
Sex		
Male	25465	9.24 (86)
Female	2624	1.48 (14)
Birth cohort		
<1904	1292	0.15 (1)
1905-1914	3591	0.49 (5)
1915-1924	7293	1.25 (12)
1925-1934	8673	2.11 (20)
1935-1944	4576	2.22 (21)
1945-1954	2027	2.25 (21)
1955+	637	2.26 (21)
Socioeconomic status		
professional and technical	7878	3.79 (35)
administrative	2440	0.95 (9)
skilled	12636	4.68 (44)
unskilled	4735	1.14 (11)
uncertain	400	0.16 (1)
Duration employed (years)		
<10	9860	5.25 (49)
10-19	6132	2.65 (25)
20-29	6598	1.82 (17)
30+	5499	1.00 (9)
Neutron monitoring status		
Never	24213	9.45 (88)
Ever	2468	0.73 (7)
Neutron dose exceeded 10% of their total dose	1408	0.54 (5)

Table 2. Maximum likelihood and Markov Chain Monte Carlo hierarchical regression estimates of excess relative rate per Gy cumulative organ-specific dose, lagged 10 years, for death due to specific types of cancer. INWORKS consortium (nuclear workers in France, UK, and USA), 1944-2016

		Maximum likelihood			Markov Chain Monte Carlo		
Cancer type	Deaths	ERR per Gy	90%	CI	ERR per Gy	90%	CrI
Oral cavity and pharynx[†]	522	-0.58	-2.79	2.16	0.47	-0.44	1.37
Esophagus[†]	1112	-0.16	-1.06	0.92	0.34	-0.38	1.00
Stomach	1236	1.00	-0.13	2.47	0.72	0.01	1.44
Colon	2379	0.41	-0.32	1.32	0.53	-0.07	1.10
Rectum	875	1.29	-0.05	3.10	0.78	0.02	1.56
Liver and gallbladder	867	.[‡]	.	.	0.13	-0.84	0.97
Pancreas	1641	0.06	-0.80	1.22	0.42	-0.27	1.10
Peritoneum	266	2.47	-0.12	6.79	0.78	-0.10	1.67
Larynx	256	3.34	0.15	8.71	0.81	-0.09	1.73
Lung	8266	0.67	0.21	1.19	0.65	0.24	1.07
Pleura and mesothelioma	645	2.84	0.70	5.63	0.92	0.05	1.84
Bone and connective[†]	216	2.48	-3.09	9.41	0.64	-0.30	1.58
Skin	622	1.44	-0.28	3.82	0.74	-0.04	1.61
Female breast	640	.[‡]	.	.	0.45	-0.58	1.39
Uterus	102	.[‡]	.	.	0.55	-0.44	1.51
Ovary[†]	208	-0.43	-14.46	19.35	0.58	-0.38	1.56
Prostate	2920	0.31	-0.23	0.96	0.44	-0.06	0.91
Testis	54	33.36	5.49	100.10	0.71	-0.21	1.72
Bladder	1062	0.33	-0.56	1.50	0.51	-0.15	1.15
Kidney	803	1.26	-0.10	3.22	0.76	-0.01	1.51
Brain	923	.[‡]	.	.	0.26	-0.65	1.13
Thyroid	66	4.23	-0.40	15.32	0.73	-0.21	1.64
Remainder	2408	0.43	-0.33	1.36	0.53	-0.05	1.13

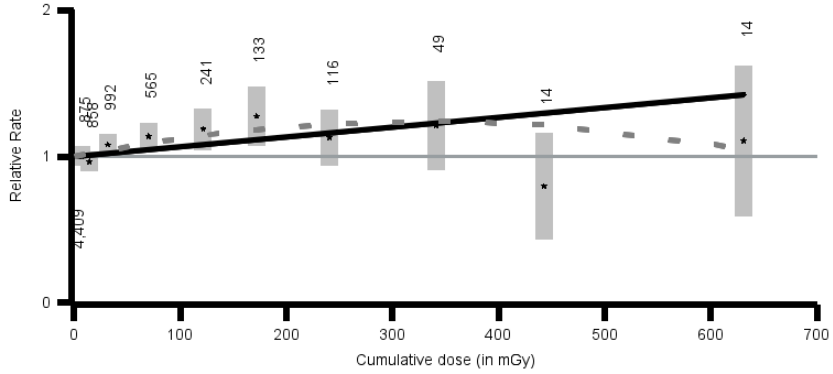
strata: country, age, sex, birth cohort, socioeconomic status, duration employed, neutron monitoring status.

[†] Wald-type lower confidence bound for maximum likelihood estimate

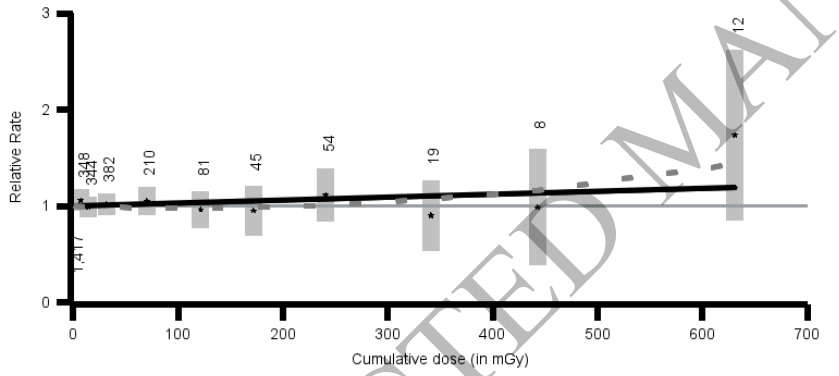
[‡] no estimate obtained due to failure of regression model convergence

CrI: credible interval

A) Lung



B) Prostate



C) Colon

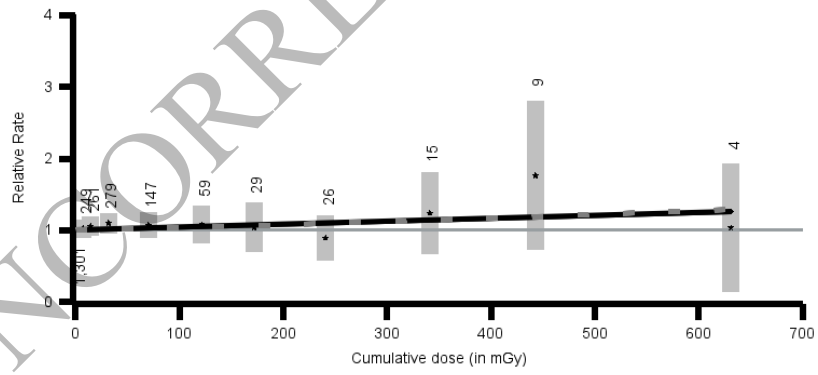


FIGURE 1. Relative rate of mortality due to lung, prostate, and colon cancer by categories of cumulative colon dose†, lagged 10 years in INWORKS. Grey bars indicate 90% confidence intervals, the black solid line depicts the fitted linear model for the change in the excess relative rate of cancer mortality with dose, and the grey dashed line depicts the fitted linear-quadratic model for the change in the excess relative rate of cancer mortality with dose. The grey solid line is a reference line.

A) Lung

B) Prostate
C) Colon

†strata: country, age, sex, birth cohort, socioeconomic status, duration employed, neutron monitoring status.

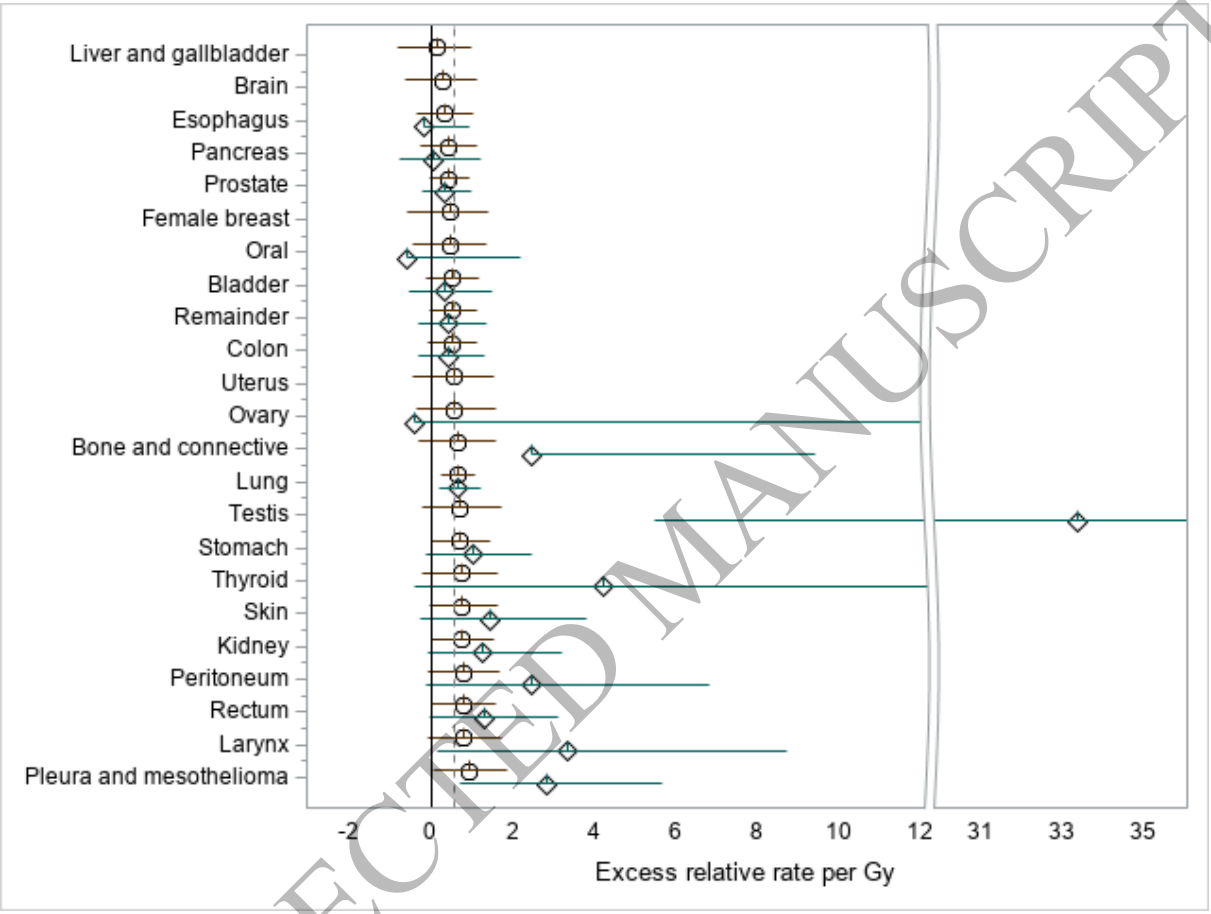


Figure 2. Maximum likelihood and Markov Chain Monte Carlo hierarchical regression estimates of excess relative rate per Gy cumulative organ-specific dose† for death due to specific types of cancer. INWORKS consortium, 1944-2016.

†10-year lag assumption.

Circles indicate cancer site-specific Markov Chain Monte Carlo hierarchical regression estimates. Diamonds indicate cancer site-specific maximum likelihood estimates. Whiskers indicate 90% credible intervals for hierarchical regression estimates and 90% profile likelihood-based confidence intervals for maximum likelihood estimates. Grey dashed line indicates estimated mean of hierarchical regression estimates.