CMD 25-H2.E

Date: 2025-06-26

Supplementary Information

Written submission from CNSC Staff in response to undertaking #1 to provide clarification or additional information

In the matter of the

Ontario Power Generation Inc.

Application to renew power reactor operating licence for the Darlington Nuclear Generating Station

Commission Public Hearing
Part 2

June 24-26, 2025

Renseignements supplémentaires

Mémoire du personnel de la CCSN en réponse à l'engagement no 1 de fournir des précisions ou des renseignements supplémentaires

À l'égard d'

Ontario Power Generation Inc.

Demande concernant le renouvellement du permis d'exploitation d'un réacteur de puissance pour la centrale nucléaire de Darlington

Audience publique de la Commission
Partie 2

24-26 juin 2025

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Canada

UNDERTAKING #1

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From:	Burtt, Julie
Sent:	June 26, 2025 2:37 PM
To:	Registry / Greffe (CNSC/CCSN)
Cc:	
Subject:	Undertaking-June 25, 2025
Attachments:	Spix et al, 2008.pdf; Lane et al, 2013.pdf; Leuraud et al, 2024.pdf; Richardson et al, 2023.pdf; Richardson et al, 2018.pdf; Richardson et al, 2025.pdf

In satisfaction of the Undertaking made in the DNGS hearing on June 25, 2025, please note the following studies which are attached and hyperlinked for ease of access.

1. KiKK Study
    a. Original publication: Spix C, Schmiedel S, Kaatsch P, Schulze-Rath R, and Blettner M, 2008. Case-control study on childhood cancer in the vicinity of nuclear power plants in Germany 1980-2003. *European Journal of Cancer* 44(2): 275-284 (Attached, or available here)
    b. CNSC website link includes history and follow-up studies: https://www.cnsc-ccsn.gc.ca/eng/resources/perspectives-on-nuclear-issues/the-kikk-study-explained-fact-sheet/

2. RADICON Study (which refutes the KiKK study for Canadian situation)
    a. Original publication: R Lane, E. Dagher, J. Burtt, and P. A. Thompson. "Radiation exposure and cancer incidence (1990 to 2008) around nuclear power plants in Ontario, Canada." (2013). (Attached, or available here: DOI: 10.4236/jep.2013.49104)
    b. CNSC website link: https://www.cnsc-ccsn.gc.ca/eng/resources/health/health-studies/radicon-study/

3. INWORKS Study
    a. Suite of original publications (2023 is the most recent "main" analysis, however I've attached several (not all) related publications): Richardson DB, Leuraud K, Laurier D, Gillies M, Haylock R, Kelly-Reif K, Bertke S, Daniels RD, Thierry-Chef I, Moissonnier M, Kesminiene A. Cancer mortality after low dose exposure to ionising radiation in workers in France, the United Kingdom, and the United States (INWORKS): cohort study. BMJ. 2023 Aug 16;382. (Attached, or available here)
    b. CNSC website link: INWORKS: Cancer mortality after low dose exposure to ionising radiation in workers

Should the Commission require any supporting information, clarification, or have follow-up questions, I remain available.

Kindest regards,
Julie Burtt

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Case–control study on childhood cancer in the vicinity of nuclear power plants in Germany 1980–2003

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ABSTRACT

The 1984 Windscale study raised concern about a possible association between living in the vicinity of nuclear power plants and childhood cancer No such effect for all cancers was seen in ecological studies in Germany (1980–1995) Results from exploratory analyses led to a new study

Pre-selected areas around all 16 major nuclear power plants in Germany formed the study area The design is a matched case–control study; cases are all cancers under five years diagnosed in 1980–2003: 1592 cases, and 4735 controls Inverse distance of place of residence to the nearest nuclear power plant at the time of diagnosis was used as the independent variable in a conditional logistic regression model

Results show an increased risk for childhood cancer under five years when living near nuclear power plants in Germany The inner 5-km zone shows an increased risk (odds ratio 1 47; lower one-sided 95% confidence limit 1 16) The effect was largely restricted to leukaemia

The results are compatible with the corresponding subgroups in the previous German ecological studies, with which this study shares most of the cases They contrast with the lack of an effect observed or expected from other studies due to low doses from routine nuclear power plant operation

1. Introduction

The German population has long been worried about the potential dangers and health effects of nuclear power In 1984, the public was frightened by reports of elevated childhood cancer rates within a 10-mile zone of the Windscale (Sellafield) nuclear power plant in England, other investigations followed shortly.[1–5] The German Childhood Cancer Registry, founded in 1980, investigated whether there had been a similar increase in Germany In an ecological study with a similar design to the UK (United Kingdom) studies,[1–4,6] the incidence rates of all cancers in children under 15 years of age during 1980–1990 in communities within a 15-km zone of all West German nuclear power plants (812 cases) were compared with those in reference communities with similar population densities and degrees of urbanisation No statistically significant increase in risk was found (relative risk [RR] 0 97; 95% confidence interval [CI] [0 87;1 08]) [7] Nevertheless, exploratory analyses of subsets showed statistically significant results particularly for acute leukaemia in children under five years of age living in the inner 5-km zone (RR 3 01; 95%CI [1 25;10 31]) When five more years of data had been accrued

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(1991–1995) the study was repeated: the RR for all cancers amongst children under 15 living within a 15-km zone was 1.05 (95% CI [0.92;1.20]) and the RR for acute leukaemia amongst children under 5 living within a 5-km zone was 1.39 (95% CI [0.69;2.57]).[8]

In the late 1990s, a third party obtained data up to 1998 from the German Childhood Cancer Registry (GCCR) by county via the Bundesamt für Strahlenschutz (Federal Office for Radiation Protection) for the State of Bavaria. The data were analysed in an exploratory manner applying linear regression to standardised incidence ratios (SIR's) by county. Elevated SIR's were observed for selected combinations of years, counties, and disease subgroups around Bavarian nuclear power plants. The GCCR criticised the methods used in this analysis.[9] Nevertheless the results, published over the Internet but never in a peer-reviewed journal and quoted briefly by the Deutsches Ärzteblatt,[10] were sufficiently alarming to the public to induce the German Federal Ministry for the Environment, Nature Conservation and Nuclear Safety to call for applications for another study. The design originated from discussions with a Bundesamt für Strahlenschutz (Federal Office for Radiation Protection)-expert committee. The design was influenced by the exploratory results of the previous studies.[11] The study is a matched case–control study in which the exposure surrogate is the distance of individual residences at the date of diagnosis from the nearest nuclear power plant. Data from 1996 to 2003 are now included.

The main question of the investigation presented here is: Is the risk of childhood cancer associated with living in the proximity of nuclear power stations? The distance measure, previously based on community midpoints, is now determined by the place of residence at the date of diagnosis. A subset of cases and controls was to be interviewed with regard to potential confounders.

Since the emissions from a nuclear power plant add only minimally to the background radiation level, no effect would be expected on the basis of the usual models for the effects of low levels of radiation, as presented by the biological effects of ionizing radiation (BEIR) – Committee and the international commission on radiological protection (ICRP).[12,13] However, these models are based mainly on data from adults, as childhood cancer is very rare. The BEIR Committee reviewed studies on leukaemia/childhood cancer of populations living around nuclear facilities but did not draw any conclusions from them, as they generally do not include individual estimates of radiation dose.[12]

This paper presents the overall results of the recent study conducted by the GCCR. Another paper presents the results for leukaemia and the comparison with the previous ecological studies in more detail.[14]

2. Materials and methods

2.1. Nuclear power plants

The study covered the data available at the GCCR for 1980–2003. The expert committee selected all 16 sufficiently large and long running German nuclear power plants, resulting in the inclusion of only West German nuclear power plants. A power plant was considered relevant for the study from 1 year after it started producing energy until 5 years after ceasing to operate (Table 1). The committee then selected areas around these power plants, with an emphasis on the east side because of the predominant west winds in Germany. For each nuclear power plant, the corresponding county, its next neighbour and usually one more county east of it were to be included. These counties define the area for this specific nuclear power plant. These areas overlap for several nuclear power plants. The total study area is shown in Fig. 1. The borders shown are county borders. As can be seen, nuclear power plants tend to sit close to district borders. A county in Germany consists either of one large city (community) or of a larger mixed/rural area with a varying number of smaller towns and villages (communities).[11]

2.2. Participants

One thousand five hundred and ninety two cases of cancer amongst children under 5 years of age, with oncologic diseases included in the International Classification of Childhood Cancer (ICCC)[15] resident in the study area at the date of diagnosis with known address and diagnosed in the relevant study period of the nearest nuclear power plant were included. All cases were matched with controls selected from the records of the appropriate registrar's offices. The controls were matched for date of birth (as closely as possible but at least within 1.5 years), age, sex and nuclear power plant area (at the date of diagnosis). Per control, a community was selected randomly out of the respective area according to the case-corresponding population (by sex, age and year of diagnosis). This community was asked to make available addresses and names of children with the matching criteria. From this address list the control closest to the date of birth of the case was selected.

Not all communities complied with our request to provide the addresses of controls. Six controls per case were requested and three of these were selected randomly. Finally, 4735 controls were used in the analysis.

For all case and control children, the geo-code of the place of residence at the date of diagnosis was obtained from the Land register.[16] For 9.9% of the case children and 8.4% of the controls, the address could not be coded and was replaced by the street mid-point (140 cases, 359 controls) or by the community or zip-code area mid-point (20 cases, 40 controls). The position of the chimney of each nuclear power plant was coded in the same way from high-resolution maps. All distances were given in metres.

2.3. Control for potential confounders

To assess potential confounding, the families of a subset of all cases and controls were invited to participate in a telephone interview covering other potential risk factors for childhood cancer.[17,18] The subset included all cases with selected diagnoses (leukaemia, lymphoma or a central nervous system tumour) diagnosed in 1993–2003 and their controls. The questions were summarised to a total of 20 potential confounders: social status, information on additional radiation exposure (parents, child), other risk factors (such as pesticides, mother's hormone intake), immune sys-

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Table 1 – Relevant nuclear power plants and their operation periods and study periods

Name	Operating period	Study period
Brunsbüttel	23.06.1976 – 31.12.2003	01.01.1980 – 31.12.2003
Brokdorf	08.10.1986 – 31.12.2003	08.10.1987 – 31.12.2003
Krümmel	14.09.1983 – 31.12.2003	14.09.1984 – 31.12.2003
Stade	08.01.1972 – 31.12.2003	01.01.1980 – 31.12.2003
Unterweser	16.09.1978 – 31.12.2003	01.01.1980 – 31.12.2003
Lingen	31.01.1968 – 05.01.1977	01.01.1980 – 05.01.1982
Emsland	14.04.1988 – 31.12.2003	14.04.1989 – 31.12.2003
Grohnde	01.09.1984 – 31.12.2003	01.09.1985 – 31.12.2003
Würgassen	10.10.1971 – 26.08.1994	01.01.1980 – 26.08.1999
Grafenrheinfeld	09.12.1981 – 31.12.2003	09.12.1982 – 31.12.2003
Biblis	16.07.1974 – 31.12.2003	01.01.1980 – 31.12.2003
Obrigheim	22.09.1968 – 31.12.2003	01.01.1980 – 31.12.2003
Neckarwestheim	26.05.1976 – 31.12.2003	01.01.1980 – 31.12.2003
Philippsburg	09.03.1979 – 31.12.2003	09.03.1980 – 31.12.2003
Isar	20.11.1977 – 31.12.2003	01.01.1980 – 31.12.2003
Gundremmingen	14.08.1966 – 13.01.1977[a]	01.01.1980 – 31.12.2003
	09.03.1984 – 31.12.2003	

All periods right censored at 31.12.2003 (end of study) and study periods left censored at 1.1.1980 (star of childhood cancer registration). The order is roughly North to South.
a The 'gap' was intentionally included in the study period.

tem related issues (such as vaccinations, breast feeding and child's social interaction), type of region and folic acid in pregnancy. In addition, we asked about previous residences of the child.

2.4. Statistical methods

The main question was whether there is a monotonic descending relation between proximity of place of residence at the date of diagnosis to the nearest nuclear power plant included in the study at the time of diagnosis and the risk for childhood cancer. On the basis of the linear no-threshold low-dose effect excess relative risk-models as proposed by the BEIR Committee, the ICRP and the dispersion models presented by the United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR), a conditional logistic regression with 1/(distance) as the continuous independent variable was used [12,13,19]. In the following 1/(distance in km) is referred to as measure of proximity. We adopted the view proposed by BEIR that a beneficial effect of radiation cannot be expected even at extremely low doses [12]. This is the basis for the one-sided analysis.

Additionally, categorical analyses were performed for the inner 5- and 10-km zones versus the respective outer zones. The results of the categorical models and the continuous model were compared by calculating the corresponding odds ratio (OR) from the continuous model, using the mean proximity of the controls in the respective inner zone. The conditional logistic regression model included one proximity measure at a time (continuous or categorical) and no other covariates.

If it is assumed that the estimated odds ratios are approximations of relative risk estimates, the categorical results can be converted to population attributable risks and to an attributable risk fraction for exposed cases with corresponding confidence intervals [20].

The primary analysis included all cases in children under 5 years of age at diagnosis. The diagnostic groups defined in advance in the study protocol were leukaemia (ICCC Ia-e), lymphoid leukaemia (ICCC Ia), acute non-lymphocytic leukaemia (ICCC Ib), central nervous system tumours including medulloblastoma (ICCC IIIa-f) and embryonal tumours except for medulloblastoma (ICCC IVa, V and VIa). Further detailed results for the leukaemia subgroups are presented elsewhere [14]. In further subgroup analyses, we divided the operating periods of the nuclear power plants by half, and we analysed only those who were to be interviewed. All regression results are presented with one-sided lower confidence limits (CI) at a significance level of 5%.

2.5. Sensitivity analyses

The randomness of the selection of the three matched controls from the maximum of six controls was assessed by repeating the regression using all available (up to 6) controls. The appropriateness of the fitted curve was investigated by fractional polynomial and Box–Tidwell-models for assessing the 'best fitting' curve (based on the deviance) [21,22].

Further sensitivity analyses were required in addition to those planned in advance, while 10% of the communities generally refused to provide control addresses, the proportion of refused addresses was higher (16%) amongst the communities situated in the inner 5-km zone. Therefore, the relevant analyses were repeated only for cases and controls from communities which provided control addresses.

The questionnaire part of the study raised a strong suspicion that communities might have sent the addresses of persons who were never resident in the respective community before the date of diagnosis of the corresponding case (about 5%). We therefore simulated artificial datasets by removing this 5% of controls from the analysis, assuming these 5% were either randomly distributed with respect to distance from the

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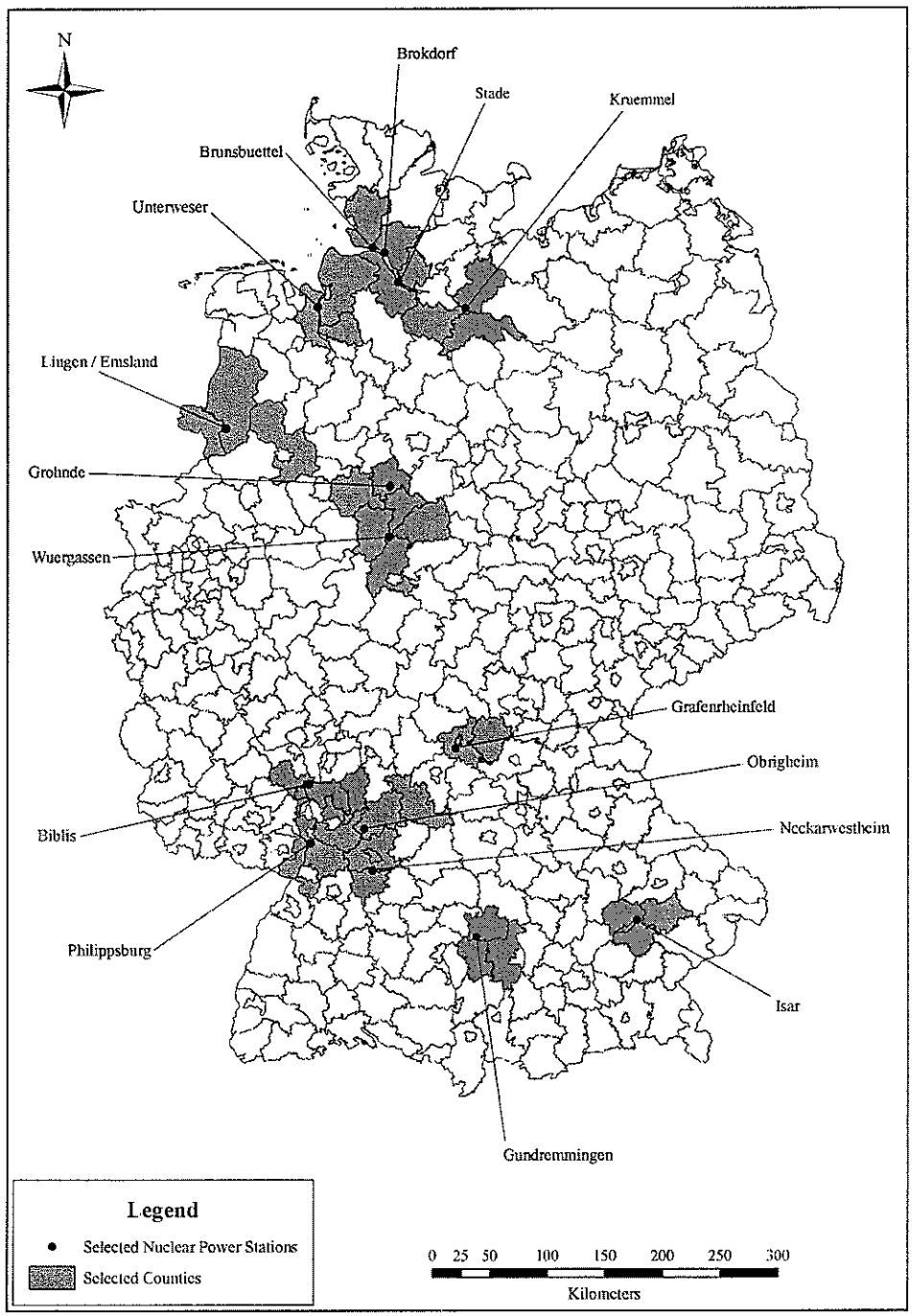

Fig. 1 – Selected nuclear power plants and study areas in Germany. Each nuclear power plant is identified by name; Lingen/ Emsland are two reactors 2 km from each other.

nuclear power plant, or more likely to live close to it or far from it. For a sub sample of the controls (45%) we were able to check the address information at the date of diagnosis of the corresponding case. Amongst these we found 15% of controls that had not lived in the indicated place at that time, though they might have lived there prior to the date of diagnosis of the corresponding case. The analysis was repeated including only controls, where the address could be checked and excluding those, whose address at the date of diagnosis of the corresponding case had been incorrect.

The previous German studies had shown single nuclear power plants to influence the results considerably, so the calculations were repeated leaving the nuclear power plants out of the analysis one by one.

As confounder assessment we planned to use a change by more than one standard deviation (out of the calculation for

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the respective subset of cases not including any confounder variables) of the continuous proximity parameter

To ensure the correctness of our analyses all relevant computations were repeated independently by the coordinating centre of clinical trials (KKS) of the University of Mainz

3. Results

Table 2 shows the characteristics of the case children and the controls. The age and sex distributions were similar, as these were matching criteria. The case children lived 1.2–81.6 km from the nearest nuclear power plant and the controls between 1.1 km and 92.0 km.

The parameter from the continuous model for the measure of proximity was $\beta = 1.18$ (lower one-sided 95% confidence limit [CL] 0.46) (Table 3, Fig. 2). The diagnostic subsets defined in the study protocol showed a statistically significant effect only for leukaemia, which was stronger than the general effect (Table 2). We also give the complementary calculation beyond the study protocol (non-leukaemia cases, Table 3). No statistically significant difference was found comparing the first and second half of the respective operating periods of the nuclear power plants. The effect in the subgroup eligible for interviewing was almost the same as that in the study as a whole, although it was not statistically significant because of small numbers ($\beta = 1.05$; lower one-sided 95% CL −0.30) (Table 3).

When the continuous model was refitted with all available (maximally 6) controls per case (1592 cases, 8527 controls), the parameter estimate was $\beta = 1.18$ (lower one-sided 95% CL 0.50), which is identical to that obtained with the three selected controls (compare to Table 3). When the model was refitted after exclusion of communities that did not provide control addresses (leaving 1310 cases and 3905 controls), a statistically significant parameter estimate was found $\beta = 1.01$ (lower one-sided 95% CL 0.24) (compare to Table 3).

When 5% of all controls were either excluded randomly from the dataset with respect to their distances from the nearest nuclear power station, or selectively from close to or far from the nearest nuclear power station, we found average statistically significant estimated regression parameters of 1.18, 1.54 or 1.09, respectively, based on 1000 simulations each. These are all close to the results found with the full data (compare to Table 3). Excluding the controls from the analysis, which had their address at the date of diagnosis checked and found incorrect, led to an estimated regression parameter of

Table 2 – Characteristics of cases of all malignancies in children under 5 years of age, as defined by the ICCC, diagnosed in 1980–2003 resident in the study areas, and their matched controls

	Cases		Controls	
	N	%	N	%
All	1592	100.0	4735	100.0
Boys	893	56.1	2.656	56.1
Girls	699	43.9	2.079	43.9
Age (years)				
0–<1	344	21.6	1.016	21.5
1–<2	330	20.7	984	20.8
2–<3	340	21.4	991	20.9
3–<4	315	19.8	947	20.0
4–<5	263	16.5	775	16.4
5–<6	0	0.0	22	0.5
Diagnostic groups[a]				
Leukaemia	593	37.3	1.766	37.3
Central nervous system tumours	242	15.2	720	15.2
Embryonal tumours	486	30.6	1.447	30.5
Other	271	17.0	802	16.9
First half of power plant operation period	698	43.8	2.073	43.8
Second half of power plant operation period	894	56.2	2.662	56.2
Eligible for interview (1993–2003, selected diagnoses)	471	29.6	1.402	29.6
Distance from nearest nuclear power plant (km)				
<5	77	4.8	148	3.1
5–<10	158	9.9	464	9.8
10–<20	523	32.9	1.589	33.6
20–<30	403	25.3	1.181	24.9
30–<40	225	14.1	726	15.3
40–<50	137	8.6	371	7.8
⩾50	69	4.3	256	5.4
Mean proximity measure[b] in the inner 5-km radius	0.3133	–	0.3245	–
Corresponding harmonic mean distance (km)	3.2		3.1	

a Controls matched to cases with respective diagnosis.
b Proximity measure = 1/distance in km (kilometres).

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Table 3 – Estimated parameters from the conditional continuous logistic regression model for all cancers, diagnostic groups and some relevant time periods

	Estimated regression coefficient	Lower one-sided 95% confidence limit	N cases	N controls
All malignancies 1980–2003	1 18	0 46	1592	4735
Diagnostic groups 1980–2003				
Leukaemia	1 75	0 65	593	1766
Central nervous system tumours	−1 02	−3 40	242	720
Embryonal tumours	0 52	−0 84	486	1447
All malignancies except leukaemia	0 76	−0 20	999	2969
First half of power plant operation period	1 89	0 85	698	2073
Second half	0 54[a]	−0 47	894	2662
Eligible for interview: diagnosed 1993–2003 with leukaemia, lymphoma, or a central nervous system tumour	1 05	−0 30	471	1402

a The difference between the first and the second half was not statistically significant

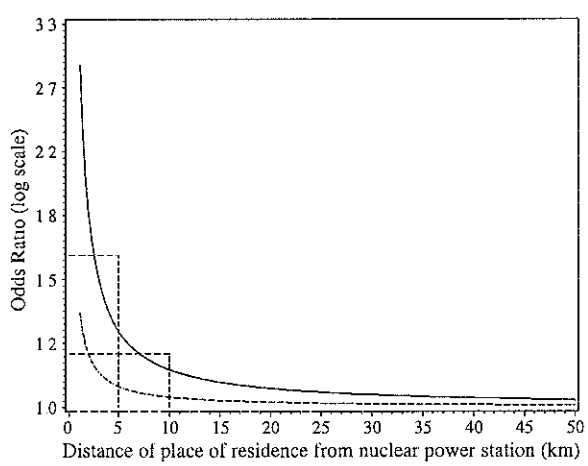

Fig. 2 – Graphical representation of the main regression analyses. Estimated regression curve for all malignancies versus distance from nearest power plant, based on 1592 cases and 4753 matched controls based on conditional logistic regression modelling. Distance axis cut off at 50 km Black line: continuous fitted regression curve Dotted curved line: lower 95%-confidence limit of continuous fitted regression curve. Dotted straight lines: categorical analysis for < 5 km and <10 km respectively

1 05, which again does not differ much from the full data (compare Table 3)

Leaving the nuclear power stations out of the data set one by one yielded statistically significant regression coefficients close to the overall estimate

Fractional polynomial modelling and the Box–Tidwell model both suggested that an alternative measure of proximity of the form $1/\sqrt{(\text{distance})}$ would fit slightly better than 1/(distance), but not significantly so

The categorical analyses showed a statistically significant effect for children living in the inner 5-km zone OR = 1 61 (lower one-sided 95% CI 1 26). In comparison of diagnostic groups, the effect was again found only for leukaemia (OR 2 19; lower one-sided 95% CI 1 51). Living in the inner 10-km zone had a far smaller effect (OR = 1 18; lower one-sided 95% CI 1 03). The fitted curve for all malignancies predicted similar OR's for the inner 5 km and 10 km zone as obtained by the categorical analysis (Table 4, Fig. 2).

Based on the categorical analysis, our result indicates that 29 out of the total observed 77 cases (38%; 95% CI [24%;61%]) diagnosed in the inner 5-km zone in 1980–2003 may be attributed to the fact that they were living in this 5-km zone. These were 1.2 cases per year, representing 0 2% (95% CI [0 1%; 0 4%]) of all 13,373 cases of cancer in children under 5 years in Germany in those years.

4. Discussion

4 1 *Principal findings*

Our results show an increased risk for cancer amongst children under 5 years of age living in the proximity to nuclear power plants in Germany. The continuous model, in agreement with the categorical analyses, identified the inner 5-km zone as the zone of increased risk (about 1 5-fold higher). The observed effect was largely restricted to leukaemia (Tables 3, 4).

Expression of the categorical estimate for living in the inner 5-km zone as an attributable risk fraction would attribute 29 out of 77 observed cases (38%; 95% CI [24%;61%]) in 1980–2003 to having lived in that zone representing 0 2% (95% CI [0 1%;0 4%]) of all 13,373 childhood cancer cases under 5 years in 1980–2003 in Germany.

4 2. *Previous studies*

The associations found in our study were strongest for leukaemia in children under 5 years of age living within a 5-km zone of a nuclear power plant. This group had yielded the most notable exploratory result in the first of the previous ecological studies [7,8]. It has to be pointed out that the cases of this study diagnosed in the study years 1980–1995 had already been included in the previous studies and that the results pre-

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Table 4 – Estimated odds ratios from the conditional categorical and continuous logistic regression models for all cancers and for diagnostic groups

	OR for inner 5 km derived from continuous model[a]		Modelling 5-km distance categorically		OR for inner 10 km derived from continuous model[b]		Modelling 10-km distance categorically	
	OR	Lower one-sided 95% confidence limit	OR	Lower one-sided 95% confidence limit	OR	Lower one-sided 95% confidence limit	OR	Lower one-sided 95% confidence limit
All malignancies	1 47	1.16	1.61	1.26	1 23	1 09	1 18	1 03
Diagnostic groups								
Leukaemia	1.76	1.24	2.19	1.51	1 37	1 12	1 33	1.06
Central nervous system tumours	0 72	0.33	0.81	0 37	0 83	0.54	1 03	0 71
Embryonal tumours	1 19	0.76	1.20	0.75	1 10	0.86	1 05	0.81

Cases diagnosed/controls resident in the study area in 1980–2003.
OR: odds ratio.
a Using the mean proximity measure of the controls in the inner 5-km radius: 1/(distance in km) = 0.3245.
b Using the mean proximity measure of the controls in the inner 5-km radius: 1/(distance in km) = 0.1786.

Table 5 – Results of studies on all malignancies under the age of 5 years in the vicinity of nuclear power plants performed at the German Childhood Cancer Registry: previous studies 1 and 2 compared to recent study (categorical estimates)

Study periods	Relative risk estimate/Odds ratio	95%-confidence interval/lower one sided 95% confidence limit	Cases 5-km radius
Previous studies			
1980–1990 Study 1	1 43	[0 89;2 43][a]	45
1991–1995 Study 2	0 97	[0 50;1 89][a]	22
1980–1995 Study 1+2	1 24	[0.84;1 85][a]	67
Recent study: Results shown for previous studies' study periods, for the period following the previous studies and for the total study period			
1980–1990 (period of study 1)	1 99	[1.33][b]	31
1991–1995 (period of study 2)	1 41	[0.90][b]	20
1980–1995 (period of previous studies 1 + 2)	1 70	[1.26][b]	51
1996–2003 (period following previous studies)	1 45	[0 96][b]	26
1980–2003 (total recent study period)	1 61	[1.26][b]	77

Relative risks and odds ratios by different study periods in the inner 5 km-radius (periods shown analogous to periods of former studies)
a Relative risk resulting from ecological study, two-sided 95% confidence interval
b Odds ratio resulting from case–control study, lower one sided 95% confidence limit

sented here are consequently not entirely independent Table 5 summarises the findings from the previous studies for all malignancies, cases under the age of five in the inner 5-km zone It compares them with the results of this case–control study split up by the previous study periods (1980–1990, 1991–1995) and separating the new study years (1996–2003) The observed effect estimate is larger in the earliest study period (Table 5) This corresponds to the observation, that the regression parameter is larger in the first half of the nuclear power plant operation periods, though not significantly so (Table 3) While the ecological effect estimates are smaller, they are generally in the same order of magnitude (Table 4) It is thus unlikely, that the previous findings were affected by ecological bias in a major way

This issue will be discussed more thoroughly for leukaemia in a separate paper [14]

4.3. *Strengths and weaknesses*

The GCCR, founded in 1980, is a nationwide childhood cancer registry cooperating with all paediatric oncology units and therapy optimisation studies in Germany Registration for cases under the age of 15 is 95% complete since the mid-1980ies [23] Almost all cases are registered with their full address at the date of diagnosis Given this data base, this is one of the largest studies with this objective world wide (1592 cases, including 593 leukaemia cases).

Distance to the nearest nuclear power plant at the date of diagnosis is a crude surrogate for potential exposure to radiation, however, it does not account for topography, weather, vegetation, differences in background radiation, other sources of individual exposure to radiation or the time actually spent by the individual in the home. Information on pre-

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vious residences of the child from the questionnaire could not be used in the analysis due to poor and selective participation in the questionnaire part of the study (see below) The extremely low number of parents reporting occupation in a nuclear installation (0 cases, 4 controls) did not allow evaluating an effect of parental radiation exposure.

The former studies investigated only the inner 15-km zone. In the case control study, the study areas around the nuclear power plants were very large and included cases and controls from up to about 100-km distance from the nuclear power plants, which increases the statistical power slightly. Adding unexposed cases and controls does not, however, cause bias

German nuclear energy providers are required to maintain the exposure of the population below 0 3 mSv/year [24] Compared to this, the annual background radiation exposure estimated for the German population is 1 4 mSv/year. The average annual dose of persons of any age from medical procedures is 1 8 mSv, though this is lower for children (no specific figures given) [25] The actual emissions from nuclear power plants are far lower; e g for a 50-year-old person in 1991 living 5 km from one of the German nuclear power stations included in the study, the expected cumulative exposure to atmospheric discharges would have ranged from 0 0000019 mSv (Obrigheim) to 0 0003200 mSv (Gundremmingen) [26] At these levels of radiation, no detectable effects are expected from the usual models [12 13]

The sensitivity analyses for the various expected and unexpected problems in control recruitment yielded statistically significant regression parameters of a similar magnitude to that reported in Table 2 We conclude that the biases due to these problems were small and the results cannot be explained by the biased control recruitment The specificity of the effect for leukaemia makes it unlikely that biased control recruitment is the explanation for the effects seen in this study The analysis excluding the nuclear power station areas one by one showed that the result is not caused by a specific nuclear power plant

With regard to uncontrolled confounding, there may be other risk factors close to nuclear power stations, although no risk factors of the necessary strength for this effect are known for childhood cancer and specifically childhood leukaemia We saw considerable self-selection by the persons who were to be interviewed, so that those who were interviewed were not representative of the study population as a whole, particularly with respect to their distance distribution from nuclear power plants. Assessing the change in the (biased) estimate by confounders as planned nevertheless, showed that none of them changed the distance parameter estimate by more than one standard deviation This is true for all diagnoses investigated in the survey subset of the study as well as for diagnosis subgroups.

4 4. *International context*

The best-known quantitative summaries of current knowledge on the effects of environmental low-dose radiation effects are based mostly on adult data Children are included, but their small number makes a negligible impact These models deal mainly with solid tumours and adult leukaemia, applying them to children or to acute leukaemia should be done with caution [12 13] The BEIR Committee has refused to assess studies of residents living near nuclear facilities, many of which had childhood cancer as the main objective, because of lack of actual data on exposure They are reviewed, but not summarised or discussed beyond this [12] Many other studies have addressed the health risks of children of parents exposed (occupationally or to radiation from the atomic bombs dropped in Hiroshima and Nagasaki) and these are therefore not comparable. If we had nevertheless applied the models proposed for adults, no detectable effect would have been predicted

A French study of a design similar to that of the earlier incidence studies in Germany, in which SIR were computed for communities by distance, found no elevated SIR for leukaemia amongst children under five living in the inner 5-km zone of French nuclear installations (670 cases, SIR 0 97; 95% CI [0 69;1 33]) [27] When this study was repeated, with distance replaced by estimated gaseous discharges, neither the highest exposure category (⩾0 001 mSv/year; 750 cases, SIR 0 93; 95% CI [0 30;2 17]), nor any other exposure category was associated with an elevated SIR for leukaemia [28] A recent study addressed the risk for leukaemia of children under six years of age in countries near the Chernobyl site (421 cases), on the basis of estimated cumulative doses from gaseous discharges and from food, derived from individual residence histories This study estimated an OR of 1 46 (95% CI [1 00;2 12]) for doses between 1 and 5 mGy compared with <1 mGy [29] 1 mGy is a far higher exposure than from a nuclear power plant under regular conditions in Germany [26]

For some of the nuclear power plants in relatively isolated communities in northern Britain, Kinlen suggested population mixing as a potential cause of elevated leukaemia risks [30] We inspected migration figures,[31] but there are no indications that any of the nuclear sites investigated here were particularly isolated and all have average migration at any time during the study period This is not to say that infective causes may not in principle be an alternative explanation for the patterns we see in this study.

5. Conclusion

The design of this study aimed to clarify issues raised by previous ecological studies in Germany by using the same data plus more recent cases in a case–control study assigning individual distance estimates (as compared to community based zones) In Germany 1980–2003 we see an increased risk for cancer in children under 5 years of age, particularly leukaemia, when living in proximity (<5 km) to a nuclear power station This observation is not consistent with most international studies, unexpected given the observed levels of radiation, and remains unexplained We cannot exclude the possibility that this effect is the result of uncontrolled confounding or pure chance

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The research group is independent from the funding agency. The authors are responsible for the content.

Conflict of interest statement

All authors declare that they have no conflict of interest and no organisational, personal or financial connection with other people or organisations that could inappropriately influence this work.

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Fact Sheet: The KiKK Study Explained

Background

In 2003, the German Federal Office for Radiation Protection (BfS), in response to concerns resulting from previous German Childhood Cancer Registry (GCCR) studies (1, 2, 3), initiated a case-control study of children less than 5 years of age living within 5 km of a nuclear power plant (NPP). This study, named the *Kinderkrebs in der umgebung von Kernkraftwerken* (KiKK) study, looked at all childhood cancer cases diagnosed between 1980 and 2003 compared to control children without cancer. The KiKK study (4) used distance from a NPP as a substitute for radiation exposure to evaluate the risk of childhood cancer and focused on cases within the 5 km zone of the 16 NPPs in Germany.

The main finding was an increased risk of leukemia in children less than five years of age with decreasing distance from a NPP. The authors of this paper caution the readers that their findings are unexpected given the very

low observed levels of radiation and they state that the cause of childhood leukemia remains unexplained and may be due to uncontrolled confounding or pure chance (4).

CNSC Perspective

CNSC staff have analyzed the KiKK and other recent scientific literature regarding the sources and health effects of radiation exposure. The reason for the increased childhood leukemia rate around German NPPs is unclear. However, the increased rates could not be explained by the actual radiation emissions from the German NPPs.

Since childhood leukemia is thought to be caused by several factors, other factors may have been responsible for the observed results. Therefore, other factors in the environment need to be considered. More extensive, interdisciplinary research on the causes and mechanisms of the development of childhood leukemia is required to fully understand the disease.

What follows are the details of recent key international studies that have examined the relationship of distance from nuclear power plants and leukemia in children.

KiKK Study Follow-Up

Kaatsch *et al* (2008) (6)

Kaatsch *et al* (6) conducted a follow-up to the initial KiKK study. The study focused on the 593 childhood leukemia cases (rather than all malignancies) registered between 1980 and 2003 at the GCCR in children who were under

5 years of age and living near one of the 16 nuclear power sites when diagnosed. Distance from a NPP served as a proxy for the radiation exposure caused by the facilities.

Kaatsch *et al* (6) indicate that "When leaving each nuclear power plant out of the calculations one by one, the results change only marginally: the regression coefficients vary between 1.39 and 2.09, all results remain statistically significant." Thus, results could not be attributed to a single reactor site, but were consistent for all 16 nuclear power sites in total.

However, the authors then state: “The maximum deviation from the overall coefficient of 1.75 is seen when analyzing the data excluding the nuclear power plant Krümmel (regression coefficient: 1.39 with lower 95% CL of 0.14) (6)." A well-known childhood leukemia cluster started in 1990 and continued to at least 2005 in the surrounding area of Krümmel. Thus, the estimated risk in the 5 km ring was highly sensitive to whether or not the Krümmel NPP was included in the KiKK study (7, 8).

The authors noted that an increasing trend with the inverse distance from the sites, considered as a continuous variable, was not detected when the distance was categorical (6). Likewise, the risk estimates obtained in the incidence analysis (9) also appeared to be lower than those obtained with the case-control approach (6). The authors also indicate that the results were largely attributed to cases in previous studies of the GCCR from 1980 to 1990 (1) and 1991 to 1995 (2), especially in the 5 km zone as there was overlap between these studies and the more recent one (1980-2003). In fact, the risk estimate of 1.78 (lower 95% CL: 0.99) determined that the most recent time period (1996-2003) was lower than in the previous time periods, and only a tendency towards an increase in risk with closer residential proximity was seen (6).

The strength of this study was the availability of individual measurements of residential proximity to the nearest NPP for each subject based on the residence at time of diagnosis. However, individual radiation exposures from the NPP emissions, other sources of radiation exposure (i.e., medical exposures), time spent at places other than their home address, and residential history of the study subjects was not available.

The authors noted the association may be influenced by other factors related to childhood leukemia (i.e., social class, pesticides, factors influencing immunological factors, exposure to other ionizing radiation). Unfortunately, the response rates to the study interview were very poor, especially in the 5 km zone, so no conclusions on the relationship between potential cofounding risk factors and the reported finding could be drawn. Without information on any of the possible causes of childhood leukemia, it is not possible to make any inference on risks.

The authors noted that the radiation exposure near a NPP in routine operation is extremely small compared to exposure to ionizing radiation of the general public from other sources (1,000-100,000 less than the annual average natural radiation (1.4 mSv) or medical (1.8 mSv) exposures in Germany). The authors did not attribute the increased childhood leukemia to the NPP emissions and noted the findings were not consistent with current radiation biological and epidemiological evidence (10). The authors concluded the observed positive distance trend remains unexplained and no statements on the cause of the increase cancer rates can be made (6).

Further Analyses

Grosche (2008) (11)

Grosche (11) conducted a further analysis of the data used in the KiKK case-control study and concluded that the observed trend in risk decreased over time, indicative of some agent being involved for which the prevalence is reduced over time. However, currently, there is no clear explanation for a causal relationship between any chemical or physical risk factor and the observed risk.

COMARE (2011) (7)

The 14th Committee on Medical Aspects of Radiation in the Environment (7) also observed that for 1991-1995 and 1996-2003, the evidence for an increased risk of leukemia in young children living within the 5 km zone of German NPPs, excluding Krümmel, is only weak. Nonetheless, the Krümmel cluster could not be explained by the routine radioactive discharges.

German Radiological Protection Commission (SSK, 2008) (12)

The German Radiological Protection Commission (SSK) appointed an interdisciplinary international working group of experts to review the current knowledge on radiation and leukaemia, to summarize an independent reanalysis of the KiKK data, and to make a final evaluation of the study's overall design, conduct, results and interpretation.

The experts noted several limitations of the KiKK study, such as the lack of information on exposure and other risk factors known to be related to childhood leukaemia. The evidence for increased childhood cancer risk was

only limited to the 5 km zone and the risk decreased with time. They stated that distance from a NPP is not suitable for establishing a correlation with radiation exposure from NPPs; and the actual exposures from the German NPPs are lower by a factor of 1,000 than those that could cause the risks reported by the KiKK study. Likewise, the natural radiation exposure within the study area, medical radiation exposure, and any fluctuations in these exposures are both greater by several orders of magnitude than the additional radiation exposures caused by the relevant NPPs.

A reassessment of the KiKK results also showed that the marked impact of the urban/rural status of the residence area on the estimated risk (12). Thus, the international expert working group concluded that the reasons for the increased childhood leukemia rate that the KiKK study observed remain unclear. Since leukemia is caused by multiple factors, numerous influencing factors could have been responsible for the observed result (12, 13).

Little *et al* (2008) (14) and Laurier *et al* (2008) (15)

Little *et al* (14) and Laurier *et al* (15) reviewed the KiKK study and came to similar conclusions that the excess leukemia in children aged 0-4 years around the 5 km zone of the German NPPs was not supported by studies from other countries and to date, nothing can explain the observed excess. The most likely explanation is the hypothesis of an infectious agent associated with population mixing around nuclear sites (16); however, the infectious agent has yet to be found. The 14th Committee on Medical Aspects of Radiation in the Environment (7) came to similar conclusions.

Other Studies

Since the KiKK study was published, several other studies in the United Kingdom (17), France (18), Switzerland (19) and Finland (20) have come to the conclusion that there is no relationship between childhood leukemia and distance from a NPP. While the French Geocap study (8) did find a relationship between distance and childhood leukemia using a case-control methodology, the use of a dose-based geographic zoning (DBGZ) methodology yielded very different results for the same data. Using DBGZ, the odds ratio and standardized incidence ratio was close to one in all of the dose categories indicating that the association cannot be explained by the NPP gaseous discharges (8, 21).

Conclusion

When drawing conclusions about the health effects of radiation, it is important to consider all the evidence. Thus any claims of a link between childhood leukemia and radiation from nuclear power plants are unfounded and not supported by a wealth of evidence resulting from multiple epidemiology studies.

The CNSC keeps up-to-date on emerging research to ensure the most recent information, based on sound science, is considered in protecting the health and safety of the public, workers and the environment. CNSC staff contributes to the scientific radiation knowledge through their roles on international scientific committees, and through the conduct of Canadian studies of the relationship between ionizing radiation, workers and members of the public.

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Radiation Exposure and Cancer Incidence (1990 to 2008) around Nuclear Power Plants in Ontario, Canada

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ABSTRACT

Radiation doses and cancer incidence among the population living within 25 km of three nuclear power plants (NPPs) in Ontario, Canada were investigated for the period 1985 to 2008 for radiation exposure and 1990 to 2008 for cancer incidence. This study design provided at least a five-year latency period between potential radiation exposure and cancer incidence. Around the NPPs, the incidence of childhood cancers, leukemia and non-Hodgkin lymphoma, in young children (aged 0 - 4) was lower than the general Ontario population, but not statistically so. Cancer incidence in children aged 0 - 14 was similar to the Ontario population. Overall, for all ages there was no consistent pattern of cancer incidence (all cancers combined and radio-sensitive cancers) across the population living within 25 km of the three NPPs. Some types of cancers were statistically higher than expected, others were statistically lower than expected, and others were similar to the general Ontario population. Although variations in all cancers combined and radiosensitive cancers were found in this study, the pattern was found to be within the natural variation of cancer in Ontario. During the period 1985 to 2000 (Pickering and Bruce NPPs) and 1985 to 2002 (Darlington NPP) radiation doses to members of the public from the operation of the NPPs, estimated on the basis of a hypothetical individual at the facility fence line, were ≤0.052 mSv/year; while for the period 2001 to 2008 (Pickering and Bruce NPPs) and 2003 to 2008 (Darlington NPP) radiation doses, more realistically estimated using the critical group concept for six age classes, were ≤0.0067 mSv/year. Hence, public doses from environmental releases of radionuclides from Ontario NPPs represent a very small fraction of natural background radiation (1.338 and 2.02 mSv/year) in the regions where the NPPs are located. Our study shows no evidence of childhood leukemia clusters around the three NPPs and that the incidence of all the cancers investigated for all age groups is within the natural variation of the disease in Ontario. The radiation exposure from NPP operation is a small contributor to the public's total exposure to radiation and is not a plausible explanation for any excess cancers observed within 25 km of any Ontario NPP.

Keywords: Cancer; Childhood Leukemia; Radiation Doses; Population; Nuclear Power Plants

1. Introduction

Several studies have evaluated the relationship between distance from a nuclear facility and cancer incidence, but few studies have assessed the relationship between radioactive discharges or radiation dose to members of the public from a nuclear facility and cancer incidence.

In Germany, a case-control study (1980 to 2003) found a statistically significant excess risk of leukemia among children under 5 years old living within 5 km of a nuclear power plant (NPP) [1,2]. However, an increasing trend with the inverse distance from the sites, considered as a continuous variable, was not detected when the distance was categorical [2]. Likewise, the risk estimates obtained in the incidence analysis [3] also appeared to be lower than those obtained with the case-control approach [2]. The results were largely attributed to cases in previous studies from 1980 to 1990 [4] and 1991 to 1995 [5], especially in the 5 km zone. Likewise, the estimated risk in the 5 km zone was highly sensitive to whether or not the Krümmel NPP was included [6,7]. Individual radiation exposures from the NPP emissions and other sources were not available. The authors concluded the observed positive distance trend remained unexplained and no statements on the cause of the increase cancer rates could be made. A further analysis [8] observed the trend in risk decreased over time, and a reassessment of the results

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showed a marked impact of the urban/rural status of the residence on the estimated risk [9]. An independent review of the study [9] concluded there was no support for a causal relationship between any chemical or physical risk factor and the observed risk of childhood leukemia. Several reviews of this study came to similar conclusions [6,10,11].

Other studies have been conducted in the United Kingdom [12], France [10], Switzerland [13] and Finland [14]. No relationship between childhood leukemia and distance from an NPP was found. A recent study conducted in France used a methodology allowing the assignment of radiation doses from nuclear facilities to the cases of leukemia [7]. This study found a significant relationship between distance and childhood leukemia; however, when dose-based geographic zoning was used, childhood leukemia could not be explained by the radiation exposures from the NPPs' gaseous discharges. Earlier, French studies found no relationship between childhood leukemia incidence and distance from NPPs [10] or radiation exposures in the municipalities near the sites [15].

In Canada, McLaughlin *et al.* [16] examined leukemia mortality (1950 to 1987) and incidence (1964 to 1986) among children aged 0 - 14 within communities near (25 km) two Ontario NPPs (Pickering, Bruce). Childhood leukemia in the vicinity of the Bruce and Pickering NPPs was greater than expected although not statistically significantly so. Prior to the opening of the Pickering NPP (1950 to 1970), the mortality ratio by residence at birth for the 25 km area was also higher than expected. The confidence intervals included the null value and were generally wide because of the small observed and expected numbers of deaths and cases. The results for leukemia in children aged 0 - 4 were similar. When the areas near Bruce and Pickering NPPs were pooled, the evidence became weaker. The statistical power of the study was also limited due to the rarity of childhood leukemia and the small number of observed and expected cases and deaths. In conclusion, there was no statistical evidence the difference was due to anything but the natural variation of the disease.

Also in Canada, rates of cancer incidence and mortality, congenital anomalies and stillbirths were examined from 1981 to 2004 in areas surrounding the Pickering and Darlington NPPs [17]. The authors concluded that although there were some elevated cancer rates (*i.e.*, thyroid, breast, brain, and kidney cancer, and leukemia (excluding CLL)), there was no clear pattern found across time periods, sexes, and for incidence and mortality statistics. All childhood cancer mortality and incidence rates were similar to the Ontario population. All other health indicators were significantly low or at provincial levels. Overall, the results were consistent with an earlier analysis for the region from 1979 to 1993 [18]. In general, disease rates did not indicate a pattern to suggest the Pickering and Darlington NPPs were causing health effects in the population.

To date, no Canadian study of cancer incidence among the population has included an analysis of exposure of members of the public to radioactive emissions from an NPP. In Ontario, twenty nuclear power reactors located on three NPP sites (Pickering, Bruce and Darlington) which began operation between 1971 and 1989. The objective of this work was to conduct an ecological hypothesis-screening study providing radiation dose estimates for members of the public from environmental radiation monitoring data and updated cancer incidence data for populations living within 25 km of the three Ontario NPPs from 1990 to 2008.

2. Methods

2.1. Radiation Doses to Members of the Public Living near Ontario Nuclear Power Plants

Radionuclides released to the environment from Canadian NPPs are listed in **Table 1**.

Data on annual radiation dose assessments for members of the public using internal and external environmental exposure pathways were collected from Ontario Power Generation (OPG) and Bruce Power annual reports [19-34]. Exposure pathways included in the dose assessments were inhalation and ingestion of food and water, exposure from air and water immersion, groundshine, and incidental soil and sediment ingestion. Concentrations of radionuclides in various environmental compartments were obtained from the results of radio-

Table 1. Major radionuclide and radionuclide groups released from Canadian NPPs.

Atmospheric Emissions	Tritium Oxide as water vapor (HTO) Elemental Tritium (HT) Carbon-14 (C-14) Radioactive Iodine (mixed fission products of iodine)[1] Radioactive Particulates (mixture of alpha emitting radionuclides)[2] Noble Gases (mixture of Argon-41, and Xenon and Krypton radioisotopes)
Liquid Effluent Discharge	Tritium Oxide as water (HTO) Carbon-14 (C-14) Gross Beta/Gamma (mixture of beta and gamma emitting radionuclides)

[1]At Pickering A and Pickering B NPPs, radioactive iodine and radioactive particulate emissions, have continually been below limits of detection (limit of detection has ranged from 1.0E+04 Bq per month to 1.0E+07 Bq per month); [2]At Pickering A and Pickering B NPPs, noble gas emissions have continually been below limits of detection (limit of detection has ranged from 1.0E+12 Bq-MeV per month to 1.0E+13 Bq-MeV per month).

logical environmental monitoring programs (REMP). Doses were calculated for members of the public using either a hypothetical individual (1985-2001 for the Pickering and Bruce NPPs; 1985-2003 for the Darlington NPP) or critical groups (2001-2008 for the Pickering and Bruce NPPs; 2003-2008 for the Darlington NPP). **Table 2** summarizes the environmental media and radionuclides monitored through the REMP and used in the dose calculations.

While the use of a hypothetical individual resulted in very conservative radiation dose estimates (individual living at the NPP fence line and consuming exclusively local food and water), critical group doses were more realistic. A critical group represents a uniform group of people whose location, age, diet, lifestyle, etc., caused them to receive higher doses than other groups in the exposed population. The three NPPs each have multiple potential critical groups. At each critical group location, age classes (adult, 15-year-old, 10-year-old, 5-year-old, 1-year-old, and nursing infant) have been attributed characteristics to reflect different diet consumption rates, and lifestyle habits. Site-specific surveys of residents and local farms surrounding the NPPs were conducted to obtain information on the characteristics of the potential critical groups [35-43]. Surveys generated information on the number of people living at each residence or farm, their age distribution, sources of water for various uses, as well as the proportion of local and store bought food consumed. If information could not be obtained from surveys, default values in the CSA standard N288.1 [36,37] were used.

Table 2. Environmental media and radionuclides monitored for the purpose of estimating doses to members of the public.

Pathway	Radionuclides Measured[1,2,3]
Atmospheric Sampling	HTO, C-14 Boundary External Gamma from Noble Gases (mainly Ar-41, Xe-133, and Xe-135) Ir-192, I-131[4] HTO and Gross Beta from precipitation and dry/wet fallout
Terrestrial Sampling	Garden and Inland Soils: Cs-137, Cs-134, Co-60 Local Fruits, Vegetables, Silage and Honey: HTO, C-14 Milk and Animal Feed: HTO, C-14, I-131[5]
Aquatic Sampling	Lake Water and Water Supply Plants: HTO, Gross Beta Well Water: HTO, Gross Beta Fish: HTO, C-14, Gamma Spectrometry (Cs-137, Cs-134, Co-60) Sediment: C-14, Cs-137, Cs-134, Co-60 Beach Sand/Silt: Gamma Spectrometry (Cs-137, Cs-134, Co-60)

[1]Cs-134 and Co-60 measured in the environment are solely from reactor operation; [2]C-14 and Cs-137 measured in the environment are from both reactor operation and nuclear weapon test fallout; [3]Organically Bound Tritium is taken into account in model equations based on relationship with HTO; [4]At all Ontario NPPs Radioactive Iodine measured in ambient air has consistently been too low to measure [19-34]; [5]At all Ontario NPPs radioactive Iodine measured in milk samples have consistently remained below detection limits (limit of detection ranges from 0.1 Bq/L - 0.2 Bq/L) [19-34].

For each NPP, all annual total dose data for each hypothetical individual or critical group from 1985 to 2008 were compiled [19-34]. The highest annual doses to critical groups were mapped using ESRI® ArcGIS™ Desktop version 10.1 (ArcGIS) mapping software. A set of maps was generated, one for each NPP, showing the highest doses received to each potential critical group over the study period. A polygon shape file was created with boundaries extending at a radius every 5 km up to 25 km from the NPP, corresponding to the geographic distribution of cancer incidence data used for this study. The Darlington and Pickering NPPs are on the shore of Lake Ontario and the Bruce NPP is on the shore of Lake Huron; therefore, a large portion of the 25 km radius included water.

For each NPP, the year with the highest critical group dose within the study period were identified and a second set of maps was created. For each NPP, atmospheric dispersion plumes for each radionuclide were generated, based on the atmospheric emissions data for the given year. The dispersion plumes were produced using the EcoMetrix® IMPACT™ (IMPACT) modelling software, which is based on CSA standard N288.1 [36,37]. Site-specific weather data and release characteristics obtained from each NPP were used in the model (available upon request). From the model outputs, a dose plume was generated in ArcGIS using air inhalation and immersion dose conversion factors. For each NPP, the dose plume represents a hypothetical annual dose that would be received by an individual due to air immersion and inhalation if that person spent the entire year outdoors at a particular location (full time occupancy).

The following equation was used to calculate the dose due to air immersion and air inhalation:

$$X_9 = X_0 \cdot P_{01}\left[P(e)_{19} + P(i)_{19}\right]$$

where

X_9 is the dose received ($\mu Sv \cdot yr^{-1}$);

X_9 is the air emission release rate ($Bq \cdot s^{-1}$);

P_{01} is the dilution factor due to atmospheric dispersion ($s \cdot m^{-3}$);

$P(e)_{19}$ is the transfer parameter for dose to humans via air immersion ($Sv \cdot yr^{-1} \cdot Bq^{-1} \cdot m^3$);

$P(i)_{19}$ is the transfer parameter for dose to humans via air inhalation ($Sv \cdot yr^{-1} \cdot Bq^{-1} \cdot m^3$).

Parameters and assumptions used in the atmospheric dispersion plume modelling and dose assessment are

based on air emission data for each radionuclide and average annual Triple Joint Frequency meteorological conditions (*i.e.*, wind speed, stability class, and wind direction) and release characteristics (*i.e.*, stack height, stack exit velocity, gas and ambient temperatures). This information came from industry reports formally submitted to the national regulator, the Canadian Nuclear Safety Commission (CNSC) [26,29,31,39-43]. Each report has undergone a critical technical review by the CNSC. Transfer parameters, $P(e)_{19}$ and $P(i)_{19}$ and dose conversion factors, DCF_a and DCF_i for air immersion and air inhalation used in the dose assessment were adopted from CSA standard N288.1 [36,37].

2.2. Cancer Incidence in Members of the Public Living near Ontario Nuclear Power Plants

Cancer incidence data collected by the Ontario Cancer Registry (OCR) [44] from 1990 to 1991 and the Canadian Cancer Registry (CCR) [45] from 1992 to 2008 were obtained for the following: all cancer sites combined; cancer of the thyroid, lung and bronchus; female breast; ovary; esophagus; stomach; colon and rectum; bladder; brain and other nervous system; liver; and leukemia and non-Hodgkin lymphoma. These types of cancer were chosen because they are sensitive to radiation [46-48]. Disease coding was based on the 3rd edition of the International Classification of Diseases for Oncology [49]. Cases coded to the 2nd edition were converted.

Population counts from the Census of Canada [50] for the census years 1991, 1996, 2001, and 2006 were obtained for the areas within 25 km of the three NPPs in Ontario (data not shown). The tables prepared in this study start in 1990 since it was the first year that Cancer Care Ontario (CCO) data had sufficient completeness for postal code information.The geographical areas in our study included combined municipalities in the 25-km radius from an NPP, based on its latitude and longitude. This study focused on a 25-km radius from each Ontario NPP to be consistent with a previous study [16] and because of the low population density around the Bruce NPP. This is less specific than information at the individual census subdivision (CSD) level and not as broad as the census division (CD) level.

CCO conducted a data quality study to investigate residence code errors at the census division (CD) and census subdivision (CSD) level through a record linkage to the Ontario property assessment files. The accuracy of the CSD of residence was 84.4% whereas the accuracy of the CD level of residence was 97.9% for the 1025 cases having this information [51]. The CD is considered the gold standard.

Standardized incidence ratios (SIRs) (O/E) based on residence at diagnosis, observed (O) and expected (E) number of cancer cases and 95% confidence intervals (CIs) were calculated [52] based on the age- and sex-specific rates of the comparison population (*i.e.*, Ontario) for the corresponding period (1990 to 2008) for the 25 km radius of each NPP. Internal calculations of observed and expected cases were stratified by five-year age groups and periods, and controlled for socio-economic status using income quintile.

The statistical power of this study depends on the statistical significance criterion used, the magnitude of the effect of interest, and the sample size. Table 7.2 given by Breslow and Day [53] was used to calculate the power using 80% as a standard for acceptance [54]. Using Ontario as the reference population and the expected cases for leukemia (all ages, both sexes combined) for people living within 25 km of the Bruce NPP (which had the smallest population) for example, the probability (%) of obtaining a result significant at the 0.01 level (one sided) of the expected value (E) of 70 (68.0 actual expected cases) assuming no excess risk, and of the true R (or SIR in our case), the sample power for R = 1.2 is 24%. For childhood cancer (leukemia and NHL) near Bruce NPP at a significance of 0.01, and E of 5, (5.2 actual) assumeing no excess risk, and a true R, the sample power for R = 1.5 is only 8.0%. As a result, the small population size and the rareness of some cancers limited the statistical power of our findings among the population living near Bruce NPP. This was generally not an issue near Darlington and Pickering NPPs which had large observed and expected numbers of cancer cases.

Age-standardized incidence rates (ASIRs), per 100,000 population, were calculated using the direct method, which involves weighing the age-specific rates for each of the age groups (<1, 1 - 4, 5 - 9 ⋯ 80 - 84, 85+) according to the age distribution of the standard 1991 Canadian population. The 95% CIs are not provided for the ASIRs when the number of rounded cases is ≤ 5 since the approximation used is less accurate for a small number of cases. SIRs were also calculated at the CD level by cancer site and for all ages and both sexes combined, for Durham Region (location of Pickering and Darlington NPPs) and Bruce County (location of Bruce NPP) using Ontario rates as the comparison population. This provided an additional comparison of cancer incidence around the NPPs with that of the 25 km radius analysis.

3. Results

3.1. Radiation Doses to Members of the Public Living near Ontario Nuclear Power Plants

Data on radiation doses to members of the public were obtained for the period 1985 to 2008 to provide exposure

information during a minimum 5-year latency period from the start of the cancer incidence data (1990-2008). Annual doses to hypothetical individuals varied from 0.052 to 0.004 mSv and from 0.016 to 0.002 mSv between 1985 and 2000 for the Pickering and Bruce NPP respectively. Annual doses for a hypothetical individual at the Darlington NPP from 1985 to 2002 were slightly lower and ranged from 0.010 to 0.001 mSv.

Tables 3-5 present the highest annual radiation dose to each age class for each critical group at each NPP over the study period. The highest estimated dose received to a critical group over the study period was in 2005 for the Pickering NPP, 2003 for the Darlington NPP and 2008 for the Bruce NPP. For comparison purposes, the annual dose from natural background radiation at each site is also presented. Radiation doses to members of the public from the operation of Ontario NPPs (represented by conservatively estimated doses to critical groups (≤ 0.0067 mSv/year)) are much less than the difference in natural background radiation between the Darlington/Pickering area and the Bruce area (0.682 mSv/year) and hence only represent a very minor contribution to the public's overall radiation exposure.

Table 3. Highest Estimated Annual Dose to Potential Critical Groups Age Classes Surrounding the Pickering NPP (2001-2008).

Potential Critical Groups at Pickering NPP	Highest Annual Dose (mSv) to Each Age Group					
	Nursing Infant	1 year old	5 years old	10 years old	15 years old	Adult
Farm Residents	0.0020	0.0012	0.001	0.0011	0.0012	0.0015
Dairy Farm Residents	0.0016	0.0018	0.0012	0.0012	0.0012	0.0016
Sport Fishers	0.0008	0.0004	0.0004	0.0005	0.0006	0.0006
Urban Residents	0.0022	0.0019	0.0013	0.0015	0.0016	0.0025
C2 Correctional Institution	NA	NA	NA	NA	0.0034	0.0037
Industrial Workers	NA	NA	NA	NA	NA	0.0041
Squires Beach Residents	0.0052	0.0033	0.0031	0.0035	0.0036	0.004
C1 Correctional Institution	NA	NA	NA	NA	0.0061	0.0067
Annual Dose from Natural Background	1.338	1.338	1.338	1.338	1.338	1.338

NA: not applicable

Table 4. Highest Estimated Annual Effective Dose to Potential Critical Group Age Classes Surrounding the Darlington NPP (2003-2008).

Potential Critical Groups at Darlington NPP	Highest Annual Dose (mSv) to Each Age Group					
	Nursing Infant	1 year old	5 year old	10 year old	15 year old	Adult
Rural Residents	0.0010	7E-04	0.0006	0.0007	0.0006	0.0008
Bowmanville Residents	0.0006	4E-04	0.0003	0.0004	0.0004	0.0004
Oshawa Residents	0.0006	3E-04	0.0003	0.0003	0.0003	0.0003
Campers	0.0004	3E-04	0.0003	0.0003	0.0003	0.0004
Non-Dairy Farm Residents	0.0017	0.001	0.0012	0.0012	0.0012	0.0009
Dairy Farm Residents	0.0008	0.001	0.0009	0.0008	0.0008	0.0007
West/East Beach Residents	0.0012	8E-04	0.0008	0.0009	0.0009	0.001
Sport Fishers	0.0001	1E-04	0.0001	0.0001	0.0001	0.0001
Industrial/ Commercial Workers	NA	NA	NA	NA	NA	0.0003
Annual Dose from Natural Background	1.338	1.338	1.338	1.338	1.338	1.338

NA: not applicable

The relative contribution of different radionuclides to the total dose was analyzed. Doses from tritium are higher in adults than in children or infants due to higher inhalation rates, whereas the reverse is observed for doses due to noble gases (as a result of increased shielding due to higher assumed body fat in adults).

Critical group doses for Pickering (2005), Darlington (2003), and Bruce (2008) were analyzed for spatial relationship between dose and distance from the three NPPs (**Figures 1-3**). The analysis revealed that the highest doses were not necessarily associated with critical groups closest to the NPP. For example, residents living closer to the Pickering NPP (such as the non-dairy-farm resident) have lower doses (0.0011 mSv) than the dairy-farm residents living several km further away (0.0013 mSv). This was also observed when comparing the doses to urban residents (0.0020 mSv) with those of residents of the correctional institution (0.0022 mSv). At the Darlington NPP, the dairy-farm residents also have a lower dose (0.0007 mSv) than the rural residents (0.0009 mSv) located further away. Sport fishers near both the Pickering and Darlington NPPs have the lowest doses of all the critical groups, as they are expected to spend at most 1% of the year at the fishing location. Similarly industrial and commercial workers are expected to spend only 20% of the time at the critical group location, also resulting in lower doses. Residents living within 5 km of

Table 5. Highest Estimated Annual Dose to Potential Critical Group Age Classes Surrounding the Bruce Power NPP (2001-2008).

Potential Critical Groups at Bruce Power NPP	Highest Annual Dose (mSv) to Each Age Group					
	Nursing Infant	1 year old	5 year old	10 year old	15 year old	Adult
Scott Point Residents	0.00151	0.00245	0.00211	0.00167	0.00168	0.00234
Baie du Dore Residents	0.00215	0.00174	0.00217	0.00238	0.0024	0.0027
Trailer Park Albert Street Residents	0.00103	0.00123	0.00108	0.00119	0.00119	0.0014
South of site Residents	0.00100	0.00152	0.000977	0.00103	0.00101	0.00161
Inverhuron Residents	0.00209	0.00116	0.00212	0.00233	0.00236	0.00268
Dairy Farm South of Tiverton Residents	0.00197	0.00071	0.00163	0.00162	0.00147	0.00185
Farm nearest Bruce A Residents	0.00111	0.00162	0.00112	0.00117	0.00112	0.0017
Farm nearest Bruce B Residents	0.00181	0.00131	0.00177	0.00185	0.0018	0.00227
Bruce Eco-Industrial Park Workers	NA	NA	NA	NA	NA	0.000285
Annual Dose from Natural Background	2.020	2.020	2.020	2.020	2.020	2.020

NA: not applicable.

the Bruce NPP (0.0012 mSv) have lower doses than residents who lived further away (0.0021 mSv). Both groups are non-farm residents with the same dietary characteristics (e.g., food coumption rates; proportion of local vs. store-bought food). The difference in doses is due primarily to differences in location relative to prevailing wind conditions.

Figures 1-3 overlay onto the year with the highest critical group doses the hypothetical atmospheric dose plume for full time occupancy of an infant, child and adult within the plume. The high value represents the dose from inhalation and immersion for full time occupancy at the stack and the low value bounds the fully dispersed atmospheric release. These dose plumes, based on site-specific average annual weather data, clearly indicate a plume extending towards and over the lake, and generally away from populated areas. The dose estimates in the dispersion plumes are higher than critical group doses not only because of the hypothetical full time occupancy in the plume but also because the IMPACT software assumes that the stack is at ground level. Actual emissions from the three NPPs are released from stacks at elevations greater than 10 m, allowing for increased air dispersion before reaching the ground (point of impingement).

3.2. Cancer Incidence in Members of the Public Living near Ontario Nuclear Power Plants

Cancer incidence data were collected for all cancer sites combined and for cancer sites sensitive to radiation. Incidence data were analyzed for the following age groups: 0 - 4, 0 - 14, 0 - 24, 25 - 64, 65+ and 0 - 65+ when the number of cases was sufficient. A blank is given if the number of cases is less than 6 and, therefore, not reported.

Table 6 shows that the SIRs for childhood cancer (leukemia and non-Hodgkin lymphoma) among children aged 0 - 4 living within 25 km of the Pickering and Darlington NPPs were lower than expected for the Ontario population but not statistically significantly so. Similarly, the incidence of childhood cancer in children aged 0 - 14 living near the three NPPs was similar to Ontario. Near the Bruce NPP, no information was available for young children (aged 0 - 4) because there were fewer than 6 cancer cases from 1990 to 2008. Similarly, for children aged 0 - 14, leukemia and non-Hodgkin lymphoma were combined to preserve confidentiality of observed cases fewer than 6.

Table 7 shows the results for all cancer sites combined and leukemia for those aged 0 - 24, 25 - 64, and 65+. Other cancer sites were not provided for those aged 0 - 24 since, in general, few cases were observed; especially near Bruce NPP. For all cancer sites combined and especially leukemia, the SIRs were either significantly less than 1.0 or similar to Ontario for those aged 0 - 24 living near all three NPPs.

The age groups 0 - 64 and 65+ were used for all other cancer sites. **Tables 8** to **10** present for all three NPPs the SIRs for all the cancer sites, by age group and for both sexes. For all three NPPs, it is very evident that lung and bronchus, female breast and colon and rectum cancer are the most common cancer sites. However, the number of cases varies considerably between the three NPPs due to the large differences in population size of people living within 25 km of Pickering, Darlington and Bruce NPPs (1,580,000; 380,000; and 24,500 respectively, based on the 2006 census year). This is expected, as these are also the most common types of cancer in the province, and in Canada [55]. There was no consistent cancer incidence pattern among people living near the three NPPs. Some types of cancer were statistically significantly higher than expected; however, some types of cancer were statistically significantly lower than expected, and some types

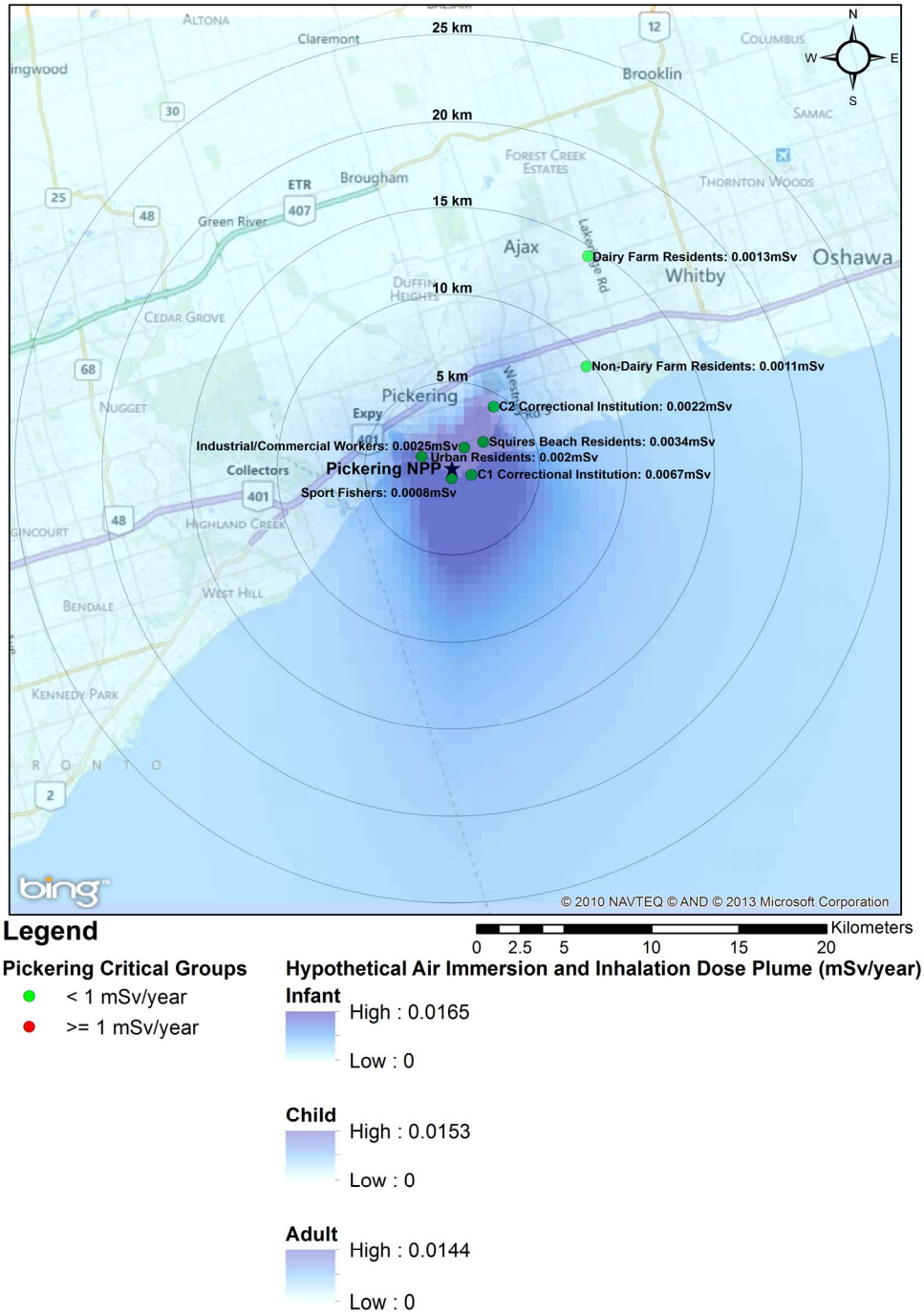

Figure 1. 2005 Critical Group Doses and Hypothetical Air Dispersion Plume for Pickering NPP.

of cancer were the same as expected compared to the general Ontario population.

As seen in **Table 8**, near the Pickering NPP all cancer sites combined had a SIR significantly less than 1.0 (SIR = 0.95, 95% CI: 0.94, 0.95, $p < 0.01$). Similarly, seven cancer sites also had SIRs significantly less than 1.0 (lung and bronchus: SIR = 0.84; female breast: SIR = 0.97; colon and rectum: SIR = 0.92; bladder: SIR = 0.91; brain and other nervous system: SIR = 0.92; esophagus: SIR = 0.84; and leukemia: SIR = 0.89). However, three cancer sites had SIRs significantly greater than 1.0 (thyroid: SIR = 1.41; stomach: SIR = 1.06; and liver: SIR = 1.32). Thyroid and liver cancer were elevated in both males and females and all age groups; whereas, the elevated incidence of stomach cancer was limited to women and those age 65+.

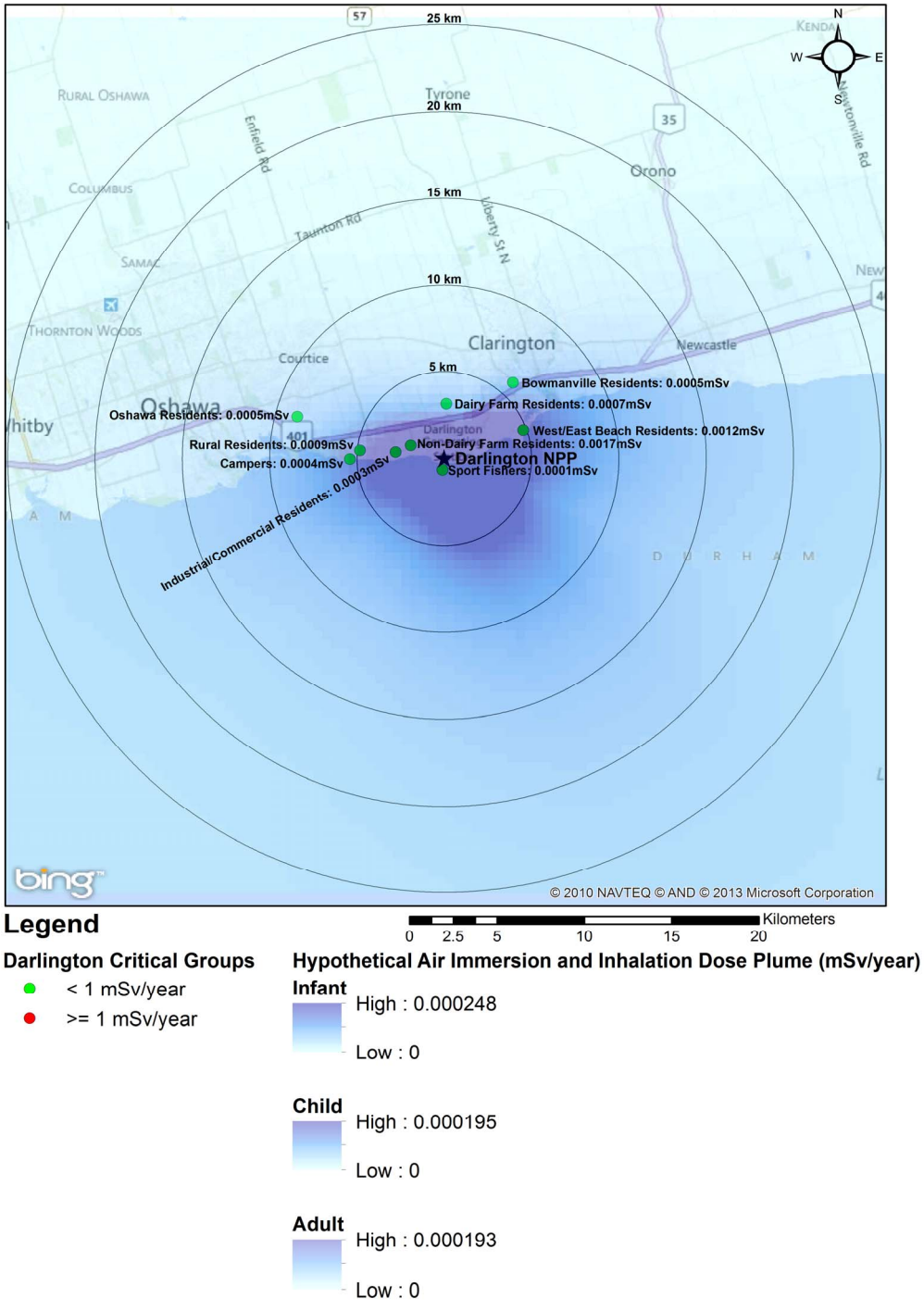

Figure 2. 2003 Critical Group Doses and Hypothetical Air Dispersion Plume for Darlington NPP.

Near the Darlington NPP, the data in **Table 9** show that for all cancer sites combined the SIR is significantly greater than 1.0 (SIR = 1.08, 95% CI: 1.07, 1.09, $p < 0.01$). Five cancer sites also had SIRs significantly greater than 1.0 (lung and bronchus: SIR = 1.12; colon and rectum: SIR = 1.07; thyroid: SIR = 1.08; bladder: SIR = 1.19; and leukemia: SIR = 1.26). While three of these cancers (lung and bronchus, bladder and leukemia) were elevated in males and females and all age groups, the increased incidence of colon and rectum and thyroid cancer were essentially attributable to men and those aged 65+, and all men, respectively. In contrast to Pickering, near Darlington liver cancer had a SIR significantly less than 1.0 (SIR = 0.83).

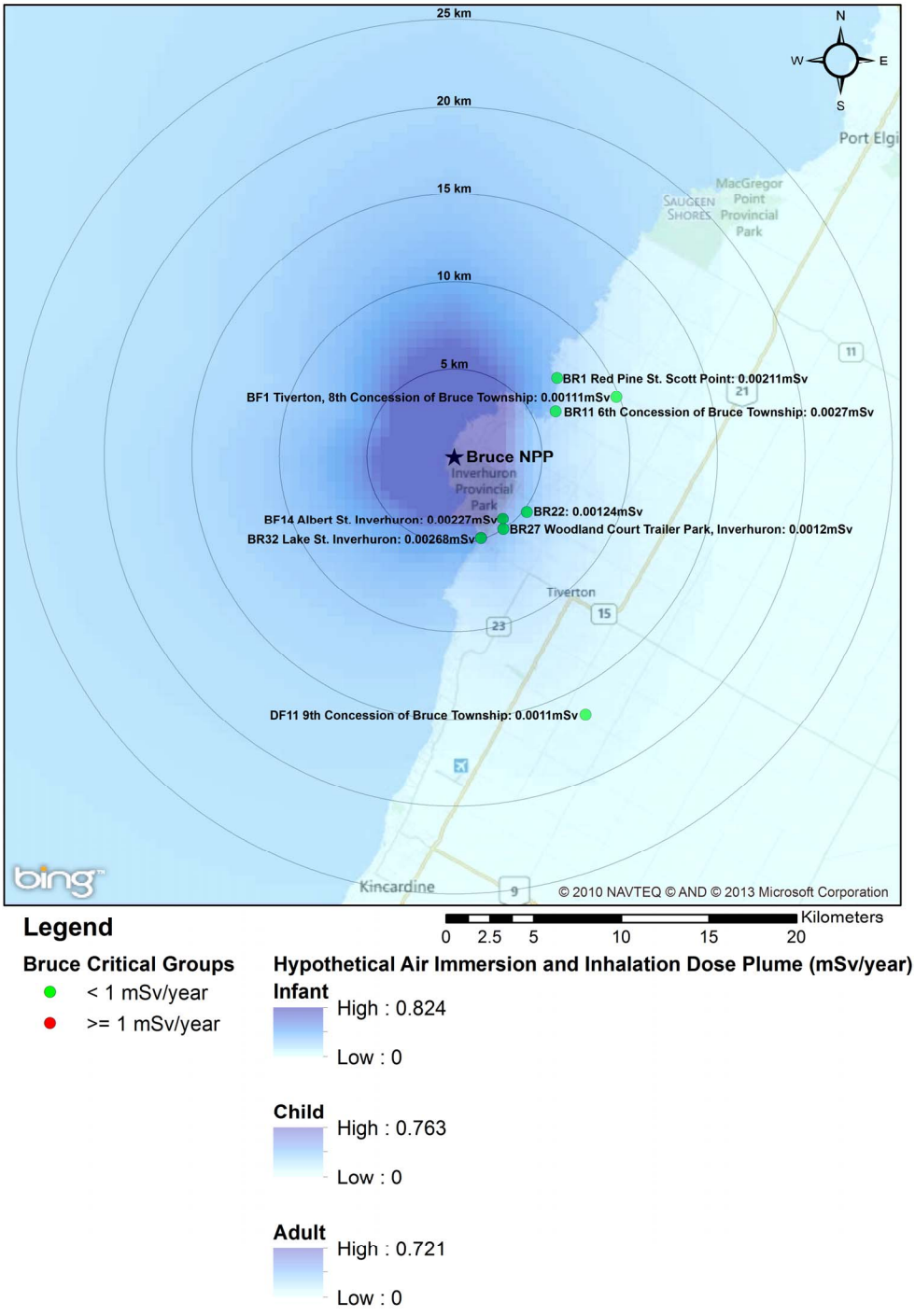

Figure 3. 2008 Critical Group Doses and Hypothetical Air Dispersion Plume for Bruce NPP.

Table 10 shows that near the Bruce NPP, all cancer sites combined had a SIR significantly greater than 1.0 (SIR = 1.09, 95% CI: 1.05, 1.13, $p < 0.01$). While SIRs were significantly greater than 1.0 for two cancer sites (lung and bronchus: SIR = 1.17; colon and rectum: SIR = 1.17), two cancer sites had SIRs significantly less than 1.0 (bladder: SIR = 0.78; and liver: SIR < 1.00). Lung and bronchus cancer was elevated in males in the 0 - 64 age group; whereas the elevated incidence of colon and rectum cancer was attributed to those aged 65+.

The SIR analysis for people living within the 25 km radius of the three NPPs was found, in general, consistent with the CD analysis of SIRs. The incidence of childhood leukemia and non-Hodgkin lymphoma in children

Table 6. Cancer incidence for children aged 0 - 4 and 0 - 14 years living within a 25 km radius of an Ontario NPP at time of diagnosis, 1990-2008.

NPP	Cancer	Age 0 - 4					Age 0 - 14				
		O	E	SIR	95% CI		O	E	SIR	95% CI	
Pickering	Non-Hodgkin lymphoma	8	11.2	0.72	0.31	1.41	42	50.4	0.83	0.60	1.**13**
	Leukemia	123	142.3	0.86	0.72	1.03	261	265.9	0.98	0.87	1.11
	Leukemia and NHL	131	153.5	0.85	0.71	1.01	303	316.3	0.96	0.85	1.07
Darlington	Non-Hodgkin lymphoma		2.7				10	12.9	0.77	0.37	1.42
	Leukemia	34	36.0	0.94	0.65	1.32	74	68.1	1.09	0.85	1.36
	Leukemia and NHL		38.7	<1.00			84	81.0	1.04	0.83	1.28
Bruce	Leukemia and NHL						6	5.2	1.16	0.42	2.51

Table 7. Cancer incidence for all cancer sites and leukemia for people living within a 25 km radius of an Ontario NPP at time of diagnosis, by age group, 1990-2008.

NPP	Cancer	Age	O	E	SIR	SIR flag	95% CI	
Pickering	All sites	Total	103259	109015	0.95	--	0.94	0.95
		0 - 24	1742	1852	0.94	-	0.9	0.99
		25 - 64	46867	49097	0.95	--	0.95	,0.96
		65+	54650	58066	0.94	--	0.93	0.95
	Leukemia	Total	2819	3151	0.89	--	0.86	0.93
		0 - 24	344	349	0.99	°	0.88	1.1
		25 - 64	1061	1163	0.91	--	0.86	0.97
		65+	1414	1639	0.86	--	0.82	0.91
Darlington	All sites	Total	24707	22853	1.08	++	1.07	1.09
		0 - 24	443	438	1.01	°	0.92	1.11
		25 - 64	11413	10597	1.08	++	1.06	1.1
		65+	12851	11817	1.09	++	1.07	1.11
	Leukemia	Total	847	674	1.26	++	1.17	1.34
		0 - 24	92	87	1.06	°	0.86	1.3
		25 - 64	299	254	1.18	++	1.05	1.32
		65+	456	334	1.37	++	1.24	1.5
Bruce	All sites	Total	2570	2362	1.09	++	1.05	1.13
		0-24	31	32	0.97	°	0.66	1.37
		25 - 64	1048	973	1.08	+	1.01	1.14
		65+	1491	1357	1.1	++	1.04	1.16
	Leukemia	Total	80	68	1.18	°	0.93	1.46
		0 - 24		6		°		
		25 - 64		23	>1.00	++		
		65+	37	39	0.95	°	0.67	1.3

$^{++}$ significantly high, **p**-value < 0.01; $^{+}$significantly high, **p**-value < 0.05; ° not significant; $^{-}$ significantly low, **p**-value < 0.05; $^{--}$ significantly low, **p**-value < 0.01.

Table 8. Cancer incidence for people living within a 25 km radius of Pickering NPP at time of diagnosis, by sex and age group, 1990-2008.

Cancer	Age	Observed	Expected	SIR (O/E)	SIR flag	95% CI LL	95% CI UL
All sites	Total	103259	109015	0.95	--	0.94	0.95
	M	51439	55378	0.93	--	0.92	0.94
	F	51820	53637	0.97	--	0.96	0.97
	0 - 64	48609	50949	0.95	--	0.95	0.96
	65+	54650	58066	0.94	--	0.93	0.95
Lung and bronchus	Total	12358	14694	0.84	--	0.83	0.86
	M	6918	8371	0.83	--	0.81	0.85
	F	5440	6323	0.86	--	0.84	0.88
	0 - 64	4347	5493	0.79	--	0.77	0.82
	65+	8011	9201	0.87	--	0.85	0.89
Female breast	Total	15043	15444	0.97	--	0.96	0.99
	F	15043	15444	0.97	--	0.96	0.99
	0 - 64	9599	9478	1.01	°	0.99	1.03
	65+	5444	5966	0.91	--	0.89	0.94
Colon and rectum	Total	8942	9768	0.92	--	0.90	0.93
	M	4415	4910	0.90	--	0.87	0.93
	F	4527	4858	0.93	--	0.90	0.96
	0 - 64	3058	3277	0.93	--	0.90	0.97
	65+	5884	6491	0.91	--	0.88	0.93
Thyroid	Total	3879	2755	1.41	++	1.36	1.45
	M	823	572	1.44	++	1.34	1.54
	F	3056	2183	1.40	++	1.35	1.45
	0 - 64	3338	2384	1.40	++	1.35	1.45
	65+	541	371	1.46	++	1.34	1.59
Bladder	Total	3183	3512	0.91	--	0.88	0.94
	M	2337	2599	0.90	--	0.86	0.94
	F	846	912	0.93	-	0.87	0.99
	0 - 64	950	1062	0.89	--	0.84	0.95
	65+	2233	2450	0.91	--	0.87	0.95
Leukemia	Total	2819	3151	0.89	--	0.86	0.93
	M	1575	1804	0.87	--	0.83	0.92
	F	1244	1347	0.92	--	0.87	0.98
	0 - 64	1405	1512	0.93	--	0.88	0.98
	65+	1414	1639	0.86	--	0.82	0.91
Stomach	Total	2348	2221	1.06	++	1.01	1.10
	M	1446	1411	1.02	°	0.97	1.08
	F	902	810	1.11	++	1.04	1.19
	0 - 64	850	839	1.01	°	0.95	1.08
	65+	1498	1382	1.08	++	1.03	1.14
Ovary	Total	1857	1928	0.96	°	0.92	1.01
	F	1857	1928	0.96	°	0.92	1.01
	0 - 64	1090	1107	0.98	°	0.93	1.04
	65+	767	821	0.93	°	0.87	1.00

Continued

Brain and other nervoussystem	Total	1805	1959	0.92	--	0.88	0.96
	M	962	1068	0.90	--	0.84	0.96
	F	843	891	0.95	°	0.88	1.01
	0 - 64	1188	1295	0.92	--	0.87	0.97
	65+	617	665	0.93	°	0.86	1.00
Liver	Total	1095	832	1.32	++	1.24	1.40
	M	845	622	1.36	++	1.27	1.45
	F	250	210	1.19	++	1.05	1.35
	0 - 64	544	407	1.34	++	1.23	1.45
	65+	551	426	1.29	++	1.19	1.41
Esophagus	Total	898	1068	0.84	--	0.79	0.90
	M	603	766	0.79	--	0.73	0.85
	F	295	302	0.98	°	0.87	1.09
	0 - 64	313	408	0.77	--	0.68	0.86
	65+	585	660	0.89	--	0.82	0.96

++significantly high, **p**-value < 0.01; +significantly high, **p**-value < 0.05; °not significant; -significantly low, **p**-value < 0.05; --significantly low, **p**-value < 0.01.

aged 0 - 14 in Durham Region and Bruce County was similar to Ontario. Breast ovary, stomach, brain and other nervous system, liver and esophagus cancer were either significantly low or similar to Ontario in Durham Region and Bruce County. All cancers sites combined, lung and bronchus, thyroid, bladder, and leukemia were significantly high in Durham Region but either significantly low or similar to Ontario in Bruce County. Colon and rectum cancer was significantly high in Bruce County but similar to Ontario in Durham Region (**Table 11**).

Finally, data on cancer incidence for the cancer sites analyzed in this study across all census divisions (CDs) in Ontario were used for comparison with cancer incidence around the three Ontario NPPs. The data in **Table 12** for all ages (0 - 85+) indicate that there is a large geographical variation in cancer age-standardized incidence rates (per 100,000 population) across the province of Ontario. These data show that the incidence rates for all the cancers found in this study to be significantly greater than expected (*i.e.*, all cancer sites combined, lung and bronchus, colon and rectum, thyroid, bladder, leukemia, stomach, liver) were well within the range of cancer incidence within the province. Likewise, the CDs with the highest cancer incidence rates were not those included in our study (Durham Region, Bruce County).

4. Discussion

The primary strength of this study is its inclusion of dose information for various age groups around each NPP generated from radiological releases and environmental monitoring data. This improves on the recent epidemiological studies that used distance of a residence from an NPP as a surrogate for radiation dose data.

Another strength of this study is the quality of the cancer incidence data. Cancer reporting to the OCR and the CCR is virtually complete and of high quality, since it is routinely checked for accuracy through regular assessments by Statistics Canada and the cancer registries [44,45]. Likewise, the Census of Canada undergoes vigorous quality and confidentiality procedures to assure the accuracy and privacy of census information [50]. Incidence data is preferred to mortality data, since detailed clinical and demographic information is collected on individual cases. If any advances in treatment occur during the study period, mortality would become a less sensitive outcome, whereas incidence would be unaffected. Likewise, cancers with high survival rates, such as thyroid cancer, would not be detected by mortality statistics.

The main limitation of an ecological study is that associations at the population level do not necessarily reflect the biological effect at the individual level [46,52,56]. Uniform doses are assigned to the group, whereas the doses received by individuals vary, and at the individual level are also highly uncertain. The very detailed and conservative public doses used in this study provide assurance that actual residents around the NPPs had lower doses. Ecological studies do not typically provide this type of detailed information.

Radioactive emissions from the three Ontario NPPs result in very low concentrations of radionuclides in the environment around the plants and consequently doses to members of the public from all exposure pathways are a small fraction of the natural background radiation in the

Table 9. Cancer incidence for people living within a 25 km radius of Darlington NPP at time of diagnosis, by sex and age group, 1990-2008.

Cancer	Age	Observed	Expected	SIR O/E)	SIR flag	95% CI LL	95% CI UL
All sites	Total	24707	22853	1.08	++	1.07	1.09
	M	12761	11695	1.09	++	1.07	1.11
	F	11946	11158	1.07	++	1.05	1.09
	0 - 64	11856	11036	1.07	++	1.06	1.09
	65+	12851	11817	1.09	++	1.07	1.11
Lung and bronchus	Total	3375	3016	1.12	++	1.08	1.16
	M	1851	1731	1.07	++	1.02	1.12
	F	1524	1285	1.19	++	1.13	1.25
	0 - 64	1317	1134	1.16	++	1.10	1.23
	65+	2058	1882	1.09	++	1.05	1.14
Female breast	Total	3230	3232	1.00	°	0.97	1.03
	F	3230	3232	1.00	°	0.97	1.03
	0 - 64	2040	2034	1.00	°	0.96	1.05
	65+	1190	1198	0.99	°	0.94	1.05
Colon and rectum	Total	2146	2014	1.07	++	1.02	1.11
	M	1115	1026	1.09	++	1.02	1.15
	F	1031	988	1.04	°	0.98	1.11
	0 - 64	739	697	1.06	°	0.99	1.14
	65+	1407	1317	1.07	+	1.01	1.13
Thyroid	Total	672	620	1.08	+	1.00	1.17
	M	172	131	1.31	++	1.12	1.52
	F	500	489	1.02	°	0.93	1.12
	0 - 64	580	544	1.07	°	0.98	1.16
	65+	92	76	1.20	°	0.97	1.48
Bladder	Total	861	724	1.19	++	1.11	1.27
	M	636	539	1.18	++	1.09	1.28
	F	225	185	1.21	++	1.06	1.38
	0 - 64	301	226	1.33	++	1.19	1.49
	65+	560	499	1.12	++	1.03	1.22
Leukemia	Total	847	674	1.26	++	1.17	1.34
	M	472	389	1.21	++	1.11	1.33
	F	375	285	1.32	++	1.19	1.46
	0 - 64	391	340	1.15	++	1.04	1.27
	65+	456	334	1.37	++	1.24	1.50
Stomach	Total	462	459	1.01	°	0.92	1.10
	M	294	294	1.00	°	0.89	1.12
	F	168	165	1.02	°	0.87	1.18
	0 - 64	163	178	0.92	°	0.78	1.07
	65+	299	281	1.06	°	0.95	1.19
Ovary	Total	433	400	1.08	°	0.98	1.19
	F	433	400	1.08	°	0.98	1.19
	0 - 64	260	235	1.11	°	0.97	1.25
	65+	173	165	1.05	°	0.90	1.22

Continued

Brain and other nervous system	Total	447	427	1.05	°	0.95	1.15
	M	255	236	1.08	°	0.95	1.22
	F	192	191	1.01	°	0.87	1.16
	0 - 64	306	292	1.05	°	0.93	1.17
	65+	141	135	1.05	°	0.88	1.23
Liver	Total	145	175	0.83	-	0.70	0.98
	M	114	131	0.87	°	0.72	1.04
	F	31	43	0.72	°	0.49	1.02
	0 - 64	75	87	0.86	°	0.67	1.08
	65+	70	87	0.80	°	0.63	1.01
Esophagus	Total	240	222	1.08	°	0.95	1.23
	M	167	160	1.04	°	0.89	1.21
	F	73	61	1.19	°	0.94	1.50
	0 - 64	87	87	1.00	°	0.80	1.23
	65+	153	135	1.14	°	0.96	1.33

++ significantly high, **p**-value < 0.01; + significantly high, **p**-value < 0.05; ° not significant; - significantly low, **p**-value < 0.05; - - significantly low, **p**-value < 0.01.

two regions where the NPPs are located (see **Table 3**). The doses are also well below the regulatory public dose limit of 1 mSv/year under the CNSC's *Radiation Protection Regulations*.

An analysis of the hypothetical dose plumes based on full time occupancy in a ground level atmospheric release shows that based on average meteorological conditions, the majority of exposure to atmospheric releases would occur over Lake Ontario (Pickering and Darling ton NPPs) and Lake Huron (Bruce NPP) (**Figures 1-3**). Near the Pickering NPP, prevailing winds travel towards the south; near the Darlington NPP they travel towards the south south east (SSE); and over Lake Huron near the Bruce NPP, towards the north. It can also be observed that almost all this hypothetical exposure is contained within 5 km from the centre point of the facility, much of which is located over the site of the facility itself. Even for such unrealistic exposure conditions, all annual doses remained below the 1 mSv/year public dose limit even for an individual hypothetically located at the stack for a full year.

Using the geographical representation of the dose plumes and the critical group doses (**Figures 1-3**) together with the 2006 census data for the Durham Region [57,58], we estimated that approximately 0.01% of the 25 km radius population reside within 5 km of the Darlington NPP (approximately 40 individuals). Hence, the majority of the population within the 25 km zone receives little or no exposure to radiation from the NPP. An analysis using the same data sources was also conducted for the area around the Pickering NPP. Approximately 1% of the 25 km radius population resides within 5 km of the Pickering NPP (approximately 16,000 people). The Bruce NPP is located in a semi-rural area with low population density; approximately 565 people reside within 5 km of the facility.

The dose plume modeling data (not shown) reveal that the hypothetical doses from air emissions were primarily due to releases of noble gases (*i.e.*, external dose from immersion) at Pickering (~75%), Bruce (~75%), and Darlington (~95%), with some dose being due to tritium oxide (internal dose from inhalation) at Bruce (~25%) and Pickering (~25%), and Carbon-14 (internal dose from inhalation and external dose from immersion) at Darlington (~5%). Radioactive particulates and radioactive iodines contributed very little to the dose (<1%). Doses from exposure to radioactive iodine were conservatively estimated using values set at the detection limit of the in-stack monitor because of extremely low releases. Milk samples have been collected weekly at farms around all three NPPs (part of the REMP) and values were below detection limits during the entire study period.

Recent epidemiological studies of childhood leukemia around nuclear facilities have used distance from the facility as a surrogate for data on exposure to radiation from the plants [1,2,10,12-14,59]. Our study has shown that doses to members of the public do not decrease uniformly with distance from an NPP; in fact the data presented in **Figures 1-3** for the three Ontario NPPs show that doses further away from the plants can be higher than doses to the closest critical groups. Radiation dose to members of the public from routine operation of NPPs is controlled by several factors, including: the type of

Table 10. Cancer incidence for people living within a 25 km radius of Bruce NPP at time of diagnosis, by sex and age group, 1990-2008.

Cancer	Age	Observed	Expected	SIR (O/E)	SIR flag	95% CI LL	95% CI UL
All sites	Total	2570	2362	1.09	++	1.05	1.13
	M	1441	1252	1.15	++	1.09	1.21
	F	1129	1110	1.02	°	0.96	1.08
	0 - 64	1079	1005	1.07	+	1.01	1.14
	65+	1491	1357	1.10	++	1.04	1.16
Lung and bronchus	Total	334	284	1.17	++	1.05	1.31
	M	197	164	1.20	+	1.04	1.38
	F	137	120	1.14	°	0.96	1.35
	0 - 64	118	93	1.26	+	1.05	1.51
	65+	216	191	1.13	°	0.98	1.29
Female breast	Total	331	333	0.99	°	0.89	1.11
	F	331	333	0.99	°	0.89	1.11
	0 - 64	181	192	0.94	°	0.81	1.09
	65+	150	141	1.06	°	0.90	1.25
Colon and rectum	Total	255	219	1.17	+	1.03	1.32
	M	128	112	1.14	°	0.95	1.36
	F	127	106	1.19	°	1.00	1.42
	0 - 64	75	67	1.12	°	0.88	1.40
	65+	180	152	1.19	+	1.02	1.37
Thyroid	Total	40	51	0.79	°	0.57	1.08
	M	13	12	1.08	°	0.57	1.84
	F	27	38	0.70	°	0.46	1.02
	0 - 64	31	42	0.74	°	0.51	1.06
	65+	9	9	1.01	°	0.46	1.92
Bladder	Total	62	79	0.78	-	0.60	1.00
	M	46	60	0.77	°	0.56	1.03
	F	16	20	0.80	°	0.46	1.31
	0 - 64	13	22	0.60	°	0.32	1.03
	65+	49	58	0.85	°	0.63	1.12
Leukemia	Total	80	68	1.18	°	0.93	1.46
	M	42	40	1.05	°	0.76	1.42
	F	38	28	1.36	°	0.96	1.86
	0 - 64	43	29	1.49	+	1.08	2.00
	65+	37	39	0.95	°	0.67	1.30
Stomach	Total	41	46	0.88	°	0.64	1.20
	M	29	30	0.97	°	0.65	1.40
	F	12	17	0.73	°	0.38	1.27
	0 - 64	18	15	1.17	°	0.69	1.85
	65+	23	31	0.74	°	0.47	1.12
Ovary	Total	32	40	0.80	°	0.55	1.13
	F	32	40	0.80	°	0.55	1.13
	0 - 64	17	21	0.82	°	0.48	1.31
	65+	15	19	0.78	°	0.44	1.29

Continued

Brain and other nervous system	Total	34	41	0.83	°	0.58	1.16
	M	15	23	0.65	°	0.36	1.07
	F	19	18	1.07	°	0.64	1.67
	0 - 64	23	25	0.93	°	0.59	1.40
	65+	11	16	0.67	°	0.34	1.21
Liver	Total		15	<1.00	--		
	M		11				
	F		4	<1.00	-		
	0 - 64		7				
	65+		9				
Esophagus	Total	32	22	1.46	°	1.00	2.06
	M	21	16	1.35	°	0.84	2.07
	F	11	6	1.72	°	0.86	3.09
	0 - 64	13	7	1.75	°	0.93	2.99
	65+	19	14	1.31	°	0.79	2.05

++ significantly high, **p**-value < 0.01; + significantly high, **p**-value < 0.05; ° not significant; - significantly low, **p**-value < 0.05; - - significantly low, **p**-value < 0.01.

release (*i.e.*, air emissions or liquid effluent discharges); the characteristics of the release (*i.e.*, stack height); the quantity, type and radioactive decay properties of the nuclear substances released; the meteorological conditions at the facility (*i.e.*, direction of prevailing winds and mixing height); and the diet and lifestyles of people. Thus, distance from an NPP as shown in this study is only one factor affecting exposure of members of the public to plant emissions, and it should not be used in isolation as a surrogate for radiation exposure data.

Cancer incidence, especially childhood leukemia, in populations living near nuclear facilities has been the topic of much scientific interest [6,59-61] and public concern since the 1980s. Authoritative reviews confirmed only three leukemia clusters have persisted over time around nuclear facilities (Sellafield in England, Dounreay in Scotland and Krümmel in Germany). Although some clusters of childhood leukemia cases exist locally, results based on multi-site studies around nuclear facilities do not indicate an excess of cancer globally. Many studies have investigated possible origins of the observed clusters around specific sites, but up to now, none of the proposed hypotheses (*i.e.*, parental pre-conception exposure [16], infectious agent associated with population mixing [62,63]) can explain them [59].

The most important finding of this study is that there is no evidence of childhood cancer clusters within 25 km of the three Ontario NPPs. In fact, cancer incidence (*i.e.*, leukemia, non-Hodgkin lymphoma) in young children (aged 0 - 4) was lower than the general Ontario population (but not statistically significantly so). Cancer incidence in children aged 0 - 14 was similar to the general Ontario population. Finally, childhood cancer (aged 0 - 14) was similar to Ontario within 10 km of the Pickering NPP (SIR = 0.84, 95% CI: 0.61, 1.13) and Darlington NPP (SIR = 0.97, 95% CI: 0.57, 1.53). Information was not provided for Bruce NPP or within the 5 km radius of the Darlington and Pickering NPPs because of few cases.

Overall, there is no consistent cancer incidence pattern among people living near the three NPPs. Some types of cancer were statistically significantly higher than expected; however, some types of cancer were statistically significantly lower than expected, and some types of cancer were the same as expected compared to the general Ontario population. The incidence of female breast, ovary, brain and other nervous system and esophagus cancer were either significantly low or similar to Ontario for people living near all three Ontario NPPs.

There was no consistent pattern for all cancer sites combined near the three Ontario NPPs. While, it was statistically significantly higher than expected for people living near Darlington and Bruce, it was significantly lower near Pickering (the NPP with the highest critical group doses (0.0067 mSv/year) among the three NPPs). It is not possible to know all of the cancers contributing to this finding, since only radiation-sensitive cancers were selected for this study. However, the most common cancers observed among people living near the three Ontario NPPs were cancers of the lung and bronchus, breast, and colon and rectum, which represent about 35% of all cancers combined, for all three NPPs. This is consistent with the rest of Ontario and Canada [44,55].

Table 11. Cancer incidence, Ontario by 2006 census division, all ages (0-85+) unless otherwise specified, 1992-2010.

Census Division	Cancers	O	E	SIR	SIR flag	95% CI	
	All sites	39565	37905	1.04	++	1.03	1.05
	Lung and bronchus	5150	4830	1.07	++	1.04	1.10
	Female Breast	5390	5340	1.01	°	0.98	1.04
	Colon and rectum	4675	4600	1.02	°	0.99	1.05
	Thyroid	1215	1140	1.07	+	1.01	1.13
	Bladder	1300	1155	1.12	++	1.06	1.19
	Leukemia	1255	1130	1.11	++	1.05	1.18
Durham Region	Stomach	715	725	0.98	°	0.91	1.06
	Ovary	660	655	1.01	°	0.94	1.09
	Brain and other nervous system	690	690	1.00	°	0.93	1.08
	Liver	235	310	0.76	--	0.67	0.87
	Esophagus	370	370	0.99	°	0.89	1.10
	Non-Hodgkin Lymphoma (aged 0 - 14)	15	20	0.75	°	0.43	1.23
	Leukemia (aged 0 - 14)	110	105	1.05	°	0.87	1.27
	NHL and Leukemia (aged 0 - 14)	130	130	1.00	°	0.84	1.19
	All sites	7090	7025	1.01	°	0.99	1.03
	Lung and bronchus	925	970	0.96	°	0.90	1.02
	Breast	835	890	0.94	°	0.88	1.00
	Colon and rectum	1000	910	1.10	++	1.03	1.17
	Bladder	185	235	0.79	--	0.68	0.91
	Leukemia	215	205	1.06	°	0.92	1.21
	Stomach	105	145	0.75	--	0.62	0.91
Bruce County	Ovary	90	110	0.81	-	0.65	0.99
	Thyroid	110	145	0.73	--	0.60	0.88
	Brain and other nervous system	105	110	0.94	°	0.77	1.14
	Esophagus	70	75	0.97	°	0.76	1.23
	Liver	25	55	0.43	--	0.27	0.63
	Non-Hodgkin Lymphoma (aged 0 - 14)	0	0	0.86	°	0.10	3.10
	Leukemia (aged 0 - 14)	15	10	1.17	°	0.62	1.99
	NHL and Leukemia (aged 0 - 14)	15	10	1.11	°	0.62	1.83

++ significantly high, **p**-value < 0.01; + significantly high, **p**-value < 0.05; ° not significant; - significantly low, **p**-value < 0.05; - - significantly low, **p**-value < 0.01.

Cancer incidence was statistically significantly higher than expected for cancer of the lung and bronchus among people living near the Darlington and Bruce NPPs. Cancer of the lung and bronchus was significantly low near the Pickering NPP. The most important risk factor for lung cancer is tobacco smoking, with relative risks for current smokers being greater than 10- to 20-fold higher than that of non-smokers [64-66]. Cancers of the bladder, stomach, and liver have been shown to be caused by tobacco smoking [66,67]. Bladder cancer was significantly high near the Darlington NPP, but significantly low near the Pickering and Bruce NPPs. Stomach cancer was significantly high near the Pickering NPP, but was similar to the Ontario average near the Darlington and Bruce NPPs. Liver cancer was significantly high near the Pickering NPP, but was significantly low near the Darlington and Bruce NPPs. The statistically significant higher-than-expected incidence for cancer of the lung

Table 12. Age-standardized incidence rates (ASIRs) per 100,000 population, Ontario by 2006 census division, all ages (0-85+), 1992-2010; presented from highest to lowest ASIR.

(a)

All cancers combined		Lung and bronchus		Breast cancer (females only)	
Census Division	**ASIR**	**Census Division**	**ASIR**	**Census Division**	**ASIR**
Sudbury DIS	450.98	Timiskaming DIS	78.89	Halton RM	108.71
Timiskaming DIS	439.21	Stormont, Dundas and Glengarry UC	74.33	Ottawa CDR	106.62
Manitoulin DIS	433.89	Cochrane DIS	73.94	Frontenac MB	104.27
Cochrane DIS	429.54	Sudbury DIS	71.31	Middlesex CTY	102.46
Thunder Bay DIS	427.49	Prescott and Russell UC	69.32	Nipissing DIS	101.56
Nipissing DIS	426.85	Greater Sudbury CDR	69.20	Thunder Bay DIS	101.53
Lambton CTY	422.01	Hastings CTY	68.38	Renfrew CTY	101.48
Greater Sudbury CDR	421.93	Nipissing DIS	66.91	Simcoe CTY	101.46
Haldimand-Norfolk CDR	420.37	Haliburton CTY	66.28	Elgin CTY	101.41
Dufferin CTY	418.34	Algoma DIS	64.90	Essex CTY	100.98
Elgin CTY	415.50	Kawartha Lakes CDR	64.15	Oxford CTY	100.89
Kawartha Lakes CDR	415.01	Thunder Bay DIS	63.59	Perth CTY	100.80
Huron CTY	413.89	Renfrew CTY	63.16	Durham RM	100.34
Durham RM	412.53	Northumberland CTY	62.92	Brant CDR	99.93
Algoma DIS	411.88	Lanark CTY	62.61	Haliburton CTY	99.78
Simcoe CTY	411.24	Parry Sound DIS	61.97	Lambton CTY	99.66
Stormont, Dundas and Glengarry UC	410.39	Leeds and Grenville UC	61.95	Ontario	99.55
Haliburton CTY	410.03	Lennox and Addington CTY	61.33	Grey CTY	99.12
Brant CDR	408.99	Lambton CTY	61.09	Hamilton CDR	98.94
Middlesex CTY	408.35	Frontenac MB	60.84	Prince Edward CDR	98.82
Lanark CTY	408.23	Peterborough CTY	60.73	Lennox and Addington CTY	98.79
Chatham-Kent CDR	406.73	Rainy River DIS	60.13	Sudbury DIS	98.73
Oxford CTY	404.28	Essex CTY	59.98	Haldimand-Norfolk CDR	98.34
Leeds and Grenville UC	403.86	Simcoe CTY	59.40	York RM	98.19
Parry Sound DIS	402.93	Chatham-Kent CDR	58.71	Dufferin CTY	97.99
Essex CTY	401.46	Manitoulin DIS	58.65	Niagara RM	97.88
Peterborough CTY	401.32	Brant CDR	57.97	Lanark CTY	97.54
Grey CTY	400.74	Prince Edward CDR	56.98	Leeds and Grenville UC	97.45
Frontenac MB	400.39	Hamilton CDR	56.51	Toronto CDR	97.29
Northumberland CTY	399.88	Haldimand-Norfolk CDR	56.50	Chatham-Kent CDR	97.22
Hastings CTY	398.98	Kenora DIS	55.70	Algoma DIS	97.01
Renfrew CTY	398.94	Durham RM	55.29	Peterborough CTY	96.88
Niagara RM	395.82	Elgin CTY	54.94	Stormont, Dundas and Glengarry UC	96.75
Hamilton CDR	395.68	Niagara RM	54.81	Timiskaming DIS	96.60
Bruce CTY	395.39	Ottawa CDR	53.61	Northumberland CTY	96.33
Perth CTY	395.03	Muskoka DM	53.20	Waterloo RM	96.03
Ontario	394.59	Middlesex CTY	52.15	Hastings CTY	95.93
Prescott and Russell UC	393.93	Ontario	52.03	Greater Sudbury CDR	95.59
Muskoka DM	393.50	Huron CTY	50.91	Wellington CTY	94.88
Halton RM	392.09	Grey CTY	50.81	Kawartha Lakes CDR	94.58
Prince Edward CDR	390.34	Bruce CTY	50.31	Huron CTY	94.09
Ottawa CDR	384.35	Dufferin CTY	50.11	Cochrane DIS	93.99
Waterloo RM	382.52	Oxford CTY	49.63	Manitoulin DIS	93.95
Lennox and Addington CTY	380.13	Perth CTY	46.01	Muskoka DM	92.86
Wellington CTY	378.69	Wellington CTY	45.78	Peel RM	92.80
Toronto CDR	374.17	Waterloo RM	45.78	Prescott and Russell UC	91.75
Rainy River DIS	367.55	Halton RM	44.13	Bruce CTY	91.59
York RM	366.12	Toronto CDR	43.62	Rainy River DIS	90.71
Peel RM	356.54	Peel RM	40.67	Parry Sound DIS	89.99
Kenora DIS	337.04	York RM	39.13	Kenora DIS	84.69

(b)

Colon and rectum cancer		Thyroid cancer		Bladder cancer	
Census Division	**ASIR**	Census Division	**ASIR**	**Census Division**	**ASIR**
Manitoulin DIS	70.09	York RM	17.82	Sudbury DIS	17.63
Sudbury DIS	67.31	Toronto CDR	15.59	Timiskaming DIS	17.11
Nipissing DIS	60.15	Peel RM	13.15	Algoma DIS	16.25
Huron CTY	58.17	Halton RM	12.13	Leeds and Grenville UC	16.09
Rainy River DIS	57.62	Algoma DIS	11.82	Elgin CTY	14.86
Cochrane DIS	57.23	Durham RM	11.80	Stormont, Dundas and Glengarry UC	14.79
Renfrew CTY	56.96	Ontario	10.82	Kawartha Lakes CDR	14.67
Timiskaming DIS	56.93	Middlesex CTY	10.66	Brant CDR	14.47
Parry Sound DIS	56.72	Huron CTY	10.39	Simcoe CTY	14.42
Greater Sudbury CDR	56.50	Oxford CTY	9.49	Haldimand-Norfolk CDR	14.28
Prescott and Russell UC	54.85	Perth CTY	9.33	Nipissing DIS	14.25
Lanark CTY	54.69	Cochrane DIS	9.10	Haliburton CTY	14.15
Thunder Bay DIS	54.65	Essex CTY	8.85	Dufferin CTY	14.07
Lambton CTY	54.41	Simcoe CTY	8.68	Durham RM	13.92
Chatham-Kent CDR	54.25	Wellington CTY	8.61	Lambton CTY	13.87
Bruce CTY	53.40	Waterloo RM	8.60	Greater Sudbury CDR	13.87
Kenora DIS	53.25	Lambton CTY	8.53	Cochrane DIS	13.79
Muskoka DM	52.91	Elgin CTY	8.50	Northumberland CTY	13.53
Stormont, Dundas and Glengarry UC	52.83	Peterborough CTY	8.17	Oxford CTY	13.47
Haldimand-Norfolk CDR	52.64	Parry Sound DIS	7.99	Hamilton CDR	13.31
Perth CTY	52.64	Bruce CTY	7.74	Huron CTY	13.27
Algoma DIS	52.45	Muskoka DM	7.68	Hastings CTY	13.15
Middlesex CTY	52.40	Kawartha Lakes CDR	7.62	Thunder Bay DIS	13.09
Haliburton CTY	52.28	Dufferin CTY	7.47	Halton RM	13.01
Elgin CTY	52.13	Sudbury DIS	7.38	Middlesex CTY	12.93
Grey CTY	51.91	Grey CTY	7.28	Chatham-Kent CDR	12.90
Oxford CTY	51.85	Greater Sudbury CDR	7.18	Prince Edward CDR	12.78
Kawartha Lakes CDR	51.70	Thunder Bay DIS	6.83	Muskoka DM	12.73
Leeds and Grenville UC	51.60	Nipissing DIS	6.51	Peterborough CTY	12.68
Simcoe CTY	51.58	Northumberland CTY	6.44	Parry Sound DIS	12.67
Peterborough CTY	51.44	Ottawa CDR	6.33	Ontario	12.55
Hastings CTY	50.12	Haliburton CTY	6.16	Lanark CTY	12.42
Durham RM	49.79	Haldimand-Norfolk CDR	6.09	Frontenac MB	12.37
Brant CDR	49.77	Chatham-Kent CDR	5.84	Renfrew CTY	12.34
Waterloo RM	49.72	Timiskaming DIS	5.84	Lennox and Addington CTY	12.33
Northumberland CTY	49.69	Hamilton CDR	5.78	Essex CTY	12.16
Prince Edward CDR	49.44	Niagara RM	5.76	Prescott and Russell UC	12.15
Hamilton CDR	49.17	Manitoulin DIS	5.36	Toronto CDR	11.86
Niagara RM	49.08	Lanark CTY	5.33	Wellington CTY	11.84
Essex CTY	48.98	Brant CDR	5.13	York RM	11.71
Ontario	48.97	Rainy River DIS	5.08	Niagara RM	11.70
Wellington CTY	48.70	Hastings CTY	5.06	Waterloo RM	11.65
Frontenac MB	48.56	Renfrew CTY	5.04	Grey CTY	11.53
Dufferin CTY	48.10	Frontenac MB	4.82	Ottawa CDR	11.36
Ottawa CDR	48.07	Lennox and Addington CTY	4.58	Peel RM	11.09
Lennox and Addington CTY	47.56	Prince Edward CDR	4.49	Manitoulin DIS	10.81
Halton RM	46.17	Prescott and Russell UC	4.46	Perth CTY	10.46
York RM	45.32	Stormont, Dundas and Glengarry UC	4.40	Bruce CTY	9.94
Toronto CDR	44.19	Leeds and Grenville UC	3.39	Rainy River DIS	8.97
Peel RM	41.85	Kenora DIS	3.28	Kenora DIS	6.42

(c)

Leukemias		Stomach cancer		Ovary Cancer (females only)	
Census Division	**ASIR**	**Census Division**	**ASIR**	**Census Division**	**ASIR**
Sudbury DIS	15.75	Cochrane DIS	9.99	Manitoulin DIS	16.81
Greater Sudbury CDR	14.27	Toronto CDR	9.39	Kenora DIS	15.00
Timiskaming DIS	14.22	Rainy River DIS	8.97	Parry Sound DIS	14.52
Manitoulin DIS	14.01	Peel RM	8.75	Timiskaming DIS	14.43
Nipissing DIS	13.60	Algoma DIS	8.47	Oxford CTY	13.95
Cochrane DIS	13.53	York RM	8.25	Huron CTY	13.93
Elgin CTY	13.49	Thunder Bay DIS	8.18	Haldimand-Norfolk CDR	13.84
Kawartha Lakes CDR	13.30	Hamilton CDR	8.15	Dufferin CTY	13.61
Durham RM	13.20	Greater Sudbury CDR	8.11	Essex CTY	13.41
Thunder Bay DIS	13.19	Nipissing DIS	8.02	Sudbury DIS	13.38
Lambton CTY	13.10	Chatham-Kent CDR	7.85	Niagara RM	13.16
Prince Edward CDR	13.04	Essex CTY	7.84	Brant CDR	13.16
Hastings CTY	12.95	Prescott and Russell UC	7.79	Greater Sudbury CDR	13.11
Perth CTY	12.92	Haldimand-Norfolk CDR	7.74	Ottawa CDR	13.05
Essex CTY	12.76	Ontario	7.73	Leeds and Grenville UC	13.04
Middlesex CTY	12.61	Sudbury DIS	7.62	Grey CTY	13.04
Oxford CTY	12.57	Durham RM	7.55	Stormont, Dundas and Glengarry UC	12.91
Haliburton CTY	12.56	Niagara RM	7.53	Prince Edward CDR	12.89
Bruce CTY	12.55	Timiskaming DIS	7.52	Perth CTY	12.88
Halton RM	12.54	Brant CDR	7.33	Chatham-Kent CDR	12.77
Muskoka DM	12.48	Muskoka DM	7.22	Waterloo RM	12.65
Huron CTY	12.40	Stormont, Dundas and Glengarry UC	7.03	Elgin CTY	12.64
Chatham-Kent CDR	12.34	Dufferin CTY	7.01	Hastings CTY	12.62
Grey CTY	12.32	Wellington CTY	6.96	Kawartha Lakes CDR	12.58
Northumberland CTY	12.23	Manitoulin DIS	6.92	Durham RM	12.56
Hamilton CDR	11.81	Middlesex CTY	6.87	Peterborough CTY	12.41
Parry Sound DIS	11.79	Renfrew CTY	6.87	Ontario	12.40
Ontario	11.76	Waterloo RM	6.83	Prescott and Russell UC	12.29
Waterloo RM	11.65	Oxford CTY	6.75	Middlesex CTY	12.27
Frontenac MB	11.61	Lambton CTY	6.67	Renfrew CTY	12.27
Simcoe CTY	11.36	Halton RM	6.61	Toronto CDR	12.26
Brant CDR	11.35	Ottawa CDR	6.59	Hamilton CDR	12.23
Algoma DIS	11.33	Elgin CTY	6.42	Northumberland CTY	12.20
Peterborough CTY	11.31	Simcoe CTY	6.39	Nipissing DIS	12.19
Wellington CTY	11.24	Grey CTY	6.12	Halton RM	12.17
Renfrew CTY	11.17	Hastings CTY	6.10	Haliburton CTY	12.13
Dufferin CTY	11.03	Kawartha Lakes CDR	6.06	Muskoka DM	12.10
Niagara RM	10.91	Parry Sound DIS	5.98	Lennox and Addington CTY	12.06
Prescott and Russell UC	10.80	Bruce CTY	5.79	Algoma DIS	11.95
Ottawa CDR	10.79	Huron CTY	5.75	Frontenac MB	11.79
York RM	10.71	Peterborough CTY	5.73	Peel RM	11.63
Stormont, Dundas and Glengarry UC	10.70	Lanark CTY	5.67	York RM	11.57
Lanark CTY	10.57	Kenora DIS	5.65	Simcoe CTY	11.25
Toronto CDR	10.55	Northumberland CTY	5.48	Lambton CTY	11.01
Haldimand-Norfolk CDR	10.54	Perth CTY	5.45	Lanark CTY	10.98
Peel RM	10.28	Frontenac MB	5.38	Thunder Bay DIS	10.80
Leeds and Grenville UC	10.15	Haliburton CTY	5.25	Wellington CTY	10.71
Lennox and Addington CTY	10.02	Lennox and Addington CTY	4.62	Rainy River DIS	10.55
Kenora DIS	9.25	Prince Edward CDR	4.47	Cochrane DIS	9.97
Rainy River DIS	7.91	Leeds and Grenville UC	4.25	Bruce CTY	9.60

(d)

Brain and other nervous system Cancer		Liver Cancer		Esophagus Cancer	
Census Division	**ASIR**	**Census Division**	**ASIR**	**Census Division**	**ASIR**
Prince Edward CDR	9.31	Toronto CDR	4.72	Sudbury DIS	6.90
Prescott and Russell UC	8.57	Frontenac MB	4.13	Lanark CTY	6.29
Dufferin CTY	8.55	York RM	4.13	Haliburton CTY	6.28
Chatham-Kent CDR	8.30	Peel RM	3.79	Muskoka DM	6.16
Thunder Bay DIS	8.13	Ottawa CDR	3.70	Dufferin CTY	6.05
Haliburton CTY	8.07	Hamilton CDR	3.38	Hastings CTY	5.73
Lennox and Addington CTY	7.96	Ontario	3.15	Algoma DIS	5.73
Wellington CTY	7.94	Middlesex CTY	3.00	Peterborough CTY	5.25
Frontenac MB	7.76	Peterborough CTY	2.97	Manitoulin DIS	5.22
Haldimand-Norfolk CDR	7.60	Lanark CTY	2.80	Cochrane DIS	5.22
Essex CTY	7.54	Hastings CTY	2.72	Lennox and Addington CTY	5.17
Northumberland CTY	7.49	Essex CTY	2.71	Stormont, Dundas and Glengarry UC	5.16
Hamilton CDR	7.46	Thunder Bay DIS	2.55	Timiskaming DIS	5.15
Kawartha Lakes CDR	7.44	Parry Sound DIS	2.54	Leeds and Grenville UC	5.11
Timiskaming DIS	7.37	Leeds and Grenville UC	2.45	Frontenac MB	5.08
Brant CDR	7.36	Stormont, Dundas and Glengarry UC	2.44	Kawartha Lakes CDR	5.08
Middlesex CTY	7.33	Durham RM	2.44	Prince Edward CDR	5.00
Simcoe CTY	7.31	Brant CDR	2.44	Chatham-Kent CDR	4.98
Huron CTY	7.30	Kawartha Lakes CDR	2.42	Thunder Bay DIS	4.89
Algoma DIS	7.23	Rainy River DIS	2.33	Renfrew CTY	4.83
Oxford CTY	7.20	Renfrew CTY	2.32	Greater Sudbury CDR	4.75
Niagara RM	7.17	Niagara RM	2.28	Parry Sound DIS	4.67
Peterborough CTY	7.15	Lennox and Addington CTY	2.27	Nipissing DIS	4.64
Ottawa CDR	7.13	Prescott and Russell UC	2.22	Brant CDR	4.56
Grey CTY	7.11	Grey CTY	2.21	Elgin CTY	4.54
Perth CTY	7.05	Simcoe CTY	2.19	Oxford CTY	4.53
Waterloo RM	7.02	Manitoulin DIS	2.17	Kenora DIS	4.52
Halton RM	7.01	Chatham-Kent CDR	2.16	Huron CTY	4.51
Ontario	7.00	Lambton CTY	2.10	Simcoe CTY	4.43
Lanark CTY	6.97	Northumberland CTY	2.06	Hamilton CDR	4.40
Durham RM	6.90	Cochrane DIS	2.02	Perth CTY	4.19
Parry Sound DIS	6.82	Perth CTY	2.00	Ottawa CDR	4.14
Lambton CTY	6.80	Muskoka DM	2.00	Niagara RM	4.02
Bruce CTY	6.73	Wellington CTY	1.97	Wellington CTY	3.98
York RM	6.72	Greater Sudbury CDR	1.97	Haldimand-Norfolk CDR	3.95
Elgin CTY	6.71	Haliburton CTY	1.92	Lambton CTY	3.95
Peel RM	6.65	Waterloo RM	1.89	Ontario	3.92
Greater Sudbury CDR	6.63	Sudbury DIS	1.84	Grey CTY	3.90
Toronto CDR	6.52	Haldimand-Norfolk CDR	1.83	Durham RM	3.87
Muskoka DM	6.50	Algoma DIS	1.83	Middlesex CTY	3.83
Cochrane DIS	6.48	Dufferin CTY	1.82	Bruce CTY	3.79
Nipissing DIS	6.43	Oxford CTY	1.82	Halton RM	3.78
Stormont, Dundas and Glengarry UC	6.42	Kenora DIS	1.80	Northumberland CTY	3.76
Renfrew CTY	6.41	Halton RM	1.76	Waterloo RM	3.68
Hastings CTY	6.34	Prince Edward CDR	1.75	Essex CTY	3.65
Leeds and Grenville UC	6.27	Nipissing DIS	1.62	Prescott and Russell UC	3.34
Manitoulin DIS	6.04	Elgin CTY	1.59	Toronto CDR	3.14
Sudbury DIS	6.03	Huron CTY	1.43	Peel RM	2.99
Rainy River DIS	5.91	Timiskaming DIS	1.40	Rainy River DIS	2.52
Kenora DIS	5.53	Bruce CTY	1.31	York RM	2.51

and bronchus, bladder, stomach and liver in this study suggests that tobacco smoking may be a confounding factor.

There was no consistent pattern for colon and rectum cancer near the three NPPs. Colon and rectum cancer incidence was significantly higher than expected near the Darlington and Bruce NPPs (especially among men aged 65+ years), but was significantly lower near the Pickering NPP. This is consistent with the main risk factors for colorectal cancer (e.g. age (particularly those over the age of 50) and sex (males)) [68,69].

There was no consistent pattern of thyroid cancer near all three NPPs. Thyroid cancer incidence was statistically significantly higher than expected near the Pickering and Darlington NPPs, but was similar to the Ontario population near for Bruce NPP. Exposure to large amounts of ionizing radiation, family history and iodine (high or low) in the diet are the main risk factors for thyroid cancer [68]. However, radiation risk decreases sharply with increasing age-at-exposure and there is little evidence of increased thyroid cancer rates for those exposed after age 20 [70,71]. Releases of radioactive iodine, which is the primary cause of radiation-related thyroid cancer [72], have been extremely low, or below detection limits at all three NPPs during the study period. Concentrations of radioactive iodine in weekly milk samples have remained below the limit of detection during the entire study period. Thus, exposure of the public to radiological emissions from the Pickering and Darlington NPPs is not a likely cause of excess thyroid cancer around these two NPPs.

There was no consistent pattern for leukemia near all three NPPs. Leukemia was statistically significantly higher than expected near the Darlington NPP. However, leukemia incidence for children aged 0 - 4, 0 - 14, and young adults aged 0 - 24 was either less than or similar to the general Ontario population near all three NPPs. Therefore those aged 25 - 64 are driving the significant finding near the Darlington NPP. Although high radiation doses can cause leukemia [46], the lack of significant findings among children (who are most vulnerable to radiation) suggests that other risk factors are involved, especially considering the very low doses (critical group doses $\leq$ 0.0067 mSv/year) found in this study.

In our study, industrial sources of radiation only contribute a small fraction of the public's overall exposure to radiation. While the critical group doses around the three NPPs are $\leq$0.0067 mSv/year, natural background radiation is on the order of 1.34 mSv/year around the Pickering and Darlington NPPs and 2.02 mSv/year around the Bruce NPP. Hence, radiation doses from the three NPPs do not provide a plausible explanation for any observable increases in cancer incidence above Ontario baseline levels.

Geographic variation of cancer incidence is not uncommon [67,73-76] and as illustrated in our spatial analysis of cancer incidence at the CD level in Ontario. A study in Ontario [77] showed that most of the geographic variation in cancer rates was found to be associated with variation in known risk factors, and no broad regional effects remained after adjustment for these factors. After known risk factors were taken into account, there was no evidence of a strong difference in cancer risk in Ontario that would be expected if environmental factors (*i.e.*, related to air or water quality) were operative at a regional scale. Another Ontario study found similar results [78]. Both of these studies cover the earlier time period of our cancer incidence data suggesting that known risk factors are a likely explanation of the variations in cancer incidence observed in our study.

5. Conclusions

The most important finding of this study is that there is no evidence of childhood cancer clusters (especially childhood leukemia) near the three Ontario NPPs studied (Pickering, Darlington and Bruce). Overall, for all ages, there is no consistent pattern of elevated cancer incidence at any of these three NPPs. Although there were some elevated cancer rates, there was no clear pattern found across age groups, sexes and NPPs. This finding is generally consistent with previous studies. Overall, the cancers are well within the natural variation of disease in Ontario.

Radiation doses to members of the public living near the three NPPs as a result of historical and current-day operations are significantly lower than natural background radiation and the public dose limit of 1 mSv/year. Therefore, on the basis of current radiation risk estimates and the supporting epidemiological literature, radiation is not a plausible explanation for any excess cancers observed within 25 km of any Ontario NPP.

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Radiation and Incidence of Cancer Around Ontario Nuclear Power Plants From 1990 to 2008 (The RADICON Study)

Executive summary

The Canadian Nuclear Safety Commission (CNSC) has completed a groundbreaking ecological study on populations living near Ontario's three nuclear power plants (NPPs). The purpose of the *Radiation and Incidence of Cancer Around Ontario Nuclear Power Plants from 1990 to 2008 study (the "RADICON" study)* was to determine the radiation doses to members of the public living within 25 km of the Pickering, Darlington, and Bruce NPPs and to compare cancer cases among these people with the general population of Ontario from 1990 to 2008. The study was conducted using data from the Canadian and Ontario Cancer Registries and the Census of Canada.

The most important finding of the RADICON study is that there is no evidence of childhood leukemia clusters around the three Ontario NPPs. The rates of cancer incidence for children aged 0–4 and aged 0–14 were similar to the general Ontario population.

Overall, for all ages, there is no consistent pattern of cancer across the populations in question living near the three facilities studied. Some types of cancer in the communities studied were higher than expected (excess cancer); however, many types of cancer were lower than expected.

While this type of study cannot determine the causes of the cancer, excess cancers (increase in cancer above what's expected in Ontario) are unlikely to be due to radiation. Radiation doses from NPPs to members of the public are extremely low – at least 100 to 1,000 times lower than natural background radiation and public dose limits. As such, doses are a minor risk factor compared to the high prevalence of major risk factors like tobacco, poor diet, obesity and physical inactivity, which account for about 60 percent of all cancer deaths in developed countries. These factors represent a public health concern throughout Ontario, including the communities located near NPPs. Other important Ontario studies found that once these main risk factors were taken into account, there was no evidence of a cancer risk due to environmental factors like radiation. Given the high frequency of these factors, the current scientific understanding of radiation risk, and the minuscule public doses, it is not realistic to attribute any excess cancers to the radiation doses from NPPs found in these communities.

The main strength of the RADICON study is the use of detailed public dose information around each NPP that was generated from radiological releases and environmental monitoring data. The data collected for this study takes into account any emission spikes from the NPPs. This methodology improves on recent epidemiological studies of childhood cancer that have used distance from an NPP as a substitute for radiation dose. Doses closest to the NPPs were not consistently higher than doses further away. Many factors influence doses to the public as a result of the

operation of an NPP, including prevailing wind directions and lifestyle characteristics (i.e., diet and lifestyle habits) of the surrounding communities. Therefore, distance is not a good substitute for dose.

To conclude, public radiation doses resulting from the operation of the NPPs are 100 to 1,000 times lower than natural background radiation and there is no evidence of childhood leukemia clusters around the three Ontario NPPs. All cancers for all age groups are well within the natural variation of the disease in Ontario. Thus, radiation is not a plausible explanation for any excess cancers observed within 25 km of any Ontario NPP.

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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.

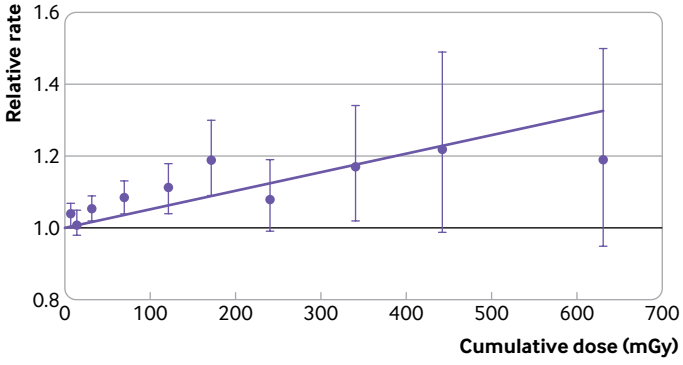

Fig 1 | Relative rate of mortality due to solid cancer by categories of cumulative colon dose, lagged 10 years in INWORKS. Bars indicate 90% confidence intervals, and purple line depicts fitted linear model for change in excess relative rate of solid cancer mortality with dose. Strata: country, age, 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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that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

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

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Leukaemia, lymphoma, and multiple myeloma mortality after low-level exposure to ionising radiation in nuclear workers (INWORKS): updated findings from an international cohort study

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Contributors

DBR conceived the study. DBR, KL, DL, MG, RH, KK-R, SB, RDD, IT-C, AK, and MKSB developed the research questions and designed the study. KL and DL worked on provision of the French data; KK-R, SB, RDD, and MKSB 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. IT-C was responsible for the dosimetry. KL did the statistical analysis and produced the initial draft of the manuscript, which was revised and approved by all authors. KL and MM had access to the raw data for France, RDD, KK-R, SB, and MM had access to the raw data for the US, and MG and RH had access to the raw data for the UK. Tabulated data were accessible to all co-authors. KL and DBR had final responsibility for the decision to submit for publication.

Declaration of interests

We declare no competing interests.

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. Data use requests may be directed to the appropriate national authorities. 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.

Summary

Background—A major update to the International Nuclear Workers Study (INWORKS) was undertaken to strengthen understanding of associations between low-dose exposure to penetrating forms of ionising radiation and mortality. Here, we report on associations between radiation dose and mortality due to haematological malignancies.

Methods—We assembled a cohort of 309 932 radiation-monitored workers (269 487 [87%] males and 40 445 [13%] females) employed for at least 1 year by a nuclear facility in France (60 697 workers), the UK (147 872 workers), and the USA (101 363 workers). Workers were individually monitored for external radiation exposure and followed-up from Jan 1, 1944, to Dec 31, 2016, accruing 10·72 million person-years of follow-up. Radiation-mortality associations were quantified in terms of the excess relative rate (ERR) per Gy of radiation dose to red bone marrow for leukaemia excluding chronic lymphocytic leukaemia (CLL), as well as subtypes of leukaemia, myelodysplastic syndromes, non-Hodgkin and Hodgkin lymphomas, and multiple myeloma. Estimates of association were obtained using Poisson regression methods.

Findings—The association between cumulative dose to red bone marrow, lagged 2 years, and leukaemia (excluding CLL) mortality was well described by a linear model (ERR per Gy 2·68, 90% CI 1·13 to 4·55, n=771) and was not modified by neutron exposure, internal contamination monitoring status, or period of hire. Positive associations were also observed for chronic myeloid leukaemia (9·57, 4·00 to 17·91, n=122) and myelodysplastic syndromes alone (3·19, 0·35 to 7·33, n=163) or combined with acute myeloid leukaemia (1·55, 0·05 to 3·42, n=598). No significant association was observed for acute lymphoblastic leukaemia (4·25, −4·19 to 19·32, n=49) or CLL (0·20, −1·81 to 2·21, n=242). A positive association was observed between radiation dose and multiple myeloma (1·62, 0·06 to 3·64, n=527) whereas minimal evidence of association was observed between radiation dose and non-Hodgkin lymphoma (0·27, −0·61 to 1·39, n=1146) or Hodgkin lymphoma (0·60, −3·64 to 4·83, n=122) mortality.

Interpretation—This study reports a positive association between protracted low dose exposure to ionising radiation and mortality due to some haematological malignancies. Given the relatively low doses typically accrued by workers in this study (16 mGy average cumulative red bone marrow dose) the radiation attributable absolute risk of leukaemia mortality in this population is low (one excess death in 10 000 workers over a 35-year period). These results can inform radiation protection standards and will provide input for discussions on the radiation protection system.

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Introduction

Within a few years of the atomic bombings of Hiroshima and Nagasaki, an excess of leukaemia, primarily myelogenous, was recognised among the survivors.[1,2] Today, it is well established that many types of leukaemia can be caused by exposure to ionising radiation.[1,3] Quantitative estimates of leukaemia risks from ionising radiation exposures are primarily derived from epidemiological studies of people exposed to acute, high doses of ionising radiation.[2,4] However, many of the questions of most relevance to the public and

radiation workers concern the excess risk of leukaemia after repeated or protracted low-dose exposures to ionising radiation, as is typically encountered in contemporary occupational, environmental, and diagnostic medical settings.

The International Nuclear Workers Study (INWORKS) was undertaken to strengthen evidence regarding associations between protracted low-dose, low dose-rate radiation exposure and mortality.[5] INWORKS includes workers from France, the UK, and the USA who were monitored for external exposure to ionising radiation using personal dosimeters, and subsequently followed up to collect information on vital status and causes of death.[6] In 2023, we published a major update of the INWORKS study, with a workers' follow-up of 35 years on average.[7] Here, we report on associations between ionising radiation and leukaemia excluding chronic lymphocytic leukaemia (CLL), hereinafter non-CLL leukaemia, as well as subtypes of leukaemia, lymphoma, and multiple myeloma mortality using information from this update of INWORKS.

Methods

Study design and participants

INWORKS is an international retrospective cohort study of nuclear workers who were employed in France, the UK, and the USA. The research consortium, led by the International Agency for Research on Cancer, has conducted related mortality investigations since the mid-1990s, carried out using a common core protocol, evaluation of the comparability of recorded dose estimates across facilities and time, and a thorough study of errors in recorded doses to identify and quantify sources of bias and uncertainties in dose estimates.[8] INWORKS is the latest stage of this work, which includes participating countries that have consistently provided the greatest contribution to previous consortium work. In addition, these countries, through periodic country-specific analyses,[9–12] have made continuous improvements to available study data, including extending follow-up.

Details describing the formation of the INWORKS cohort have been described elsewhere.[5] Briefly, participating facilities were those including workers who were primarily exposed to low-linear energy transfer (LET) penetrating radiations from external sources and had records of annual doses from monitoring of external radiation exposure using personal dosimeters. Records were obtained from the French Alternative Energies and Atomic Energy Commission, Orano, and Electricité de France; from the UK National Registry for Radiation Workers (NRRW) which includes information from the British Atomic Weapons Establishment, British Nuclear Fuels, the UK Atomic Energy Authority, British Energy Generation, Magnox Electric, and the UK Ministry of Defence; 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.[5] The inclusion criteria in the INWORKS study were to have been employed for at least 1 year in one of the participating companies and to have been badge-monitored as part of regulatory radiation protection monitoring.

Given the retrospective nature of the study and because there is minimal risk to participants, the French Data Protection Authority and the National Institute for Occupational Safety

and Health institutional review board waived requirements for individual informed consent. UK workers can refuse to participate in the National Registry for Radiation Workers and associated studies; less than 1% did. The study was approved by the International Agency for Research on Cancer's ethical review committee (No 11–09 and later amendments) and relevant ethical committees of the participating countries. This study was reviewed and approved by the National Institute for Occupational Safety and Health Institutional Review Boad.

Procedures

Individual quantitative annual estimates of body dose due to external exposure to ionising radiation, primarily photons, were available from company records for UK workers and government and company records for US and French workers. Unless otherwise stated, any reference to dose in this paper implies estimated absorbed dose to red bone marrow expressed in Gy, where bone marrow doses were derived by dividing recorded external penetrating radiation dose estimates by an organ-specific dose factor.[13] Available records of estimated neutron doses were used to construct categories of time-varying 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.[13] As only a few bioassay results were available for the entire cohort, information on monitoring status and workstation risk potential were also used to identify workers with no risk of internal radionuclide contamination (so-called not monitored) and workers with known or suspected internal contaminations (so-called monitored).[13]

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 medical causes of death only since 1968, French workers only entered follow-up on Jan 1, 1968, or later.[6] A worker exited the study on the earliest of the following: date of death, date lost to follow-up, or date of end of follow-up.

Vital status was ascertained until Dec 31, 2012, for the UK cohort, Dec 31, 2014, for the French cohort, and Dec 31, 2016 for the US cohort through linkage with national and regional death registries, employer records, tax records, and Social Security Administration records. Information on underlying causes of death was abstracted from death certificates and generally was coded according to the revision of the ICD in effect at the time of death.[5]

Outcomes

Analyses examine the following mortality outcomes: non-CLL leukaemia (ICD9 codes 204–208 excluding 204.1, 204.9, 208.1, and 208.9), chronic myeloid leukaemia (ICD9 codes 205.1 and 206.1), acute myeloid leukaemia (ICD9 codes 205.0, 205.3, 206.0, 207.0, and 207.2), myelodysplastic syndromes (ICD10 code D46), acute lymphoblastic leukaemia (ICD9 code 204.0), CLL (ICD9 code 204.1), non-Hodgkin lymphoma (ICD9 codes 200, 202, 273.3), Hodgkin lymphoma (ICD9 code 201), and multiple myeloma (ICD9 code 203). An exhaustive list of ICD codes is shown in the supplementary material (appendix 2 p 1). We report on non-CLL leukaemia as it is now recognised that there are clinical

and etiological links between CLL and lymphomas and that CLL and small lymphocytic lymphoma are different forms of the same disease.[14]

Statistical analysis

Analyses were conducted using multiway tabulations of person-years at risk and deaths by country, sex, attained age (in 5 year intervals), year of birth (in 10 year intervals), socioeconomic status (French, US, and UK workers employed by the Atomic Energy Authority and Atomic Weapons Establishment were classified into five categories, based on job title: professional and technical workers, administrative staff, skilled workers, unskilled workers, and uncertain [5778 or 2% workers]; other UK workers were classified into two broader categories of non-industrial and industrial employees), duration of employment or radiation work (in 5 year intervals), neutron monitoring status (in three categories: 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), internal contamination monitoring flag (not monitored *vs* monitored), period of first employment, and cumulative dose (in categories <5, 5<10, 10<20, 20<50, 50<100, 100<200, 200<300, and ≥300 mGy). For each cell of this table, the person-time weighted cell-specific mean doses to red bone marrow were calculated. The distribution of person-years by country, birth cohort or attained age, and sex in INWORKS is presented in appendix 2 (p 2).

An excess relative rate (ERR) regression model was fitted of the form $\lambda(c, s, b, a, d)=\lambda_0(c, s, b, a)[1 + \beta d]$, where λ is the rate of death depending on country (c), sex (s), year of birth (b), attained age (a), and cumulative red bone marrow dose (d) in Gy in a linear dependence, λ_0 is the baseline mortality rate modelled through stratification, and β quantifies the ERR per Gy. Stratification on attained age and year of birth provides control for calendar year of death (noting that a decedent's year of birth and attained age identify the calendar year of death). Parameter estimates were obtained by Poisson regression methods. Cumulative doses were lagged to allow for an induction and latency period between exposure and death, by 2 years for the analysis of non-CLL leukaemia and separate types, and by 10 years for the analysis of lymphoma and multiple myeloma. These lag values were chosen a priori to facilitate comparison of results with those from previous analyses of haematological cancers in INWORKS.[6,15] Sensitivity analyses investigated the effect of different lag periods (2, 5, 10, and 15 years) and results were compared based on goodness of model fits.[16]

Further investigations were performed for non-CLL leukaemia mortality. The dose-response association was examined by fitting a regression model with indicator variables for cumulative dose categories, and ERRs were plotted against mean dose values. Departure of the dose-response relationship from linearity was formally tested by fitting alternative dose-response models: a linear-quadratic model ($ERR(d)=\beta_1 d + \beta_2 d^2$) and a quadratic model ($ERR(d)=\beta d^2$). We examined the dose-response association over restricted dose ranges by truncating the follow-up of workers when they had accumulated the maximum dose chosen (<300, <200, <100, and <50 mGy). Variations in the effect of cumulative dose on non-CLL leukaemia mortality across attained age categories (<60, 60–79, and ≥80 years), neutron monitoring status, and internal contamination monitoring flag were also assessed. We compared the effect of radiation dose on non-CLL leukaemia mortality among workers

hired before 1958 with that among workers hired from 1958 onwards, as previous studies have raised concerns regarding workers hired in the early years of the industry;[17] and, we repeated this analysis using 1965 as the cutoff year. The a priori choice of a set of variables (ie, country, birth cohort, attained age, and sex) for modelling the baseline rate of death from non-CLL leukaemia was assessed by fitting models using alternative stratification strategies, considering socioeconomic status, duration of employment, year of hire, neutron monitoring status, and internal contamination status. We assessed the effect of each country by removing one at a time from the analysis. We estimated the excess number of deaths associated with radiation exposure, which we calculated as the difference between the fitted number of deaths within a stratum defined by levels of the stratification variables and the background number of deaths (obtained by multiplying the stratum-specific baseline mortality rate by the person-time in that stratum).

Consistent with prior analyses,[6,11,18] we report maximum likelihood estimates of ERR per Gy and associated 90% likelihood-based CI. When the likelihood-based CI could not be estimated, we report a Wald-type CI. We report the change in deviance upon 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.[19] All models were fitted with EPICURE software (version 1.81; Risk Sciences International, Ottawa, ON, Canada). Data protection regulations in Europe did not allow the transfer of raw personnel data between countries, and only aggregated data tables could be shared. Accordingly, descriptive statistics as medians and IQR were not calculable (table 1).

Role of the funding source

The funders of the study had no role in the study design, the data analysis and interpretation, the writing of the report, or in the decision to submit the paper for publication.

Results

Table 1 shows characteristics of the cohort. The study included 309 932 workers, of whom 269 487 (87%) were males and 40 445 (13%) females. On average, the workers were followed up for 35 years and were 66 years of age at the end of follow-up. The extension of follow-up resulted in a 30% increase in the number of person-years, which reached 10·72 million (8·22 million in the previous study).[5] The average cumulative red bone marrow dose was 16·2 mGy in the total cohort, and 19·3 mGy among 259 994 exposed workers (ie, those with at least one positive recorded dose, who represent 84% of the study cohort). At the end of the follow-up (Dec 31, 2016), 200 168 (65%) of workers were alive and 6211 (2%) had emigrated or were otherwise lost to follow-up for vital status ascertainment; 103 553 deaths were recorded, among them 771 were due to non-CLL leukaemia, 1146 to non-Hodgkin lymphoma, 122 to Hodgkin lymphoma, and 527 to multiple myeloma. Less than 2% (1772) of decedents had a missing or unknown underlying cause of death. Most deaths from leukaemia, lymphoma, and multiple myeloma were observed among workers who accumulated less than 5 mGy of dose, consistent with the distribution of person-years with respect to cumulative dose (appendix 2 p 3).

Using a linear ERR model, a positive dose-response association was obtained for non-CLL leukaemia (ERR per Gy 2·68, 90% CI 1·13 to 4·55), driven by a large radiation-related excess of chronic myeloid leukaemia (9·57, 4·00 to 17·9; table 2). A positive dose-response association was observed for myelodysplastic syndromes (3·19, 0·35 to 7·33) and for acute myeloid leukaemia and myelodysplastic syndromes combined (1·55, 0·05 to 3·42). The estimated ERR per Gy for multiple myeloma was 1·62 (90% CI 0·06 to 3·64, n=527). Estimates of association were quite imprecise and not significant for acute myeloid leukaemia (0·75, −0·96 to 2·92, n=435), acute lymphoblastic leukaemia (4·25, −4·19 to 19·32, n=49), CLL (0·20, −1·81 to 2·21, n=242), Hodgkin lymphoma (0·60, −3·64 to 4·83, n=122) and non-Hodgkin lymphoma (0·27, −0·61 to 1·39, n=1146; table 2). Based on a simple linear ERR model, an estimated 40·4 deaths due to non-CLL leukaemia were in excess among the 771 observed (appendix 2 p 4). As males represent 87% of the cohort, the association between radiation dose and non-CLL leukaemia mortality was quantified in males only (ERR per Gy 2·55; 90% CI 1·02 to 4·41; n=691). In females, 74 (93%) out of 80 deaths from non-CLL leukaemia were observed in those who cumulated less than 20 mGy and the estimated ERR per Gy (16·13, 90% CI <0 to 49·65) was extremely imprecise.

Estimates of ERR per Gy of cumulative red bone marrow dose for death due to leukaemia, lymphoma, and multiple myeloma under different exposure lag assumptions are shown in appendix 2 (p 5). For non-CLL leukaemia the best model fit was obtained under a 5-year lag (ERR per Gy 2·95, 90% CI 1·32–4·91); under our a priori 2-year lag, model fit was poorer. For chronic myeloid leukaemia the best model fit was observed under a 5-year lag. For acute myeloid leukaemia, the best fit was obtained under a 15-year lag, although the estimate of association was imprecise. For acute lymphoblastic leukaemia, the shorter the lag, the better the model goodness of fit, while for CLL, non-Hodgkin lymphoma, and Hodgkin lymphoma, the longer the lag, the better the model fit (albeit with highly imprecise estimates of association for these outcomes). For multiple myeloma, the model fit was marginally better under a 5-year lag than under the a priori 10-year lag (while estimates of ERR per unit dose were similar under these lags).

The graphical representation of relative rates of death from non-CLL leukaemia by dose category did not show any strong deviation from linearity (figure), a conclusion supported by a formal comparison of the fit of the linear model to linear-quadratic and purely quadratic models. Model fit was not improved under a linear-quadratic model when compared with a linear model, and a quadratic model did not fit better than the linear ERR model. Similar conclusions were drawn for multiple myeloma: neither a linear-quadratic nor a pure quadratic model fitted the data better than a linear dose-risk model (appendix 2 p 10).

We investigated the radiation-associated risk of non-CLL leukaemia on restricted dose ranges; over the dose range 0–300 mGy, we observed a positive association, somewhat larger in magnitude than that obtained over the full dose range (ERR per Gy 3·10, 90% CI 1·22 to 5·35; appendix 2 p 6). The slopes of the dose-response relation over the 0–200 mGy and 0–100 mGy dose range were comparable in magnitude to (but less precise than) that estimated in the whole cohort; however, the estimated ERR per Gy diminished to 0·35 (90% CI −5·45 to 7·24) when the dose range was restricted to 0–50 mGy (appendix 2 p 6).

Attained age showed a modifying effect on the dose-response association for non-CLL leukaemia, although not significantly, with an increasing ERR per Gy with increasing attained age (appendix 2 p 7). Consistent with this result, when excluding years of follow-up from age 80 years onwards, the slope of the dose-response relationship decreased (ERR per Gy 1·71, 90% CI 0·09 to 3·72; n=614; not shown).

We examined the impact of neutron monitoring status and internal contamination status on the dose-response association for non-CLL leukaemia but observed no significant modifying effect for either neutron monitoring status or for internal contamination status (appendix 2 p 7).

We compared the ERR of death from non-CLL leukaemia as a function of the date of hire and we observed no differences between the dose-response associations by hire date, whether for a cutoff date of 1958 or a cutoff date of 1965 (appendix 2 p 7).

The effect that a single country could have on the non-CLL leukaemia results was investigated by excluding one country at a time from the analysis: excluding France or the USA decreased the estimated ERR per unit dose (ERR per Gy 2·17, 90% CI 0·68–3·99 without France and 2·04, 0·11–4·59 without the USA) and excluding the UK had an opposite effect (4·33, 1·94–7·32; appendix 2 p 9). We found some heterogeneity among the national risk estimates that was no longer observed when attained age was restricted to younger than 80 years (results not shown).

Upon further adjustment for socioeconomic status, duration of employment, or year of hire, the estimated ERR per unit dose changed by less than 10%; upon further adjustment for neutron monitoring status the estimated ERR per Gy diminished to 2·30 (90% CI 0·64–4·43), whereas upon adjustment for internal contamination status the estimated ERR per Gy increased to 3·28 (1·50–5·48; appendix 2 p 8).

Table 3 shows the comparison between this updated analysis and the previous INWORKS estimates;[6] the extended follow-up resulted in a 45% (771 *vs* 531 in the previous analysis) increase in non-CLL leukaemia deaths, 61% (1146 *vs* 710) increase in non-Hodgkin lymphoma deaths and 17% (122 *vs* 104) increase in Hodgkin lymphoma deaths, and an 80% (527 *vs* 293) increase in multiple myeloma deaths.

Discussion

In INWORKS, we report an association between low-dose ionising radiation and non-CLL leukaemia mortality, driven by a large ERR of chronic myeloid leukaemia per unit red bone marrow dose. The association between non-CLL leukaemia mortality and cumulative dose is reasonably described by a linear dose-response model. For the first time, we examined mortality due to myelodysplastic syndromes in this cohort, and a positive association was observed with cumulative dose. There also is evidence of a positive association between radiation dose and multiple myeloma mortality (albeit with wide CIs), whereas there is minimal evidence of association between radiation dose and death from non-Hodgkin lymphoma or Hodgkin lymphoma. A strength of this update of INWORKS when compared with the previous analysis,[6] is that the precision of ERR estimates has improved, with

narrower CIs for most outcomes examined (table 3); for non-CLL leukaemia, the magnitude of the estimate is consistent with the value reported in the previous analysis, for lymphoma the current estimates are lower than in the previous analysis, and for multiple myeloma, the magnitude of the estimate of association is twice as large as that reported in our previous INWORKS analysis.

The Radiation Effects Research Foundation Life Span Study (known as the Life Span Study, LSS) of Japanese atomic bomb survivors serves as an important basis for the international radiation protection system.[20] Although the acute high dose rate radiation exposures caused by the bombs differ from the protracted low-dose rate exposures typically received by nuclear workers, our estimate of the ERR per Gy absorbed dose to the red bone marrow for death from leukaemia was of similar magnitude to the estimate of ERR per Gy reported in the 2021 analyses of the LSS: when restrictions were made on the study population to make it comparable with the INWORKS population features, the ERR per Gy in the LSS was 2·75 (90% CI 1·73–4·21)[21] based on a linear model, which is very close to the estimated ERR per Gy in the present INWORKS analysis (ERR per Gy 2·68, 90% CI 1·13–4·55). There are differences however, in that a linear-quadratic model with an upward curvature described the data better in the LSS, whereas no departure from linearity is observed in INWORKS (albeit over a much narrower dose range than that examined in the LSS), and in the LSS the ERR per Gy decreased with attained age, whereas the opposite is true in INWORKS (noting that INWORKS considers only exposures at adult working ages [≥20 years] whereas the LSS involves people exposed at all ages).

Other epidemiological studies have investigated radiation induced risk of leukaemia.[1,3] Some reported positive dose-response associations for non-CLL leukaemia,[3,22,23] although others encompassed small numbers of cases or were based on narrow dose distributions and yielded imprecise risk estimates.[3,22,24]

The UK NRRW study examined non-CLL leukaemia incidence and reported a significant dose-response relationship (ERR per sievert [Sv] 1·38, 90% CI 0·04–3·34) in male workers (who represent more than 90% of the cohort), with a strong association for chronic myeloid leukaemia (6·77, 2·13–15·4).[18] The risk coefficients per unit dose are lower than those estimated in INWORKS, but in the NRRW the authors used dose equivalents in Sv and not absorbed red bone marrow dose.

We report a positive association between radiation and myelodysplastic syndromes mortality. Myelodysplastic syndromes is now considered to be a disease of neoplastic nature and the boundary between myelodysplastic syndromes and acute myeloid leukaemia has become thinner.[25] Until the mid-1980s, cases were often misdiagnosed as acute myeloid leukaemia. A positive finding was observed between external radiation and myelodysplastic syndromes in the Nagasaki atomic bomb survivors, with an ERR per Gy of 4·3 (95% CI 1·6–9·5),[26] which is compatible with association observed in INWORKS.

We observed minimal evidence of association between radiation dose and non-Hodgkin lymphoma mortality (ERR per Gy 0·27, 90% CI –0·61 to 1·39). Few epidemiological studies have reported a significant positive dose-risk association for non-Hodgkin lymphoma,

whether for medical, environmental, or occupational exposures.[1] In 2013 report from the LSS, Hsu and colleagues[2] showed a non-significantly increased risk of non-Hodgkin lymphoma incidence in men (ERR per Gy 0·46, 95% CI −0·08 to 1·29; p=0·11), but not in women. The UK NRRW cohort reported a significant association between radiation dose and non-Hodgkin lymphoma incidence (ERR per Sv 1·11, 95% CI 0·02 to 2·60; p=0·045; n=711),[10] but not mortality (ERR per Sv 1·31, 90% CI −0·25 to 3·77; n=353).[9] A positive association also was reported in analyses of mortality among US nuclear workers for all lymphoma combined (ERR per Sv 1·8, 95% CI 0·03 to –4·4).[27]

A recent study[28] assessed associations between radiation and incidence of lymphoid neoplasms by histological subtype[29] in the LSS cohort. A significant association was reported for all non-Hodgkin lymphoid neoplasms (ERR per Gy 0·54, 95% CI 0·14–1·09) although a direct comparison with our results is complicated because of differences in outcome classifications. Evidence of a positive association between ionising radiation dose and lymphoid malignancies also has been reported in a study of patients exposed to CT scan during childhood.[30]

We observed minimal evidence of association between red bone marrow dose and Hodgkin lymphoma mortality, consistent with the conclusions of the United Nations Scientific Committee on the Effects of Atomic Radiation[1] and studies of accidental[2] and occupational[31] exposures. In the LSS, a non-significant association with Hodgkin lymphoma incidence was reported of similar magnitude to that reported in INWORKS (ERR per Gy 0·61; 95% CI less than −0·09 to 7·17; n=15).[28]

With updated follow-up the number of deaths due to multiple myeloma increased by 80%. An interesting new result in this study is evidence of a positive association between radiation dose and multiple myeloma mortality (albeit with wide CIs); notably, however, the association is negligible upon excluding the USA from the pooled analysis (appendix 2 p 9). Our estimated ERR per Gy is larger than, but statistically compatible with, the estimate of the radiation dose-multiple myeloma mortality association reported in the LSS (ERR per Gy 0·54, 95% CI −0·04 to 1·58),[32] and smaller than, but statistically compatible with, the estimate of the radiation dose-multiple myeloma incidence association in the UK NRRW (ERR per Gy 2·63, 95% CI 0·30 to 6·37).[10]

The study’s strengths lie in its large size, long duration of follow-up, and individual dose estimates based on personal dosimetry.[13] Uncertainties in dose estimates are certainly larger in earlier periods of employment, when dosimeters were less accurate than contemporary ones.[13] We investigated whether excluding workers with earlier date of first employment affected the estimate of the slope of the dose-response relationship for non-CLL leukaemia but found minimal evidence that associations were sensitive to such exclusions.

Despite its large size, the cohort is limited to inform on risks in females, because whatever the outcome, the few deaths were predominantly (83–100% depending on the outcome) observed in women who had accumulated less than 20 mGy (result not shown).

We have no precise data on doses due to incorporation of radionuclides such as uranium or plutonium, but considering workers’ status with regard to a possible contamination did

not change the dose-response relationship between external dose and non-CLL leukaemia mortality (appendix 2 p 8). We also found that considering neutron monitoring status did not change the dose-response relationship.

Information on other potential confounders is limited in INWORKS. Considering agents with sufficient evidence of carcinogenicity,[33] excluding alkylating agents and x-rays and gamma (γ) rays, there are three agents with sufficient evidence of carcinogenicity for non-lymphocytic leukaemia in human: benzene, formaldehyde, and tobacco smoking.[33] While formaldehyde is not widely used in the nuclear industry (except perhaps in nuclear waste processing), benzene cannot be ruled out as a potential confounder. Previous studies in US nuclear workers found that early workers (ie, workers first hired in the first decades of nuclear industry) were at greater risk of benzene exposure and when these workers were excluded, there was no potential for substantial confounding.[34] We showed that excluding early workers did not significantly impact the association between radiation and non-CLL leukaemia mortality, which argues against the hypothesis of strong confounding by benzene. In a sensitivity analysis, we adjusted for duration of employment, which led to minimal change in the estimate of association between radiation dose and mortality due to non-CLL leukaemia (appendix 2 p 8), arguing against substantial confounding due to preferential retention of workers in better health (sometimes termed healthy worker survivor bias) for this outcome. As for tobacco smoking, a 2023 analysis of INWORKS[7] reported that radiation dose had minimal association with chronic obstructive pulmonary disease, an outcome strongly associated with smoking; this provides indirect evidence against the hypothesis of strong confounding by smoking.

In contrast to a previous analysis of non-CLL leukaemia mortality in this population,[6] we observed evidence of heterogeneity in association by country (appendix 2 p 9). The estimate for the French cohort appeared higher than for the UK and US cohorts; in the French cohort the effect of attained age is particularly significant.[11] When the age at the end of follow-up was constrained to younger than 80 years, heterogeneity by country reduced markedly. Outcome misclassification among older adults could contribute to heterogeneity in association by country (and its reduction upon excluding those at the oldest attained ages).

In conclusion, studies of people exposed to low doses of radiation add to our understanding of radiation risks at the exposure levels of contemporary concern, and thus can inform radiation protection efforts.[35] The United Nations Scientific Committee on the Effects of Atomic Radiation[3] and the US National Cancer Institute[22] have examined studies on leukaemia risk after low-dose external exposure and concluded that most of them were consistent with a positive dose–risk relationship. This analysis of INWORKS supports those findings. Nevertheless, the absolute excess risk remains low at low doses: in a population of 10 000 workers exposed to an average occupational dose of 16 mGy, we would expect 1·3 non-CLL deaths attributable to exposure (among 25 non-CLL leukaemia deaths) over a 35-year period. The evidence of associations between cumulative radiation dose and multiple myeloma and myelodysplastic syndromes in INWORKS should be further examined in future studies.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Research in context

Evidence before this study

A formal literature search was not done; rather, we drew upon major reviews of the literature. The primary quantitative basis for radiation protection standards comes from studies of populations exposed to acute, high doses of ionising radiation. We previously showed the feasibility of pooling data for radiation workers from some of the world's most informative cohorts in the UK, France, and the USA. Findings from the INWORKS study contributed to discussions by the organisations that advise on ionizing radiation protection.

Added value of this study

This update of the INWORKS study, with 10·72 million person-years of follow-up, strengthens evidence of positive dose–response relationships between cumulative low-dose external exposure to ionising radiation and death caused by leukaemia (excluding chronic lymphocytic leukaemia), but also myelodysplastic syndromes and multiple myeloma, improving knowledge of the causes of these diseases. The excess risk coefficient per unit dose for leukaemia derived from this study is consistent with values reported from analyses of other populations exposed to radiation at higher doses and higher dose rates, whereas the excess risk coefficient per unit dose for multiple myeloma was larger than values reported in those studies.

Implications of all the available evidence

The updated results of INWORKS shed new light on the radiogenicity of haemopathies such as myelodysplastic syndromes and multiple myeloma, and adds to our knowledge of cancer risks associated with the low-dose exposure patterns that are experienced in many contemporary settings. These findings show the importance of adherence to the basic principles of radiation protection, to optimise protection to reduce exposures as much as reasonably achievable and, in the case of patient exposure, to justify that the exposure does more good than harm.

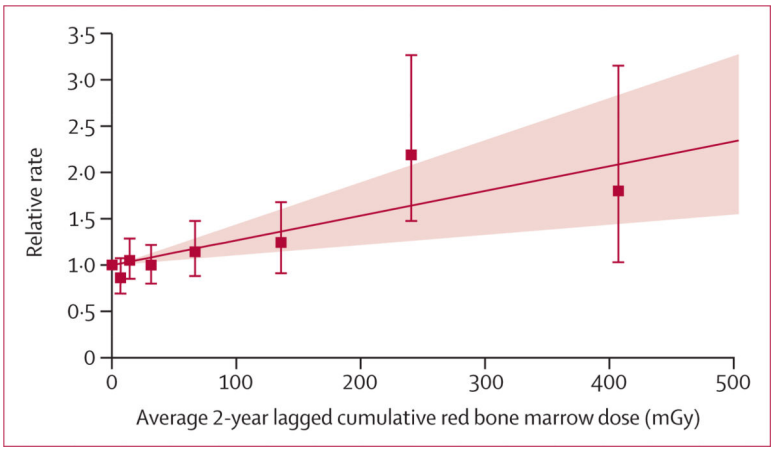

Figure: Relative rates of mortality due to leukaemia (excluding chronic lymphocytic leukaemia) by category of 2-year lagged cumulative red bone marrow dose

The vertical bars indicate 90% CIs, and the solid line is the fitted linear excess relative rate of leukaemia with dose (dotted lines depict 90% Cl). The model is stratified on country, sex, birth cohort, and attained age.

Table 1:

Characteristics of the cohorts included in INWORKS: nuclear workers in France, the UK, and the USA, 1944–2016

	France	UK	USA	INWORKS
Calendar years of follow-up	1968–2014	1955–2012	1944–2016	1944–2016
Workers	60 697	147 872	101 363	309 932
Sex				
Male	52 895	134 768	81 824	269 487
Female	7 802	13 104	19 539	40 445
Follow-up (million person-years)	2·08	4·67	3·98	10·72
Males	1·80	4·27	3·17	9·24
Females	0·28	0·40	0·81	1·48
Deaths (all causes)	12 270	39 933	51 350	103 553
Leukemia excluding CLL	122	264	385	771
Chronic myeloid leukaemia	21	46	55	122
Acute myeloid leukaemia	54	160	221	435
Myelodysplastic syndrome	19	34	110	163
Acute lymphoblastic leukaemia	12	17	20	49
CLL	37	90	115	242
Non-Hodgkin lymphoma	160	387	599	1146
Hodgkin lymphoma	21	41	60	122
Multiple myeloma	74	186	267	527
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 cumulative dose, mGy [*]	11·88	18·47	15·39	16·17
Males	13·29	19·84	18·33	18·09
Females	2·33	4·37	3·06	3·34
Exposed workers [†]	43 785 (72%)	131 253 (89%)	84 956 (84%)	259 994 (84%)
Males	40 272 (76%)	119 420 (89%)	71 600 (88%)	231 292 (86%)
Females	3513 (45%)	11 833 (90%)	13 356 (68%)	28 702 (71%)
Average cumulative dose (mGy) [*‡]				
All	16·47	18·47	18·36	19·28
Males	17·45	22·39	20·95	21·08
Females	5·17	4·84	4·48	4·71

Ethnic and racial backgrounds of the workers are not available in the cohort. CLL=chronic lymphocytic leukaemia. INWORKS=International Nuclear Workers Study.

[*] To red bone marrow.

[†] Those with at least one positive recorded dose.

[‡] Among exposed workers only.

Table 2:

Estimates of ERR per Gy of cumulative red bone marrow dose, for death from leukaemia, myelodysplastic syndromes, lymphoma, and multiple myeloma in INWORKS

	Deaths	Lag assumption (years)	ERR per Gy*	90% CI
Leukemia excluding CLL	771	2	2·68	1·13 to 4·55
Chronic myeloid leukaemia	122	2	9·57	4·00 to 17·91
Acute myeloid leukaemia	435	2	0·75	−0·96 to 2·92
Myelodysplastic syndromes	163	2	3·19	0·35 to 7·33
Acute myeloid leukaemia with myelodysplastic syndromes	598	2	1·55	0·05 to 3·42
Acute lymphoblastic leukaemia	49	2	4·25	−4·19 to 19·32
CLL	242	2	0·20	−1·81 to 2·21†
Non-Hodgkin lymphoma	1146	10	0·27	−0·61 to 1·39
Hodgkin lymphoma	122	10	0·60	−3·64 to 4·83†
Multiple myeloma	527	10	1·62	0·06 to 3·64

CLL=chronic lymphocytic leukaemia. ERR=excess relative rate. INWORKS=International Nuclear Workers Study.

*Linear ERR model stratified by country, birth cohort, age, and sex.

†Wald-type CI (likelihood-based CI lower bound could not be estimated).

Table 3:

Comparison of estimates of ERR per Gy of red bone marrow cumulative dose for death due to leukaemia, lymphoma, and multiple myeloma in different updates of INWORKS

	Deaths	ERR per Gy*	90% CI
Previous INWORKS report (308 297 workers to 8·2 million person-years)[6]			
Leukemia excluding chronic lymphocytic leukaemia†	531	2·96	1·17 to 5·21
Non-Hodgkin lymphoma‡	710	0·47	−0·76 to 2·03
Hodgkin lymphoma‡	104	2·94	NE to 11·49
Multiple myeloma‡	293	0·84	−0·96 to 3·33
Current INWORKS report (309 932 workers to 10·7 million person-years)			
Leukemia excluding chronic lymphocytic leukaemia†	771	2·68	1·13 to 4·55
Non-Hodgkin lymphoma‡	1146	0·27	−0·61 to 1·39
Hodgkin lymphoma‡	122	0·60	NE to 6·67
Multiple myeloma‡	527	1·62	0·06 to 3·64

ERR=excess relative rate. NE=not estimated. INWORKS=International Nuclear Workers Study.

*Stratified by country, birth cohort, age, and sex.

†2-year lagged cumulative dose.

‡10-year lagged cumulative dose.

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Site-specific Solid Cancer Mortality After Exposure to Ionizing Radiation:

A Cohort Study of Workers (INWORKS)

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Abstract

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.

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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.

The other authors have no conflicts to report.

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).

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.

There is considerable scientific interest in associations between radiation dose and the occurrence of specific types of cancer.[1–3] Such estimates have practical utility for decision makers, as well as scientific relevance for those interested in variation in associations between exposure to ionizing radiation and different types of cancer.

We report estimates of radiation dose–mortality associations derived using information from the International Nuclear Workers Study (INWORKS), a collaborative study of mortality among nuclear workers in France, the United Kingdom, and the United States. These workers were monitored for external exposure to radiation using personal dosimeters and have been followed over decades to collect information on vital status and causes of death. Using INWORKS data, we previously reported that the estimated excess relative rate per Gy for death attributable to solid cancer was 0.47 (90% CI = 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 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 examined[4] 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

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

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 jth 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]

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 death[27]; 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 model[6] under which the distribution of the β^j parameters is modeled as a function of the overall mean effect and residual effects:

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

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, auto-correlation 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).

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; 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 appropach 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 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 type[36]; 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 ascertainments 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 cancer[4]; 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.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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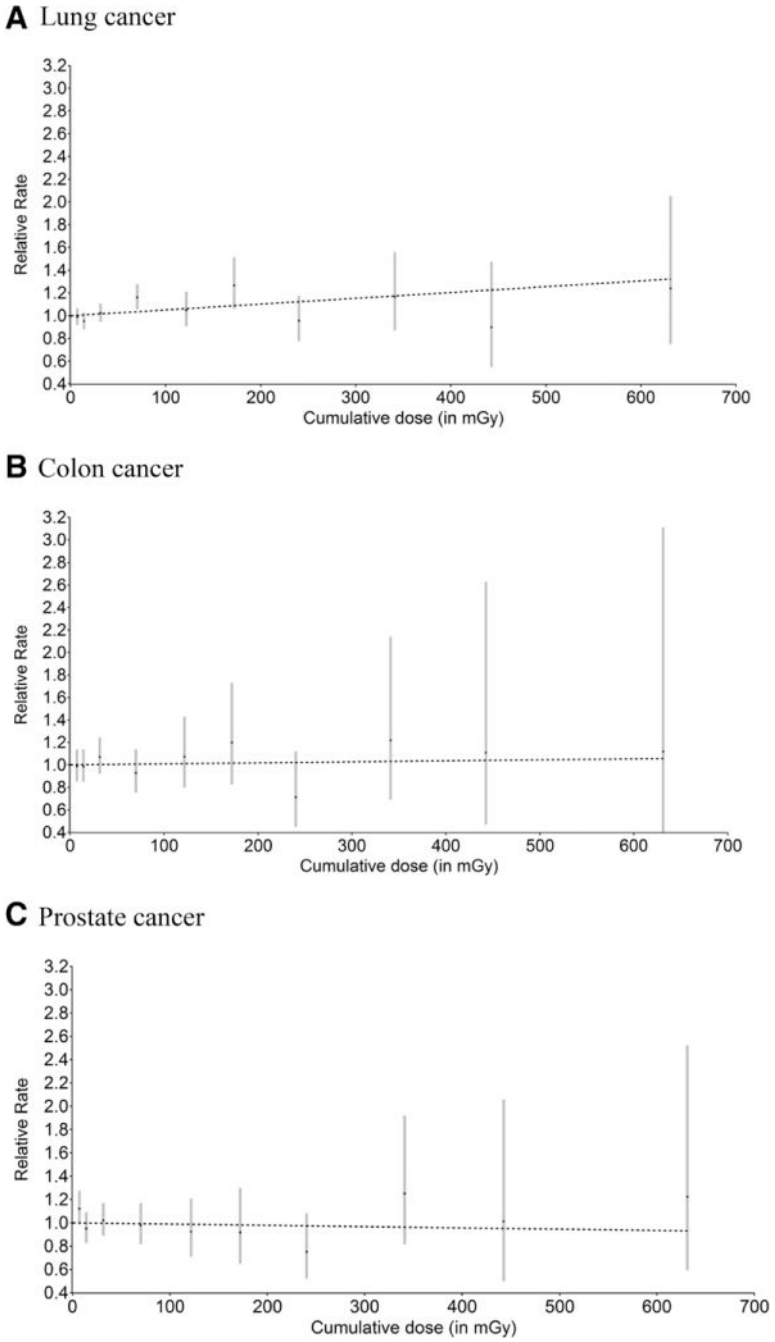

FIGURE 1.

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.

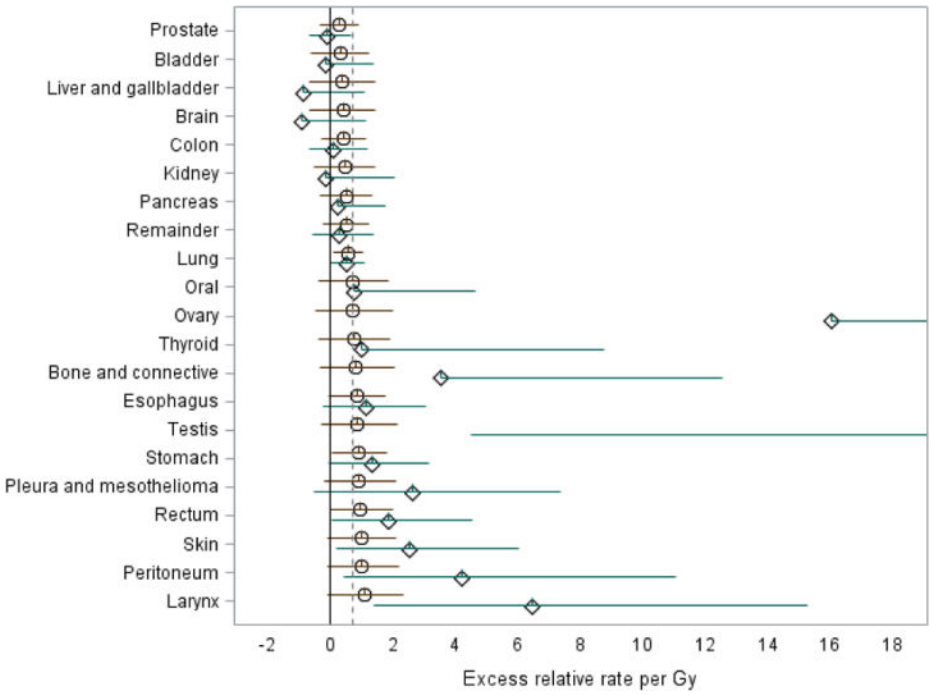

FIGURE 2.

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.

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.

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

[a]ICD-10 code C45.

TABLE 3

Characteristics of Estimated Cumulative Dose to Select Organs, in mGy,[a] INWORKS Consortium, 1944–2005

		Males			Females		
		Cumulative Organ Dose (mGy)			Cumulative Organ Dose (mGy)[b]		
Target Tissue	Related Cancer Types	Mean[a]	Median (IQR)[a]	95th Percentile[a]	Mean	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

[a] Among 228,990 male workers with cumulative dose >0.

[b] Among 28,178 female workers with cumulative dose >0.

IQR, interquartile range.

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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

	Maximum Likelihood			Hierarchical Bayes		
Cause of Death	**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

[a] 10-year lag assumption. Estimates not reported for female breast and uterus attributable to poor model convergence.

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Original Contribution

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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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 the United States were monitored for external radiation exposure. Associations of radiation 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 to 0.91), and colon cancer (ERR per Gy = 0.53; 95% CrI, −0.07 to 1.11). The results contribute evidence regarding associations between low-dose radiation and cancer.

Key words: ionizing radiation; cohort studies; mortality study; occupational exposures; nuclear workers; cancer.

Introduction

The International Nuclear Workers Study (INWORKS) includes nuclear workers in France, the United Kingdom, and the United States who were monitored for external exposure to ionizing radiation using personal dosimeters and subsequently were 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 regard 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 death 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 was used to stabilize estimates by shrinkage toward the mean of the site-specific solid cancer estimates via a hierarchical regression.[8,9]

Methods

The INWORKS is a collaborative occupational cohort mortality study of workers from France, the United Kingdom, and the United States who were employed in the nuclear industry for at least 1 year and monitored, using personal dosimeters, for external radiation exposure.[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

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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* 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 *International Classification of Diseases* 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 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 were classified into 5 categories, based on job title: professional and technical workers, administrative staff, skilled workers, unskilled workers, and uncertain; other UK workers were classified into 2 broader categories of nonindustrial and industrial employees), duration of employment or radiation work (in 10-year intervals), neutron monitoring status, and cumulative dose (in categories of <5, 10, 20, 50, 100, 150, 200, 300, 400, and 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 the following 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 denote 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 quantify the association between Z^j and the j^{th} cancer type as the excess relative rate (ERR; 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 3 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 3 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 ERR per Gy and associated 90% profile likelihood-based CIs. An ERR 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 "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. 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:

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

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 toward 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 ERR 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 ERR per Gy were obtained as the mean of the posterior distribution, and estimates of associated 90% highest posterior density credible intervals (CrIs) were obtained using a Markov chain Monte Carlo algorithm implemented in SAS PROC MCMC.

Table 1. Characteristics of the cohorts included in the International Nuclear Workers Study, 1944-2016.

Characteristic	Deaths due to solid cancer	Person-years (millions), no. (%)
Country		
France	4446	2.08 (19)
United Kingdom	11 574	4.67 (44)
United States	12 069	3.98 (37)
Age, years		
<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	25 465	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 or later	637	2.26 (21)
Socioeconomic status		
Professional and technical	7878	3.79 (35)
Administrative	2440	0.95 (9)
Skilled	12 636	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	24 213	9.45 (88)
Ever	2468	0.73 (7)
Neutron dose exceeded 10% of total dose	1408	0.54 (5)

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, whereas average estimated cumulative doses to the liver (19.5 mGy), pancreas (19.2 mGy), and brain (18.6 mGy) were slightly lower. 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.

The analysis includes 28 089 deaths due to solid cancer, representing a substantial update from the previous analysis of INWORKS (Table S1). Although 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 cancers; the least common were testis and thyroid cancers (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 2 cancer types with the fewest deaths). For the most common cancer types, lung, prostate, and colon cancer (collectively accounting for half of all solid cancers), estimates of the ERR ranged 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 degrees of freedom [df]), prostate (LRT = 0.14; 2 df), or colon cancer (LRT = 1.13; 2 df).

Under a 5-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 df]; $P = .25$) or colon (LRT = 0.0 [1 df]; $P = .92$), 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 df]; $P = .04$), 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 (ie, 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 df]; $P = .89$), colon (LRT = 0.3 [1 df];

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: International Nuclear Workers Study Consortium (1944-2016).[a]

Cancer type	No. of deaths	Maximum likelihood		Markov chain Monte Carlo	
		ERR[b] per Gy	90% CI	ERR per Gy	90% CI
Oral cavity and pharynx[c]	522	−0.58	−2.79 to 2.16	0.47	−0.44 to 1.37
Esophagus[c]	1112	−0.16	−1.06 to 0.92	0.34	−0.38 to 1.00
Stomach	1236	1.00	−0.13 to 2.47	0.72	0.01-1.44
Colon	2379	0.41	−0.32 to 1.32	0.53	−0.07 to 1.10
Rectum	875	1.29	−0.05 to 3.10	0.78	0.02-1.56
Liver and gallbladder	867	–[d]	–	0.13	−0.84 to 0.97
Pancreas	1641	0.06	−0.80 to 1.22	0.42	−0.27 to 1.10
Peritoneum	266	2.47	−0.12 to 6.79	0.78	−0.10 to 1.67
Larynx	256	3.34	0.15-8.71	0.81	−0.09 to 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[c]	216	2.48	−3.09 to 9.41	0.64	−0.30 to 1.58
Skin	622	1.44	−0.28 to 3.82	0.74	−0.04 to 1.61
Female breast	640	–[d]	–	0.45	−0.58 to 1.39
Uterus	102	–[d]	–	0.55	−0.44 to 1.51
Ovary[c]	208	−0.43	−14.46 to 19.35	0.58	−0.38 to 1.56
Prostate	2920	0.31	−0.23 to 0.96	0.44	−0.06 to 0.91
Testis	54	33.36	5.49 to 100.10	0.71	−0.21 to 1.72
Bladder	1062	0.33	−0.56 to 1.50	0.51	−0.15 to 1.15
Kidney	803	1.26	−0.10 to 3.22	0.76	−0.01 to 1.51
Brain	923	–[d]	–	0.26	−0.65 to 1.13
Thyroid	66	4.23	−0.40 to 15.32	0.73	−0.21 to 1.64
Remainder	2408	0.43	−0.33 to 1.36	0.53	−0.05 to 1.13

[a]Strata: country, age, sex, birth cohort, socioeconomic status, duration employed, neutron monitoring status.
[b]ERR, excessive relative rate.
[c]Wald-type lower confidence bound for maximum likelihood estimate.
[d]No estimate obtained, due to failure of regression model convergence.

$P = .58$), or lung (LRT = 3.0 [1 df]; $P = .08$) 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 cancers (Table S4). All other cancer sites had positive estimated coefficients. The magnitudes of the estimated ERR per Gy for lung cancer (1.28; 90% CI, 0.37-2.32), prostate (0.57; 90% CI, −0.55 to 2.00), and colon cancer (1.40; 90% CI, −0.02 to 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 cancers. Focusing on lung, liver, and bone cancers, sites that receive the greatest doses from internal depositions of plutonium and uranium, the magnitude of the estimated ERR per 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 per 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 death resulting from 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 per Gy for lung cancer (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 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 mean of the posterior distribution, and the 90% CrI, obtained by this hierarchical regression method were similar to the point estimates and 90% CIs 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 ERR per Gy tended to be shrunk substantially toward 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).

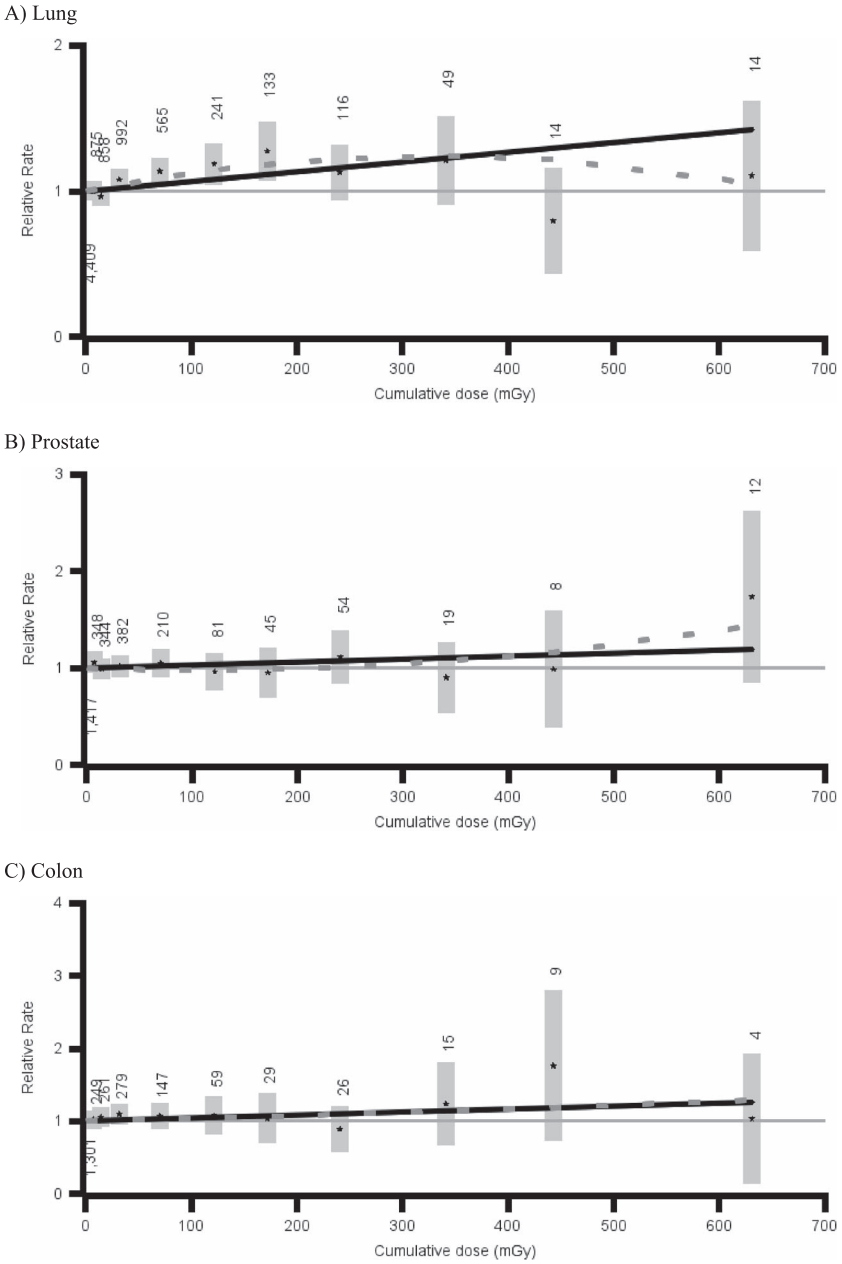

Figure 1. Relative rate of mortality due to lung, prostate, and colon cancers by categories of cumulative colon dose (strata: country, age, sex, birth cohort, socioeconomic status, duration employed, neutron monitoring status), lagged 10 years in the International Nuclear Workers Study. Gray bars indicate 90% CIs, the black solid line depicts the fitted linear model for the change in the excess relative rate of cancer mortality with dose, and the gray dashed line depicts the fitted linear-quadratic model for the change in the excess relative rate of cancer mortality with dose. The gray solid line is a reference line. A) Lung. B) Prostate. C) Colon.

In a sensitivity analysis, we recalculated the shrinkage estimates in analyses illustrating a more informative prior for δ [ie, a N(0.32, 5) prior]. Results were extremely similar to those obtained using a vague prior [ie, N(0,10) prior] for δ (Table S7). In a separate sensitivity analysis, we recalculated 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 cancers of the lung, stomach, and pleura/mesothelioma; the estimated value of was 0.65 (90% CrI, 0.19-1.11); τ^2 was estimated as 0.59 (90% CrI, 0.03-1.24). We also recalculated 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 was 1.40 (90% CrI, 0.63-2.16); τ^2 was estimated as 1.65 (90% CrI, 0.05-3.51).

Discussion

The INWORKS pools information for some of the most informative cohorts of nuclear industry workers in the world; the

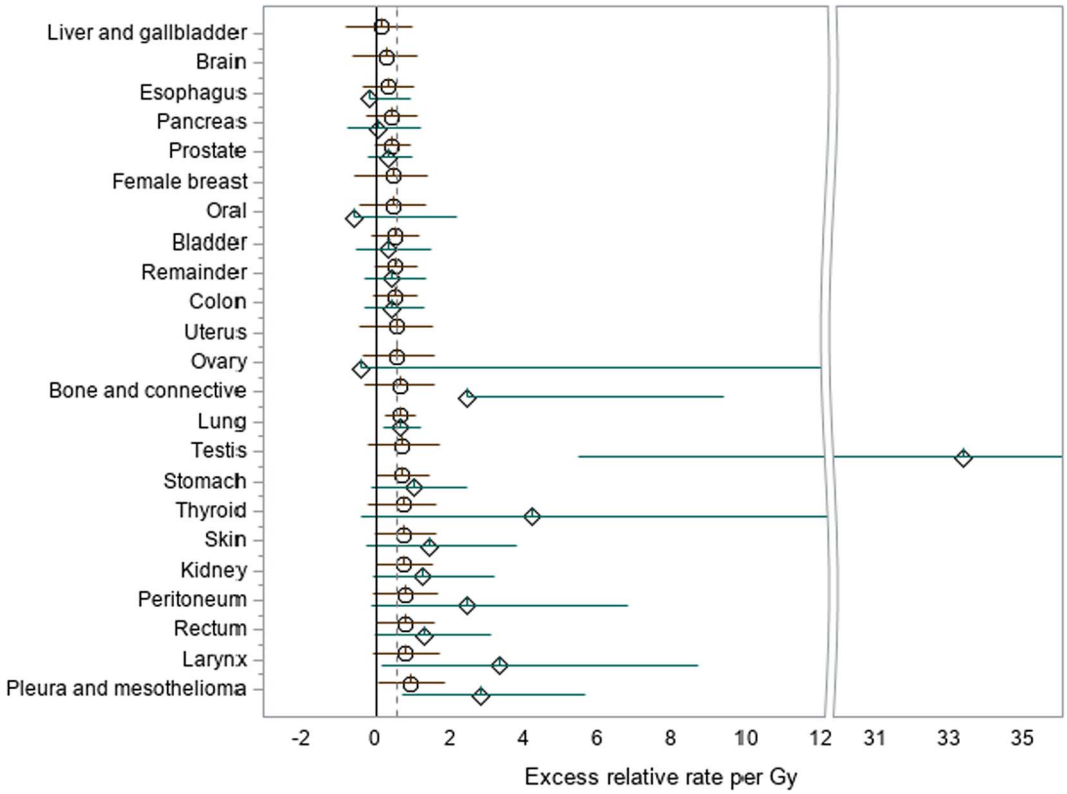

Figure 2. Maximum likelihood and Markov chain Monte Carlo hierarchical regression estimates of excess relative rate per Gy cumulative organ-specific dose (10-year lag assumption) for death due to specific types of cancer. International Nuclear Workers Study consortium, 1944-2016. Circles indicate cancer 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 CIs for maximum likelihood estimates. Gray dashed line indicates estimated mean of hierarchical regression estimates.

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% CIs for estimates of ERR per Gy derived in this 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 imprecise (Table 2). Considering cancer of the lung, which is the most common cancer among the INWORKS participants, 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 years.[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 to 0.2).[29] Considering death due to prostate cancer, our maximum likelihood regression estimate (ERR per Gy = 0.31; 90% CI, −0.23 to 0.96) is similar to that reported in the LSS of atomic bomb survivors (ERR per Gy = 0.33; 95% CI, < 0 to 1.25), although we note 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] Few prior environmental and occupational studies reported a strong indication of a positive association between radiation dose and prostate cancer mortality.[31,32] Considering death due to colon cancer, the maximum likelihood estimate (ERR Gy = 0.41; 90% CI, −0.32 to 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 to 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 cancers. Cancers of the 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 death due to oral cavity and pharynx, esophageal, and ovary cancers were observed in analyses of cancer mortality in the LSS cohort with follow-up from 1950 to 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 per 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 CrIs tended to be narrower than profile likelihood-based CIs 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 per 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 we used allows for radiation–cancer type associations to vary between cancer types, under a model that assumes the parameters describing cancer type–specific associations follow a normal distribution. Although 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 atomic 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 CrIs 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, because the ensemble of parameters tends to be pulled toward 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 women were hired at the study facilities than men, women tended to be assigned to jobs that accrued lower radiation doses than men, 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 present 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] and found minimal evidence of association between radiation dose and chronic obstructive pulmonary disease. In the present 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 (eg, lung and esophageal cancers) 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 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 pleura/mesothelioma cancer (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 cancers, 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 radiation. 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] Furthermore, 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 per Gy for lung cancer, for example, was larger in analyses restricted to 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 the new industry.[51,52] Because large numbers of healthy men had been selected out of the workforce by World War II military conscription, questions have been 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 cancers 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 than in the unrestricted analyses, with exception of liver and gallbladder, pancreas, skin, female breast, and testis, which were smaller 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. 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, because 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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Supplementary material

Supplementary material is available at the *American Journal of Epidemiology* online.

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Conflict of interest

The authors declare no conflict of interest.

Disclaimer

The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the National Institute for Occupational Safety and Health, US Centers for Disease Control and Prevention. 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.

Data availability

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

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Original Contribution

INWORKS: Cancer mortality after low dose exposure to ionising radiation in workers

A recent epidemiological study published in the *British Medical Journal*, titled "Cancer mortality after low dose exposure to ionising radiation in workers in France, the United Kingdom, and the United States (INWORKS): cohort study", evaluated the effects of long-term exposure to low-dose ionizing radiation on cancer mortality. This study by Richardson et al. (2023) is an update of previous work, discussed below.

On this page

History of the INWORKS studies

The **IN**ternational **WORK**ers **S**tudy (INWORKS) is an international study that combines cohorts of nuclear workers in France, the United Kingdom, and the United States. INWORKS is one of the largest, most statistically robust mortality studies. Overall, the study includes 309,932 workers, of which 40,445 are women (~13%). A detailed description of the INWORKS cohorts can be found in Hamra et al. (2016).

The INWORKS studies were born out of an earlier 15-country study, which included Canada, on the mortality of nuclear energy workers (Cardis et al., 2007). Within the 15-country study, the cohorts from France, the United Kingdom, and the United States were selected for the series of subsequent INWORKS studies because they were the most informative: their data had been recently updated, they provided over half of the person-years [1] of follow-up, and they included most of the cancer and leukemia deaths.

Those INWORKS studies investigated the relationship between exposure to ionizing radiation and cause-specific risk of death from:

- leukemia and lymphoma (Leuraud et al., 2015)
- all solid cancers combined (Richardson et al., 2015)
- circulatory diseases and other non-cancer outcomes (Gillies et al., 2017)
- site-specific solid cancers (Richardson et al., 2018)

Overall, these studies found strong evidence of positive associations between chronic low-dose radiation exposure and risk of death from leukemia, all solid cancers combined, many site-specific solid cancers (the most common being lung, prostate, and colon), and non-cancer causes (circulatory diseases primarily). Risk of death increased with cumulative dose for all solid cancers combined.

Summary of the 2023 INWORKS study

The 2023 INWORKS study (Richardson et al., 2023) is an update of the 2015 study (Richardson et al., 2015); both studies investigated the association between chronic, low dose exposure to ionizing radiation and dying from solid cancer (i.e., all solid cancers combined, but not cancers that develop in the blood, bone marrow, or lymph nodes). According to the 2023 INWORKS study, the risk of radiation-induced solid cancer mortality resulting from chronic exposure to low doses of radiation may be slightly higher than previously reported. The study supports a linear association between prolonged low-dose external exposure to ionizing radiation and solid cancer mortality.

Limitations of the 2023 INWORKS study

The authors acknowledge that, like all studies, the 2023 INWORKS study has limitations. For example, only external exposures were considered; doses from internal exposures, such as inhalation and ingestion, were excluded. As a result, the risk may be overestimated. This study used effective dose (whole body and estimated dose to the colon) rather than absorbed dose to the organ, which would have provided more precise risk estimates. This study also lacks individual-level data on risk factors, such as smoking, that could affect the radiation–cancer association; therefore, indirect methods were used to assess confounding by smoking. Despite its limitations, the study incorporates one of the more relatively robust methodologies in the field of radiation epidemiology with worker cohorts and provides reasonable risk estimates.

Results from INWORKS (2015, 2023) are comparable to Life Span Study results

The general understanding of radiation-induced risk was first established from the long-standing Life Span Study (LSS) of the atomic bomb survivors, who have been studied since 1958. The atomic bomb survivors received a single, acute (short-term), whole-body exposure to relatively high levels of ionizing radiation. The doses in the LSS are different than the chronic (long-term), low dose exposures experienced by nuclear energy workers.

The INWORKS studies add to our understanding of radiation risk and are more comparable to modern workers than the LSS given the chronic low dose exposures, actual individual dose measurement (rather than estimation), and the detailed follow-up of workers.

The relationship between ionizing radiation and solid cancer mortality in the 2023 INWORKS study is slightly higher than, albeit comparable to, the LSS results (Richardson et al., 2023; Ozasa et al., 2012; Brenner et al., 2022). Results are statistically comparable because the confidence intervals overlap (see table 1). Compared to the previous analysis on solid cancer mortality (Richardson et al., 2015), the 2023 INWORKS study includes more data, with follow-up extended by 10 years, resulting in more precise risk estimates (i.e., a tighter gap between the lower and upper bounds of the confidence intervals). Compared to the LSS analysis on solid cancer mortality, which has 3.1 million person-years of follow-up data, the 2023 INWORKS study has 10.7 million person-years of follow-up data.

Table 1. Comparison of INWORKS and LSS solid cancer mortality results

Study	Excess relative risk[1] per Gy (% confidence interval)*

Study	Excess relative risk[1] per Gy (% confidence interval)*
INWORKS (Richardson et al., 2015)	0.47 (90% CI: 0.18, 0.79)
INWORKS (Richardson et al., 2023)	0.52 (90% CI: 0.27, 0.77)
Life Span Study (Ozasa et al., 2012)	0.37 (90% CI: 0.17, 0.60)
Life Span Study (Brenner et al., 2022)	0.44 (95% CI: 0.35, 0.54)

[1]The rate of disease in an exposed population divided by the rate of disease in an unexposed population, minus 1, expressed as the excess relative risk (ERR) per unit dose (e.g., per gray or per sievert). An ERR of 0.47 per Gy (equivalent to 1 Sv or 1,000 mSv) means that the probability of an individual dying from a radiation-induced cancer is 1.47 times higher for an individual exposed to 1 Gy compared to an unexposed individual.

*A 90% confidence interval (CI) indicates how often (i.e., 90 out of 100 times) the estimated results fall between the upper and lower bounds, while a 95% confidence interval implies a 5% greater certainty.

Epidemiological studies inform national radiation protection

Epidemiological studies such as the INWORKS studies that look at worker health over their entire careers improve our understanding of the risks associated with exposure to low doses of radiation. Most epidemiological studies show a linear relationship between radiation dose and cancer risk, informing the shape of the dose-response curve.

A linear-non-threshold (LNT) model is the dose-response curve used internationally by most health agencies and nuclear regulators, including the CNSC, to set dose limits for workers and members of the public. This is a conservative approach to account for any uncertainties around how exposure to low doses of radiation may affect health outcomes. Further, current average doses to Canadian nuclear workers are far below dose limits as licensees must keep doses to workers as low as reasonably achievable (ALARA), with social and economic factors being considered. Regulatory dose limits are in place to reduce the risk of cancer, which is a stochastic effect (i.e., a health effect that occurs with a probability that is proportional to the dose magnitude).

INWORKS studies will inform the international radiation protection framework

The 2023 INWORKS study results will inform discussions on radiation protection among the international community (e.g., the International Commission on Radiological Protection, or ICRP) on risk assessment in low dose and low-dose rate settings.

The ICRP aims to publish the next set of general recommendations, which will include dose limits, in the early 2030s. The ICRP will consider all relevant studies published in the literature, including this 2023 INWORKS study, when drafting its next set of recommendations.

Conclusion

There is no immediate action needed in response to the 2023 INWORKS study. The study results continue to support the use of the LNT model as a suitable tool for establishing radiation dose limits that align with the international radiation protection framework and the CNSC's robust regulatory framework for ensuring the health and safety of people and the protection of the environment. The results of the 2023 INWORKS study, combined with other studies on nuclear workers and other radiation-exposed populations, such as medical patients and members of the public, add to the weight of evidence of our understanding of the health effects from low doses of radiation.

- Learn more about radiation.
- Learn more about what the CNSC is doing in low dose research.
- Learn more about radiation health effects and stochastic effects.
- Learn more about the linear-non-threshold (LNT) model.

Footnotes

1 Person-years: a measurement that considers the number of people in the study and the amount of time each person spent in the study.

Date modified:

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