

Site-specific Solid Cancer Mortality After Exposure to Ionizing Radiation

A Cohort Study of Workers (INWORKS)

David B. Richardson,^a Elisabeth Cardis,^{b,d} Robert D. Daniels,^e Michael Gillies,^f Richard Haylock,^f Klervi Leuraud,^g Dominique Laurier,^g Monika Moissonnier,^h Mary K. Schubauer-Berigan,^e Isabelle Thierry-Chef,^h and Ausrele Kesminiene^h

Background: There is considerable scientific interest in associations between protracted low-dose exposure to ionizing radiation and the occurrence of specific types of cancer.

Methods: Associations between ionizing radiation and site-specific solid cancer mortality were examined among 308,297 nuclear workers employed in France, the United Kingdom, and the United States. Workers were monitored for external radiation exposure and

follow-up encompassed 8.2 million person-years. Radiation–mortality associations were estimated using a maximum-likelihood method and using a Markov chain Monte Carlo method, the latter used to fit a hierarchical regression model to stabilize estimates of association.

Results: The analysis included 17,957 deaths attributable to solid cancer, the most common being lung, prostate, and colon cancer. Using a maximum-likelihood method to quantify associations between radiation dose- and site-specific cancer, we obtained positive point estimates for oral, esophagus, stomach, colon, rectum, pancreas, peritoneum, larynx, lung, pleura, bone and connective tissue, skin, ovary, testis, and thyroid cancer; in addition, we obtained negative point estimates for cancer of the liver and gallbladder, prostate, bladder, kidney, and brain. Most of these estimated coefficients exhibited substantial imprecision. Employing a hierarchical model for stabilization had little impact on the estimated associations for the most commonly observed outcomes, but for less frequent cancer types, the stabilized estimates tended to take less extreme values and have greater precision than estimates obtained without such stabilization.

Conclusions: The results provide further evidence regarding associations between low-dose radiation exposure and cancer.

(*Epidemiology* 2018;29: 31–40)

Submitted December 17, 2016; accepted September 27, 2017.

From the ^aDepartment of Epidemiology, University of North Carolina, Chapel Hill, NC; ^bCenter for Research in Environmental Epidemiology (CREAL), Barcelona, Spain; ^cUniversitat Pompeu Fabra (UPF), Barcelona, Spain; ^dCIBER Epidemiología y Salud Pública (CIBERESP), Madrid, Spain; ^eNational Institute for Occupational Safety and Health, Cincinnati, OH; ^fPublic Health England Centre for Radiation, Chemical and Environmental Hazards (PHE-CRCE), Chilton, United Kingdom; ^gInstitut de Radioprotection et de Sécurité Nucléaire (IRSN), Fontenay-aux-Roses, France; and ^hInternational Agency for Research on Cancer, Lyon, France.

Supported, partly, by the US Centers for Disease Control and Prevention (RO3 OH010056) and Ministry of Health, Labour and Welfare of Japan (grant number 2012-02-21-01). The French cohort was coordinated by Institut de Radioprotection et de Sécurité Nucléaire, with part funding from AREVA and EDF. US funding was provided by the National Institute for Occupational Safety and Health, US Department of Energy through an agreement with the US Department of Health and Human Services and a grant received by the University of North Carolina from the National Institute for Occupational Safety and Health (RO3 OH010056). The UK cohort was coordinated by Public Health England who operates the UK's National Registry for Radiation Workers.

K.L. and D.L. report other support from AREVA and from EDF, during the conduct of the study. R.D.D. and M.K.S.-B. report other support from the US Department of Energy during the conduct of the study. D.B.R. reports grants from the US Centers for Disease Control and Prevention during the conduct of the study. The other authors have no conflicts to report.

The findings and conclusions in this report are those of the authors and do not necessarily represent views of the National Institute for Occupational Safety and Health.

Availability of data: This study's data are not freely available. For reasons of ethics and permissions from different agencies, the data are maintained at the International Agency for Research on Cancer (Lyon, France); further, it is not possible to send the data outside of the agency.

SDC Supplemental digital content is available through direct URL citations in the HTML and PDF versions of this article (www.epidem.com).

Correspondence: David Richardson, Department of Epidemiology, School of Public Health, University of North Carolina at Chapel Hill, Chapel Hill, NC 27599. E-mail: david.richardson@unc.edu.

Copyright © 2017 Wolters Kluwer Health, Inc. All rights reserved.

ISSN: 1044-3983/18/2901-0031

DOI: 10.1097/EDE.0000000000000761

0.18, 0.79).^{4,5} Here, we report on associations between ionizing radiation and site-specific solid cancer mortality. We employ a standard maximum-likelihood approach to fitting Poisson regression models to estimate radiation dose–mortality associations for specific types of cancer; we also employ a recently described hierarchical method for Poisson regression analysis to obtain stabilization of cause-specific estimates of association.⁶ The set of estimates derived using the latter approach complement the maximum-likelihood estimates and tend to have improved precision, less extreme values, and lower mean squared error than standard maximum-likelihood estimates.^{6–9} In addition, the current paper examines associations between radiation dose and many site-specific cancers, some of which are relatively rare; this type of hierarchical regression analysis serves as an alternative to classical multiple-comparisons procedures and the resultant stabilized estimates may be of interest as an approach to identification of associations for further investigation.^{6,10,11}

METHODS

We assembled data on workers from France, the United Kingdom, and the United States who were employed in the nuclear industry for at least 1 year and monitored for external radiation exposure through the use of personal dosimeters (Table 1). We obtained data from the Commissariat à l’Energie Atomique, AREVA Nuclear Cycle, and Electricité de France;¹² from the National Registry for Radiation Workers which includes information from the Atomic Weapons

Establishment, British Nuclear Fuels, Ltd, United Kingdom Atomic Energy Authority, British Energy Generation, Magnox Electric, and Ministry of Defence;¹³ 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.¹⁴ In a previous report, we provided a fuller description of the study design and population.¹⁵

Monitoring data for exposure to ionizing radiation were available from company records for UK workers and government and company records for the United States and French workers, providing individual annual quantitative estimates of whole-body dose attributable to external penetrating radiation. We derived target organ doses by dividing recorded external penetrating radiation dose estimates by an organ-specific dose factor.^{16–18} Unless otherwise stated, any reference to dose in this paper implies estimated absorbed dose to a specified organ expressed in grays (Gy). Under most working conditions, absorbed doses from external exposures were accrued from exposures to photons of energies between 100 and 3,000 keV, with a radiation weighting factor of 1.¹⁷ We used available records of estimated neutron doses, which were recorded in a unit of measure for equivalent dose (that is, rem or sievert), 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. We did not add recorded estimates of doses from tritium intakes to

TABLE 1. Characteristics of INWORKS Cohorts

	France	United Kingdom	United States	INWORKS
No. workers	59,003	147,866	101,428	308,297
Males	51,567	134,812	81,883	268,262
Females	7,436	13,054	19,545	40,035
Calendar year of birth				
Mean (SD)	1947 (13)	1944 (18)	1934 (17)	1941 (18)
Range	1894–1975	1877–1983	1873–1973	1873–1983
Age at start employment (years)				
Mean (SD)	27 (7)	28 (11)	30 (9)	28 (10)
Age at last observation (years)				
Mean (SD)	56 (13)	54 (15)	65 (13)	58 (15)
Duration of employment (years)				
Mean (SD)	21 (10)	13 (10)	14 (11)	15 (11)
Calendar years of follow-up				
Range	1968–2004	1946–2001	1944–2005	1944–2005
Duration of follow-up (years)				
Mean (SD)	25 (9)	23 (12)	33 (13)	27 (12)
Vital status				
Alive	52,565	118,775	65,573	236,913
Deceased	6,310	25,307	35,015	66,632
Emigrated or lost to follow-up	128	3,784	840	4,752
Person-years (millions)	1.5	3.4	3.3	8.2

SD, standard deviation.

recorded estimates of dose attributable to external exposures. Available measures of incorporated radionuclides included positive bioassay results, indication of confirmed uptake, or an assigned committed dose. We grouped these measures as an indication of a known or suspected internal contamination. French and US workers with a known or suspected uptake were identified, as were UK workers who were known to have been monitored for internal exposure.

We ascertained vital status through 2004, 2001, and 2005 for the French, the UK, and the US cohorts, respectively, through linkage with death registries, employer 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 subdivided the broad category of all solid cancer mortality that we previously examined⁴ into site-specific cancers. The range of ICD codes associated with each cancer type examined is reported in Table 2.

A worker entered the study 1 year after the date of first employment or the date of first dosimetric monitoring, whichever was later. However, because in France, the national death

registry provides individual information on causes of death only since 1968, French workers only enter follow-up on 1 January 1968 or later. A worker exited the study on the earliest of the following: date of death, date lost to follow-up, or end of follow-up.

Statistical Methods

We use the term cancer types to refer to deaths attributable to the specific types of solid cancer (Table 2). Letting j denote cancer type, and s index levels defined by the cross-classification of covariates, a model for the cancer type-specific rates, λ^j , can be expressed as

$$\lambda^j(\alpha_s^j, \beta^j) = \exp(\alpha_s^j)(1 + \beta^j Z^j), j = 1, 2, \dots, J, \quad (\text{expression 1})$$

where α_s^j is the cancer type-specific effects of covariates, Z^j denotes 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. The target organs selected for the cancer types that we examined are indicated in Table 3 and are similar to the target organs used in a prior analysis of site-specific cancer mortality in the Life Span Study of Japanese atomic bomb survivors (LSS).¹⁹

TABLE 2. Solid Cancer Deaths Among Workers Included in the INWORKS Consortium (Nuclear Workers in France, United Kingdom, and United States), 1944–2005

	France	United Kingdom	United States	INWORKS
Deaths (ICD-9 codes)				
Solid cancer (140–199)	2,356	6,994	8,607	17,957
Oral (140–149)	109	100	150	359
Esophagus (150)	92	329	226	647
Stomach (151)	99	542	263	904
Colon (152–153)	172	542	856	1,570
Rectum (154)	61	313	165	539
Liver and gallbladder (155–156)	132	115	206	453
Pancreas (157)	139	325	512	976
Peritoneum (158–159)	47	67	31	145
Larynx (161)	57	63	65	185
Lung (162)	595	2,244	2,963	5,802
Pleura (163) and mesothelioma ^a	48	133	92	273
Bone and connective (170–171)	21	44	76	141
Skin (172–173)	51	102	216	369
Female breast (174)	70	67	246	383
Uterus (179–182)	16	21	34	71
Ovary (183)	21	22	79	122
Prostate (185)	149	630	906	1,685
Testis (186)	8	28	12	48
Bladder (188, 189.3–189.9)	56	273	250	579
Kidney (189.0–189.2)	70	174	247	491
Brain (191–192)	84	227	283	594
Thyroid (193)	6	16	16	38
Remainder (160, 164–165, 175, 184, 187, 190, 194–199)	253	617	713	1,583

^aICD-10 code C45.

TABLE 3. Characteristics of Estimated Cumulative Dose to Select Organs, in mGy,^a INWORKS Consortium, 1944–2005

Target Tissue	Related Cancer Types	Males			Females		
		Cumulative Organ Dose (mGy)			Cumulative Organ Dose (mGy)		
		Mean ^a	Median (IQR) ^a	95th Percentile ^a	Mean ^b	Median (IQR) ^b	95th Percentile ^b
Bladder	Bladder, kidney, prostate, testis	23.4	5.0 (1.1, 20.2)	109.1	5.3	1.4 (0.4, 4.4)	21.1
Skin	Skin, oral	23.0	5.0 (1.1, 20.0)	107.7	4.8	1.2 (0.4, 4.0)	19.2
Colon	Colon, rectum, peritoneum, bone/connective, remainder	22.8	4.9 (1.1, 19.8)	106.6	5.0	1.3 (0.4, 4.2)	19.9
Lung	Lung, pleura/mesothelioma	22.8	4.9 (1.1, 19.7)	106.3	4.8	1.2 (0.4, 3.9)	18.8
Stomach	Stomach, esophagus, larynx	22.8	4.9 (1.1, 19.7)	106.3	4.9	1.3 (0.4, 4.1)	19.6
Liver	Liver/gallbladder	21.3	4.6 (1.0, 18.5)	99.6	4.8	1.2 (0.4, 4.0)	19.0
Pancreas	Pancreas, thyroid	21.0	4.5 (1.0, 18.2)	98.2	4.8	1.2 (0.4, 4.0)	19.0
Brain	Brain	20.2	4.3 (0.9, 17.5)	94.2	4.3	1.1 (0.4, 3.6)	17.1
Female breast	Female breast	—	—	—	5.6	1.5 (0.5, 4.7)	22.4
Uterus	Uterus	—	—	—	4.6	1.2 (0.4, 3.8)	18.1
Ovary	Ovary	—	—	—	4.4	1.1 (0.4, 3.7)	17.6

^aAmong 228,990 male workers with cumulative dose >0.^bAmong 28,178 female workers with cumulative dose >0.

IQR, interquartile range.

Maximum-likelihood Poisson Regression

For cancer type j , person-years at risk and deaths were tabulated by categories of the associated organ-specific cumulative dose and other study covariates. We fitted a Poisson regression model of the form shown in expression 1 for each cancer type^{20,21}; an estimate of the coefficient of primary interest, β^j , was adjusted to account for the effects of country, attained age (in 5-year intervals), sex, year of birth (in 10-year intervals), socioeconomic status (in five categories, based on job title, for French, US, and UK workers employed by the Atomic Energy Authority and Atomic Weapons Establishment; other UK workers were classified as nonmanual or manual skilled workers, based on employment category), duration of employment or radiation work (in 10-year intervals), and exposure to neutrons (whether a worker had a positive recorded neutron dose, and if so, whether their recorded neutron dose equivalent ever exceeded 10% of their total external radiation dose equivalent).^{15,16}

We report maximum-likelihood estimates of excess relative rate per Gy and associated 90% likelihood-based confidence intervals (CI), facilitating comparison of the precision of our estimated associations with findings reported in other important epidemiological studies of radiation-exposed populations.^{12,13,22–25} Expression 1 implies a constraint on β^j to have a valid rate ratio $(1 + \beta^j Z^j) \geq 0$.²⁶ The constraint implies that $\beta^j \geq \frac{-1}{\max[Z^j]}$, where $\max[Z^j]$ is the maximum value for the organ-specific cumulative dose associated with cancer type j . If the lower bound of the likelihood-based confidence interval was not determined, then we indicate the lower bound as $< \frac{-1}{\max[Z^j]}$.

We lagged cumulative doses by 10 years to allow for an induction and latency period between exposure and

death²⁷; a 10-year lag was chosen to facilitate comparison of results with those from other studies of cancer mortality among nuclear workers.^{13,23} We undertook sensitivity analyses in which person-years at risk and deaths were classified with respect to cumulative dose lagged 5 or 15 years. For each cancer type, we compared results obtained under alternative lags with respect to goodness of model fit.²⁸ To assess departures from linearity in the effect of cumulative dose, we fitted a model that included a higher order polynomial function of cumulative dose and evaluated the improvement in model goodness of fit. For select cancer types, the dose–response association was 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. We also undertook sensitivity analyses in which we restricted our analysis to male workers.

Hierarchical Poisson Regression Using Markov Chain Monte Carlo

We also obtained estimates of the β^j parameters using a hierarchical approach to estimation of the regression model shown in expression 1, employing a form of the Poisson regression model in which the coefficients for the stratum-specific effects, α_s^j , are not part of the expression for the likelihood.^{6,21} These estimates were obtained by joint modeling of the associations between organ-specific cumulative doses (lagged 10 years) and deaths attributable to the J cancer types using a tabulation of person-years at risk and deaths by cancer type, study covariates, and cumulative radiation dose. For each cell of this multidimensional person–time table, we calculated the person–time–weighted cell-specific mean dose to

each of the target organs of interest. We employed a hierarchical regression model¹⁶ under which the distribution of the β^j parameters is modeled as a function of the overall mean effect and residual effects:

$$\beta^j \sim N(\delta, \tau^2), \text{ for } j = 1 \dots J \quad (\text{expression 2})$$

where δ is the prior mean and interpreted as 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-specific effect from a common mean effect. The model represents an assumption that, although radiosensitivity may differ by solid cancer type, a normal distribution of effects is a reasonable initial guess about the pattern of variation in associations by cancer type; however, the hierarchical modeling approach has sufficient flexibility to allow the cancer-specific estimates to deviate from the mean if there is substantial evidence in the data to support it. A normal (0, 100) prior was specified for δ ; a large variance was specified so that this prior was only weakly informative, thereby allowing the data to drive inference as much as possible. We performed a sensitivity analysis in which a normal (0.32, 5) prior was specific 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 exposed at ages 20–60 years (excess relative rate per Gy = 0.32).²³ Following recommendations regarding prior distributions for variance parameters in hierarchical models, we specified that the prior for the variance parameter, τ^2 , followed a uniform (0.01, 10) distribution.²⁹

The degree to which the cancer-type-specific estimates are shrunk towards the common mean depends upon τ^2 . As τ^2 approaches 0, the fitted exposure–response associations will be shrunk towards a common mean; when τ^2 is large the cancer-type-specific estimates will be close to those obtained via estimation of associations one cancer type at a time.^{6,8,29} The parameter, τ^2 , was treated as an unknown parameter that was estimated.^{8,29} Estimates were obtained using a Markov chain Monte Carlo (MCMC) algorithm implemented in SAS PROC MCMC; the model was run for 100,000 iterations with the first 10,000 iterations discarded to allow for initial convergence. From MCMC samples, we derived cancer type-specific estimates of the excess relative rate per Gy, obtained as the mean of the posterior distribution and estimates of associated 90% highest posterior density credible intervals (CrI). Trace, autocorrelation function, and density plots were examined to assess convergence.³⁰ Analyses were conducted using the EPICURE and SAS statistical packages.^{20,31}

RESULTS

The study includes 268,262 male workers and 40,035 female workers and encompasses 8.2 million person-years of follow-up (Table 1). The mean year of birth for the US cohort is 1934, whereas the mean years of birth for French and UK

cohort members were 1947 and 1944, respectively. The average age at the start of employment was 28 years; the average age at the end of follow-up was 58 years (Table 1).

There were 17,957 deaths attributable to solid cancer identified among the decedents, with the most common categories of solid cancer mortality being lung, prostate, colon, pancreas, and stomach cancer (Table 2). Overall, 83% of workers had a recorded dose >0 mGy. Among males, estimated average cumulative doses to the bladder, skin, colon, lung, and stomach were similar in magnitude, whereas estimated average cumulative doses to the liver, pancreas, and brain were slightly lower (Table 3). Among females, estimated average cumulative organ-specific doses were substantially lower than that among males, as females tended to have lower annual occupational radiation doses than males.¹⁶

Maximum-likelihood Poisson Regression Estimates

Positive estimates of the excess relative rate per Gy of cumulative dose, lagged by 10 years, were found for deaths attributable to oral, esophagus, stomach, colon, rectum, pancreas, peritoneum, larynx, lung, pleura, bone and connective tissue, skin, ovary, testis, and thyroid cancer. Negative estimates of the excess relative rate per Gy of cumulative dose, lagged by 10 years, were found for deaths attributable to liver and gallbladder, prostate, bladder, kidney, and brain cancer. An estimate of excess relative rate per Gy was not obtained for cancer of the female breast or uterus as a consequence of the constraint on the parameter that quantifies the association between dose and these cancers (Table 4).

Associations for most cancers were smaller in magnitude under a 5-year lag, and model goodness of fit 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-year than under a 10-year lag assumption (eTable 1; <http://links.lww.com/EDE/B277>). A 15-year lag assumption yielded better goodness of model fit for oral, colon, rectum, liver and gallbladder, pancreas, peritoneum, and ovary cancers than the fit obtained under a 10-year lag assumption.

A model describing a linear increase in the excess relative rate with dose appeared to provide a reasonable description of the data for cancers of the lung, colon, and prostate (the three leading cancer types) upon visual examination (Figure 1). To assess departure from linearity, we fitted a model that also included a parameter for the square of cumulative dose; this led to very little improvement in the model goodness of fit for any cancer type, except thyroid cancer (likelihood ratio test statistic = 5.3; 1 degree of freedom; $P = 0.02$). In analyses restricted to males, maximum-likelihood point estimates and confidence intervals were very similar to those obtained for the full INWORKS cohort (eTable 2; <http://links.lww.com/EDE/B277>).

TABLE 4. Maximum-likelihood and Hierarchical Regression Estimates of Excess Relative Rate per Gy Cumulative Organ-specific Dose^a for Death Attributable to Specific Cancer Categories, INWORKS Consortium, 1944–2005

Cause of Death	Maximum Likelihood			Hierarchical Bayes		
	Excess Relative Rate per Gy	90% CI		Excess Relative Rate per Gy	90% CrI	
Oral	0.73	<−0.83	4.63	0.70	−0.39	1.83
Esophagus	1.11	−0.26	3.04	0.83	−0.06	1.77
Stomach	1.31	−0.07	3.16	0.88	0.01	1.82
Colon	0.09	−0.71	1.17	0.42	−0.32	1.13
Rectum	1.87	0.04	4.52	0.95	−0.03	2.00
Liver and gallbladder	−0.87	<−0.87	1.06	0.37	−0.69	1.41
Pancreas	0.22	<−0.89	1.77	0.50	−0.37	1.34
Peritoneum	4.21	0.42	11.07	1.00	−0.12	2.18
Larynx	6.44	1.36	15.28	1.08	−0.11	2.31
Lung	0.51	0.00	1.09	0.56	0.08	1.02
Pleura and mesothelioma	2.62	−0.56	7.37	0.88	−0.20	2.09
Bone and connective	3.51	<−0.87	12.55	0.79	−0.38	2.03
Skin	2.53	0.15	6.01	0.98	−0.10	2.07
Ovary	16.05	<−0.87	58.75	0.72	−0.49	1.99
Prostate	−0.11	−0.71	0.67	0.25	−0.38	0.87
Testis	32.55	4.48	105.70	0.85	−0.33	2.14
Bladder	−0.17	<−0.87	1.37	0.33	−0.63	1.21
Kidney	−0.16	<−0.87	2.04	0.47	−0.54	1.44
Brain	−0.92	<−0.92	1.14	0.42	−0.68	1.43
Thyroid	0.98	<−0.87	8.76	0.75	−0.42	1.89
Remainder	0.27	−0.58	1.38	0.50	−0.24	1.21

^a10-year lag assumption. Estimates not reported for female breast and uterus attributable to poor model convergence.

Hierarchical Poisson Regression

Upon using a hierarchical model to stabilize estimates, none of the posterior mean estimates were negative, although posterior mean values for prostate, bladder, and liver cancer were relatively close to the null (Table 4). To facilitate convergence of the hierarchical model, parameters for associations between radiation dose and death attributable to breast and uterus cancer, cancer types that failed to converge in the maximum-likelihood model fittings and similarly exhibited poor model convergence in the MCMC models, were not estimated.

Estimates of radiation dose–mortality associations for specific cancer sites obtained using a hierarchical Poisson regression modeling 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 most frequently observed specific cancer, the mean of the posterior distribution, and 90% CrI, for the association between radiation dose and lung cancer obtained by this hierarchical regression method, was similar to the point estimate and 90% CI for the association between radiation dose and lung cancer obtained by maximum-likelihood methods (Table 4). In contrast, for many of the less common cancer types, posterior mean estimates of the excess relative rate per Gy tended to have less extreme values and were stabilized substantially (as reflected by a much narrower 90%

CrI than the 90% CI). The estimated value of δ , the common mean effect of exposure on the cancer types, was 0.68 (90% CrI: 0.18, 1.17); the variance parameter, τ^2 , was estimated as 0.52 (90% CrI: 0.01, 1.22). Diagnostic plots are provided as Supplemental Digital Content (<http://links.lww.com/EDE/B277>). Analyses restricted to males yielded posterior central estimates and 90% CrIs very similar to those obtained for the full INWORKS cohort (eTable 2; <http://links.lww.com/EDE/B277>), as did analyses conducted with a somewhat more informative prior for δ , a normal (0.32, 5) distribution (eTable 3; <http://links.lww.com/EDE/B277>).

DISCUSSION

We estimated dose–response associations for subcategories of solid cancer mortality among nuclear workers from France, the United Kingdom, and the United States. In a prior publication on the INWORKS cohort, we reported on analyses of radiation dose–mortality associations for all solid cancers aggregated together. That analysis combined different types of solid cancer into the broad category of all solid cancers.⁴ The observation of an association between exposure to ionizing radiation and a major category of cause of death, such as all solid cancers, is of interest for radiation protection and risk assessment. However, such an analysis does not allow inferences regarding effects of exposure on specific cancer types;

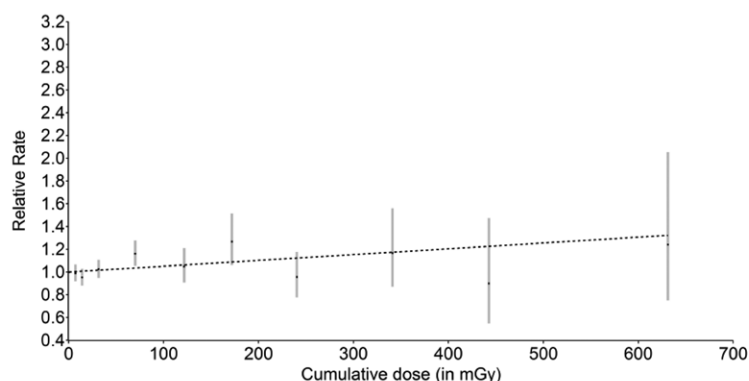
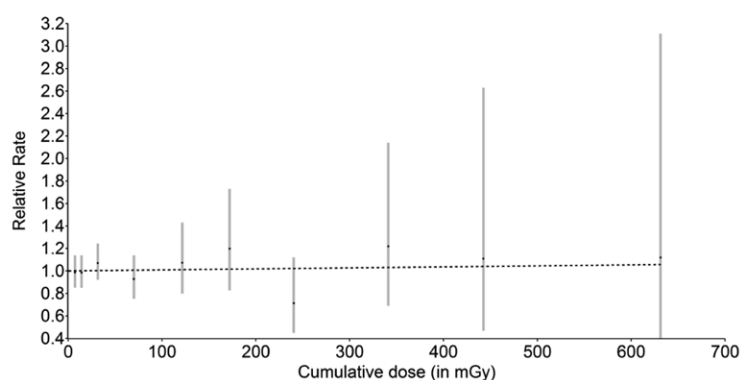
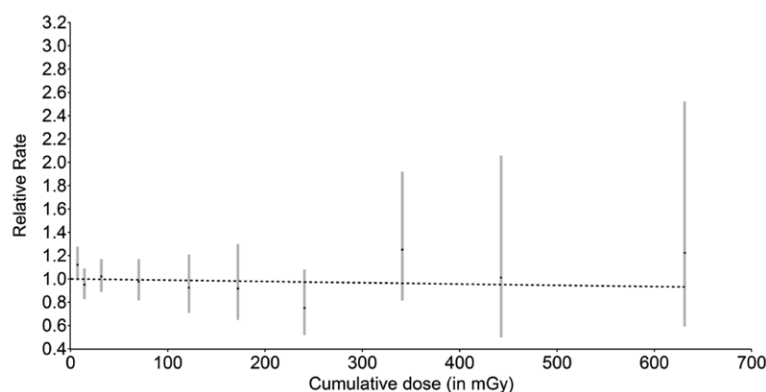
A Lung cancer**B** Colon cancer**C** Prostate cancer

FIGURE 1. Relative rate of cancer site-specific mortality by categories of cumulative dose, lagged 10 years in INWORKS. Gray lines indicate 90% confidence intervals, and the dashed line depicts the fitted linear model for the change in the excess relative rate of mortality with dose. A. Lung cancer. B. Colon cancer. C. Prostate cancer.

implicit in such an analysis is the assumption that the effect size is similar from one cancer type to the next. In the current paper, we fitted maximum-likelihood Poisson regression models to derive cancer type-specific estimates of association for a number of specific cancers. We also employed a hierarchical model to derive stabilized estimates of associations; this model allows that radiation-cancer type associations may vary from one cancer type to the next with parameters describing cancer type-specific associations modeled as following a normal distribution. The National Academy of Sciences' BEIR VII committee noted that in analyses of the Japanese

A-bomb survivors that variability in site-specific radiation dose-cancer associations is generally consistent with random fluctuation around a common effect. Moreover, the approach employed here for modeling the parameters describing site-specific dose-response associations has been applied in previous analyses of radiation dose-cancer associations among atomic bomb survivors and other radiation-exposed populations, allowing for comparison of results and lending support for the approach employed here.^{2,6,19} Simulations and theoretical work have shown that hierarchical models tend to be robust to moderate violations of the assumption of normality

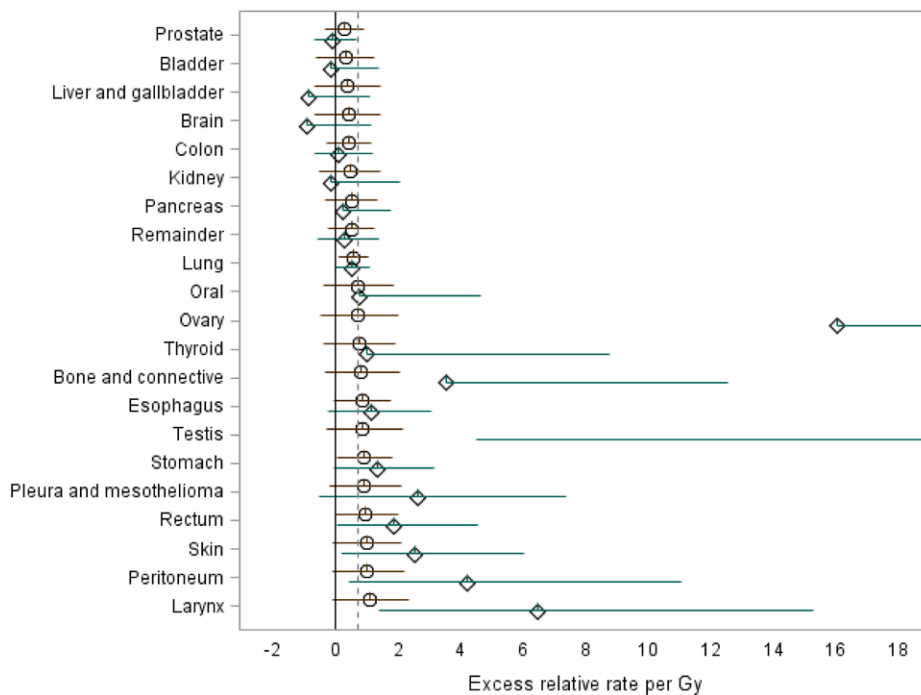


FIGURE 2. Maximum-likelihood and hierarchical regression estimates of excess relative rate per Gy cumulative organ-specific dose (10-year lag assumption) for death attributable to specific cancer categories. INWORKS consortium, 1944–2005. Circles indicate cancer site-specific hierarchical regression estimates. Diamonds indicate cancer site-specific maximum-likelihood estimates. Whiskers indicate 90% credible intervals for hierarchical regression estimates and 90% confidence intervals for maximum-likelihood estimates; if a lower bound was not determined, the plotted point indicates only the upper confidence bound. Gray dashed line indicates estimated mean of hierarchical regression estimates. The maximum-likelihood estimate for cancer of the testis (32.55 per Gy) was not plotted because it was outside the range of the plotted data.

of effects.^{32–34} Posterior estimates for cancer-specific associations obtained from fitting a hierarchical model either tended to be similar to values obtained by fitting a separate model for each cancer type (e.g., lung cancer) or intermediate between the maximum-likelihood estimate for all solid cancers combined and the maximum-likelihood estimate for each cancer type obtained when fitting the models one cancer type at a time (Figure 2). Estimated associations for rare cancer types tended to be imprecise and were more impacted by the use of a hierarchical model for stabilization than common outcomes. This is consistent with expectation for this type of approach, in which the ensemble of estimates is stabilized and may tend to have reduced mean squared error.

The results of our hierarchical modeling are interesting to compare to a similar analysis conducted using data from the Life Span Study (LSS) of atomic bomb survivors.⁶ Estimates of excess relative rate per Gy for cancer of the lung, prostate, and colon (the most common cancers in INWORKS) from our hierarchical regression analysis [0.56 (90% CrI = 0.08, 1.02), 0.25 (90% CrI = −0.38, 0.87), and 0.42 (90% CrI = −0.32, 1.13), respectively] were slightly lower than estimates from a hierarchical regression analysis of the LSS [0.67 (95% CrI = 0.44, 0.92); 0.33 (95% CrI = −0.11, 0.76); and 0.49 (95% CrI = 0.28, 0.69), respectively].⁶ Among other leading cancers in INWORKS, posterior estimates of the excess relative rate per Gy from INWORKS [for cancer of the pancreas 0.50 (90% CrI = −0.37, 1.34), for stomach 0.88 (90% CrI = 0.01, 1.82), and for esophagus 0.83 (90% CrI = −0.06, 1.77)] were somewhat larger than estimates from the LSS (pancreas 0.42 [95% CrI = 0.09, 0.78]; stomach 0.33 [95% CrI = 0.22, 0.44], and esophagus 0.56 [95% CrI = 0.17, 0.97]).⁶ Lung cancer

was among the sites with the largest hierarchically adjusted magnitudes of association, which is consistent with other studies that suggest lung cancer to be relatively radiosensitive, whereas sites such as prostate tend to be among the sites with the smallest adjusted estimates of association, again consistent with other studies. However, there are exceptions as well. For example, some other studies suggest relatively weak associations between radiation and cancers of the oral cavity and rectum, although our results included these among the most positive.

INWORKS relies upon death certificate information for classification of workers with respect to the occurrence of cancer; consequently, one potential source of bias in our estimates of occupational exposure–mortality associations relates to outcome misclassification.³⁵ The sensitivity and specificity of the death certificate as a tool for ascertaining cancer occurrence is imperfect and varies by cancer type³⁶; therefore, variation in the estimated associations by cancer type could reflect outcome misclassification. Prior work suggests that estimates of the rate ratio were relatively insensitive to changes in hypothetical values of sensitivity but changed substantially when specificity was altered, although impact tended to be modest under plausible values of sensitivity and specificity.^{35,37} Empirical studies of the accuracy of death certificate–based cancer ascertainment suggest very high levels of specificity (>99%) for classifications based upon underlying cause of death information for most site-specific cancers, implying minimal potential for outcome misclassification to be a major source of bias in our cancer type–specific estimates of excess relative rate per Gy.^{36,38,39} Bias also may occur attributable to errors in dose estimation, generally expected to be nondifferential

with respect to the outcomes under investigation. Substantial work has been done to characterize, and account for, the performance of the historical dosimeters used by the workers from France, the United Kingdom, and the United States included in INWORKS.^{16–18} Prior work involving sensitivity analyses has suggested that radiation risk estimates based on doses quantified by individual dosimeters are not substantially impacted under a range of assumptions about factors that may lead to measurement error in dose.⁴⁰ Nonetheless, limitations in dose estimation, particularly as related to internal depositions and neutrons, remain a potential source of bias; in prior analyses of solid cancer mortality in the INWORKS cohort, analyses that excluded workers ever flagged for incorporated radionuclides or internal monitoring led to a modest increase in the estimated excess relative rate per Gy.⁴ Variation in the estimated associations by cancer type may also be impacted by patterns of confounding that differ by cancer type. Although we adjusted for country-specific variation in age, sex, birth cohort, and socioeconomic status in our models for cancer site-specific rates, there remains potential for residual confounding of site-specific associations. For example, there is potential for residual confounding attributable to differences between facilities within country in factors associated with mortality and exposure. In prior analyses, we undertook a sensitivity analysis to assess potential confounding by differences (other than external radiation doses) between the major employers in each country; to do this, we fitted a model that adjusted for each of the main facilities included in INWORKS and observed that there was little evidence of residual confounding by facility.⁴ Consideration of potential confounders depends, in part upon, the outcome examined. For example, smoking, which was unmeasured in our study, may be an important confounder in analyses of lung cancer, a somewhat less important confounder in analyses of other smoking-related cancers and of little consequence as a confounder in analyses of cancers that have little or no association with smoking. Contrary to the pattern that would be expected if there was confounding by smoking, we noted previously that the magnitude of the estimated excess relative rate per Gy of solid cancer was essentially unchanged upon excluding lung cancer⁴; moreover, we previously noted the lack of association between radiation dose and chronic obstructive pulmonary disease,⁴ an outcome strongly associated with smoking.⁴¹ Asbestos is a potential confounder of the radiation–lung cancer association, and we lack individual information on asbestos exposure. We examined the association between radiation and cancer of pleura and mesothelioma and observed a positive, albeit imprecise, association. In a prior analysis, we observed that the association between radiation dose and mortality attributable to all solid cancers other than lung and pleura cancer was positive (excess relative rate = 0.43 per Gy; 90% CI = 0.08 to 0.82) and similar in magnitude to the point estimate obtained for all solid cancers.⁴

Studies of nuclear workers have the potential to improve knowledge on health effects associated with low dose and low

dose rate radiation exposure. 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. In addition, as follow-up of cohorts included in INWORKS continue to be updated, 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.

REFERENCES

1. United Nations Scientific Committee on the Effects of Atomic Radiation. *Effects of Ionizing Radiation*. New York: United Nations Scientific Committee on the Effects of Atomic Radiation; 2006.
2. Preston DL, Krestinina LY, Sokolnikov ME, et al. How much can we say about site-specific cancer radiation risks? *Radiat Res*. 2010;174:816–824.
3. International Agency for Research on Cancer. *A Review of Human Carcinogens. Part D: Radiation* Lyon, France: International Agency for Research on Cancer; 2012.
4. Richardson DB, Cardis E, Daniels RD, et al. Risk of cancer from occupational exposure to ionising radiation: retrospective cohort study of workers in France, the United Kingdom, and the United States (INWORKS). *BMJ*. 2015;351:h5359.
5. Leuraud K, Richardson DB, Cardis E, et al. Ionising radiation and risk of death from leukaemia and lymphoma in radiation-monitored workers (INWORKS): an international cohort study. *Lancet Haematol*. 2015;2:e276–e281.
6. Richardson DB, Hamra GB, MacLehose RF, Cole SR, Chu H. Hierarchical regression for analyses of multiple outcomes. *Am J Epidemiol*. 2015;182:459–467.
7. Witte JS, Greenland S. Simulation study of hierarchical regression. *Stat Med*. 1996;15:1161–1170.
8. Greenland S. Principles of multilevel modelling. *Int J Epidemiol*. 2000;29:158–167.
9. MacLehose RF, Dunson DB, Herring AH, Hoppin JA. Bayesian methods for highly correlated exposure data. *Epidemiology*. 2007;18:199–207.
10. Greenland S. Hierarchical regression for epidemiologic analyses of multiple exposures. *Environ Health Perspect*. 1994;102(8 suppl):33–39.
11. Greenland S. A semi-Bayes approach to the analysis of correlated multiple associations, with an application to an occupational cancer-mortality study. *Stat Med*. 1992;11:219–230.
12. Metz-Flamant C, Laurent O, Samson E, et al. Mortality associated with chronic external radiation exposure in the French combined cohort of nuclear workers. *Occup Environ Med*. 2013;70:630–638.
13. Muirhead CR, O'Hagan JA, Haylock RG, et al. Mortality and cancer incidence following occupational radiation exposure: third analysis of the National Registry for Radiation Workers. *Br J Cancer*. 2009;100:206–212.
14. Schubauer-Berigan MK, Daniels RD, Bertke SJ, Tseng CY, Richardson DB. Cancer mortality through 2005 among a pooled cohort of U.S. nuclear workers exposed to external ionizing radiation. *Radiat Res*. 2015;183:620–631.
15. Nakashima E. Radiation dose response estimation with emphasis on low dose range using restricted cubic splines: application to all solid cancer mortality data, 1950–2003, in atomic bomb survivors. *Health Phys*. 2015;109:15–24.
16. Grant EJ, Furukawa K, Sakata R, et al. Risk of death among children of atomic bomb survivors after 62 years of follow-up: a cohort study. *Lancet Oncol*. 2015;16:1316–1323.
17. Thierry-Chef I, Marshall M, Fix JJ, et al. The 15-Country Collaborative Study of Cancer Risk among Radiation Workers in the Nuclear Industry: study of errors in dosimetry. *Radiat Res*. 2007;167:380–395.
18. Thierry-Chef I, Pernicka F, Marshall M, Cardis E, Andreo P. Study of a selection of 10 historical types of dosimeter: variation of the response to Hp(10) with photon energy and geometry of exposure. *Radiat Prot Dosimetry*. 2002;102:101–113.
19. Pawel D, Preston D, Pierce D, Cologne J. Improved estimates of cancer site-specific risks for A-bomb survivors. *Radiat Res*. 2008;169:87–98.

20. Preston DL, Lubin JH, Pierce DA, McConney ME. *Epicure: User's Guide*. Seattle, WA: Hirosoft International Corporation, 1993.
21. Richardson DB, Langholz B. Background stratified Poisson regression analysis of cohort data. *Radiat Environ Biophys*. 2012;51:15–22.
22. Cardis E, Gilbert ES, Carpenter L, et al. Effects of low doses and low dose rates of external ionizing radiation: cancer mortality among nuclear industry workers in three countries. *Radiat Res*. 1995;142:117–132.
23. Cardis E, Vrijheid M, Blettner M, et al. Risk of cancer after low doses of ionising radiation: retrospective cohort study in 15 countries. *BMJ*. 2005;331:77.
24. Preston DL, Ron E, Tokuoka S, et al. Solid cancer incidence in atomic bomb survivors: 1958–1998. *Radiat Res*. 2007;168:1–64.
25. Gilbert ES, Cragle DL, Wiggs LD. Updated analyses of combined mortality data for workers at the Hanford Site, Oak Ridge National Laboratory, and Rocky Flats Weapons Plant. *Radiat Res*. 1993;136:408–421.
26. Richardson DB. A simple approach for fitting linear relative rate models in SAS. *Am J Epidemiol*. 2008;168:1333–1338.
27. Richardson DB, Cole SR, Chu H, Langholz B. Lagging exposure information in cumulative exposure-response analyses. *Am J Epidemiol*. 2011;174:1416–1422.
28. Salvan A, Stayner L, Steenland K, Smith R. Selecting an exposure lag period. *Epidemiology*. 1995;6:387–390.
29. Gelman A. Prior distributions for variance parameters in hierarchical models. *Bayesian Anal*. 2006;1:515–533.
30. Hamra G, MacLehose R, Richardson D. Markov chain Monte Carlo: an introduction for epidemiologists. *Int J Epidemiol*. 2013;42:627–634.
31. SAS Institute Inc. SAS OnlineDoc® 9.2. Available at: <http://support.sas.com/documentation/92/>. Accessed 15 March 2014.
32. Neuhaus JM, McCulloch CE, Boylan R. A note on type II error under random effects misspecification in generalized linear mixed models. *Biometrics*. 2011;67:654–656; discussion 656.
33. McCulloch CE, Neuhaus JM. Prediction of random effects in linear and generalized linear models under model misspecification. *Biometrics*. 2011;67:270–279.
34. McCulloch CE, Neuhaus JM. Misspecifying the shape of a random effects distribution: why getting it wrong may not matter. *Stat Sci*. 2011;26:388–402.
35. Björ B, Burström L, Jonsson H, Nathanaelsson L, Damber L, Nilsson T. Fifty-year follow-up of mortality among a cohort of iron-ore miners in Sweden, with specific reference to myocardial infarction mortality. *Occup Environ Med*. 2009;66:264–268.
36. Richardson DB. Use of multiple cause of death data in cancer mortality analyses. *Am J Ind Med*. 2006;49:683–689.
37. Villeneuve PJ, Morrison HI, Lane R. Radon and lung cancer risk: an extension of the mortality follow-up of the Newfoundland fluorspar cohort. *Health Phys*. 2007;92:157–169.
38. Ron E, Carter R, Jablon S, Mabuchi K. Agreement between death certificate and autopsy diagnoses among atomic bomb survivors. *Epidemiology*. 1994;5:48–56.
39. Percy CL, Miller BA, Gloeckler Ries LA. Effect of changes in cancer classification and the accuracy of cancer death certificates on trends in cancer mortality. *Ann NY Acad Sci*. 1990;609:87–97; discussion 97.
40. Gilbert ES, Fix JJ. Accounting for bias in dose estimates in analyses of data from nuclear worker mortality studies. *Health Phys*. 1995;68:650–660.
41. Richardson DB, Laurier D, Schubauer-Berigan MK, Tchetgen Tchetgen E, Cole SR. Assessment and indirect adjustment for confounding by smoking in cohort studies using relative hazards models. *Am J Epidemiol*. 2014;180:933–940.