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Source: Radiation Research, 194(4) : 431-444

Published By: Radiation Research Society

URL: <https://doi.org/10.1667/RADE-19-00007.1>

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Ischemic Heart Disease Mortality and Occupational Radiation Exposure in a Nested Matched Case-Control Study of British Nuclear Fuel Cycle Workers: Investigation of Confounding by Lifestyle, Physiological Traits and Occupational Exposures

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de Vocht, F., Hidajat, M., Martin, R. M., Agius R. and Wakeford, R. Ischemic Heart Disease Mortality and Occupational Radiation Exposure in a Nested Matched Case-Control Study of British Nuclear Fuel Cycle Workers: Investigation of Confounding by Lifestyle, Physiological Traits and Occupational Exposures. *Radiat. Res.* 194, 431–444 (2020).

Epidemiological studies have suggested a link between low-level radiation exposure and an increased risk of cardiovascular disease, but the possibility of bias or confounding must be considered. We analyzed data from a matched case-control study nested in a cohort of British male industrial (i.e., blue-collar) nuclear fuel cycle workers using paired conditional logistic regression. The cases were comprised of workers from two nuclear sites who had died from ischemic heart disease (IHD) and were matched to controls on nuclear site, date of birth and first year of employment (1,220 pairs). Radiation doses from external sources and to the liver from internally deposited plutonium and uranium were obtained. Models were adjusted for age at start of employment at either site, decade of start, age at exit from study (death or censoring), process/other worker and socio-economic status. Included potential confounding factors of interest were occupational noise, shift work, pre-employment blood pressure, body mass index and tobacco smoking. Cumulative external doses ranged from 0–1,656 mSv and cumulative internal doses for those monitored for radioactive intakes ranged from 0.004–5,732 mSv. In a categorical analysis, additionally adjusted for whether or not a worker was monitored for internal exposure, IHD mortality risk was associated with cumulative external unlagged dose with a 42% excess risk (95% CI: 4%, 95%) at >103 mSv (highest quartile relative to lowest quartile), and 35% (95% CI: –1%, 84%) at >109 mSv 15-year lagged dose. The log-linear increase in risk per 100 mSv was 2% (95% CI: –4%, 8%) for unlagged external dose and 5% (95% CI: –2%, 11%) for 15-year lagged dose. Associations with external dose for workers

monitored only for exposure to external radiation reflected those previously reported for the cohort from which the cases and controls were drawn. There was little evidence of excess risk associated with cumulative doses from internal sources, which had not been assessed in the cohort study. The impact of the included potential confounding variables was minimal, with the possible exception of occupational noise exposure. Subgroup analyses indicated evidence of heterogeneity between sites, occupational groups and employment duration, and an important factor was whether workers were monitored for the potential presence of internal emitters, which was not explained by other factors included in the study. In summary, we found evidence for an increased IHD mortality risk associated with external radiation dose, but little evidence of an association with internal dose. External dose associations were minimally affected by important confounders. However, the considerable heterogeneity in the associations with external doses observed between subgroups of workers is difficult to explain and requires further work. © 2020 by Radiation Research Society

INTRODUCTION

It has been recognized for many years that acutely delivered high doses of ionizing radiation can cause heart disease (1), including damage to the structure of the heart and arteries (2, 3). At protracted exposures to low doses or low dose rates, there is also evidence of an excess circulatory disease risk, such as that found in studies of radiation workers (4–9). However, while plausible, if not completely understood, mechanisms exist by which acute high doses can affect the circulatory system (10), for low-dose or low-dose-rate radiation exposures only tentative mechanisms have been proposed (11). It has further been postulated that radiation exposure may not only be an independent risk factor for the development of circulatory disease, but may also influence established risk factors (11). Whether the observed associations are causal or not will have considerable importance for radiological protection,

Editor's note. The online version of this article (DOI: <https://doi.org/10.1667/RADE-19-00007.1>) contains supplementary information that is available to all authorized users.

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since it is currently assumed that low-level radiation exposure does not increase the risk of circulatory diseases (12).

Since the evidence for associations between low-dose or low-dose-rate exposures to ionizing radiation and circulatory disease risk remain solely based on observational epidemiological studies, the possibility that these result from biases and unmeasured or insufficiently measured confounding factors cannot be excluded (13). A variety of other potentially important confounding factors have been proposed, including tobacco smoking, diabetes, obesity, elevated blood pressure, and high levels of blood low-density lipoprotein, other occupational exposures (including shift work, stress, noise exposure), chemical exposures (such as polycyclic aromatic hydrocarbons and compounds of lead), possibly low-frequency electromagnetic fields, as well as socio-economic status (5, 6, 14–16). The need to conduct more detailed epidemiological studies that are capable of addressing potential confounding factors (and misclassifying factors and possible biases, such as selection bias) has been explicitly discussed (3). However, relevant information is often not available for occupational cohorts (12), although it may be available for smaller case-control studies where it can be specifically collected at the individual level.

A dose-response association between exposure to ionizing radiation from external sources and ischemic heart disease (IHD) mortality was previously observed in a large cohort of 64,937 nuclear fuel cycle workers employed at four sites operated by the former British Nuclear Fuels Ltd (BNFL) (5). Here we investigated whether this dose response could be the result of confounding, and thus may also have confounded associations observed in other cohorts of radiation workers (3). Because individual-level information on known risk factors for IHD was not available for the entire BNFL worker cohort (or would be prohibitively expensive to collect), we used data from a previously constructed matched case-control study nested in the cohort, which included this information. The workers in this study were employed at the BNFL sites at Sellafield or Springfields, in Northwest England. Operations at Sellafield included nuclear reactors, nuclear fuel reprocessing, plutonium processing, radioactive waste processing and storage, as well as various other operations such as tritium production and processing, while those at Springfields included uranium processing and nuclear fuel manufacturing (5).

MATERIALS AND METHODS

This study was approved by the University of Bristol Faculty of Health Sciences Research Ethics Committee (Application 40782) and by the NDA-PHE Research Governance Group, which includes representatives of employees, Sellafield Ltd, the Nuclear Decommissioning Authority (NDA) and Public Health England (PHE).

This study is a matched case-control study of male industrial (weekly waged, blue-collar) workers employed at one of two nuclear

installations formerly operated by BNFL, involved in production and manual skilled and unskilled work associated with operating and maintaining nuclear fuel cycle plants. The study sample was drawn from a cohort of all male industrial workers who started work at age 50 years or less between January 1, 1950 and December 31, 1998 and had worked for BNFL for at least one month. The study was originally set up to investigate IHD mortality in relationship to shift work (17, 18) and subsequently occupational noise (19). No information on radiation exposure was originally collected because it was not thought at the time that low-level irradiation affected cardiovascular disease risk. Cases were defined as having died from IHD (ICD-8/9, depending on year of death, codes 410–414) at ages 75 years or younger in 1950–1998, as the underlying cause of death provided on the death certificate. Controls were matched to cases 1:1 using incidence density sampling based on nuclear site, year of birth and year of starting employment (both with a 3-year difference being allowed), and still alive at the time of death of the matched case; neither cases nor controls were required to still be working at Sellafield/Springfields at the time of death or censoring.

Estimates of annual equivalent doses from sources of external and internal (uranium and plutonium) radiation were provided by Public Health England using the latest dosimetric models. The estimates of external doses were the same as those used in previously published studies of cancer (20) and non-cancer (5) mortality in workers at BNFL sites, but differed slightly from those used in the UK National Registry for Radiation Workers (NRRW) analyses, which included other dose corrections and dosimeter threshold adjustments, and may have treated notional doses differently (21, 22). The underlying data, dose assessment methodologies and discussion of uncertainties are described in detail elsewhere (23, 24). In short, external doses from penetrating photons, primarily gamma rays, were obtained from personal dosimeters, usually film badges, and some radiation workers may also have had neutron doses recorded (25). Estimated and notional doses were added for missing doses, and “transfer doses” received during employment at other nuclear sites were included where relevant. Recorded whole-body doses were used to estimate annual total external equivalent doses (26). For older, pre-1970 records, internal tritium doses may have been included with external doses since tritium delivers a whole-body dose. Estimates of annual internal equivalent doses were those to the liver from deposited plutonium (the main intake at Sellafield) and uranium (the intake at Springfields), and the methodology is described elsewhere (23, 27). Briefly, these were based on urinalysis measurements, and samples were provided by workers with the potential for non-trivial intakes of plutonium or uranium. Internal doses from other radionuclides, most notably tritium, were not included, but in general these will not contribute significantly to overall doses (28).

For each control, annual doses were censored at the date of death of the matched case. Cumulative external radiation doses were included as a continuous variable and as categories based on quartiles in the distribution in the cases, resulting in 304–305 cases and 291–321 controls per quartile (Supplementary Table S1; <https://doi.org/10.1667/RADE-19-00007.1.S1>). The distribution of cumulative external doses in the quartiles is shown graphically in Supplementary Fig. S1. Cumulative internal dose to the liver was categorized as tertiles based on the distribution in the cases, and a non-monitored group was also included; monitoring for internal emitters was incorporated into models for external radiation exposure as a confounding variable as “monitored for internal exposure”. “Monitored for internal exposure” was considered a confounding factor in the association between cumulative external dose and IHD mortality because it is correlated with cumulative external dose ($r = 0.26$; $P < 0.001$) and with IHD mortality ($r = -0.05$; $P = 0.008$), but it is highly unlikely that it acts as a mediator because external radiation exposure does not directly affect internal exposure. Although putative biological mechanisms that might guide latency considerations are unclear, the strongest associations with external irradiation in the cohort analysis (5) were

found when exposures during the 15 years prior to the index date were ignored (i.e., 15-year lagged dose); for comparison, results for unlagged as well as 15-year lagged doses are presented (with some results for dose lags of 5 and 10 years provided in the Supplementary Materials; <https://doi.org/10.1667/RADE-19-00007.1.S1>).

In the cohort from which these cases and controls were drawn (5), workers were classified as “radiation workers” if they were ever monitored for exposure to external sources of radiation by the end of follow-up, or as “non-radiation workers” if not. Direct comparison of radiation worker dose responses from this nested case-control study with those from the cohort from which the study subjects were drawn could only be done for matched pairs of workers for which the occupational histories of the matched controls were not censored at the dates of death of the corresponding cases; controls who were not monitored for external radiation exposure up to the death of the corresponding case but were monitored afterwards (information we do not have) would erroneously be included in the comparison exercise and classified as “non-radiation workers”, thereby biasing results. Some radiation workers were further monitored for potential exposure to internal sources of radiation from intakes of radioactive materials. Since, in this study, we have temporal data on internal monitoring of workers, the lag applied to external doses is similarly applied to the potential confounding factor, “monitored for internal exposure”. This is an advance on the cohort study (5), which only had data on “ever monitored for internal exposure”, regardless of when the monitoring had occurred. Similar to external exposures, we compare the internal monitoring results with those from the cohort, but are only able to do this appropriately for worker pairs with controls having uncensored occupational histories.

Pre-employment medical examination data included information on systolic and diastolic blood pressure and body mass index (BMI), and tobacco smoking (17–19). Information on shift work and occupational exposure to noise was also available for complete workers’ careers from previously published studies (17–19). Occupational noise was estimated using a job-exposure matrix derived from independent coding by occupational hygienists based on noise monitoring surveys and was expressed as the noise immission level (NIL), with excessive noise classified as noise levels above 85 dB(A) (NIL₈₅). Shift work was ascertained from personnel records, records in the dosimetry department and occupational health department records, and classified as “ever or never engaged in shift work for at least one month”. Information on occupation was ascertained from job titles listed in employment records, and longest-held occupation was used to classify workers as either “process workers” (the most frequent job) or “other workers”, and to code socio-economic status on a 5-level scale based on the Registrar General’s 1970 Classification of Occupations (29). All factors examined were previously suggested as possibly confounding observed associations between IHD mortality and external radiation dose (5).

Paired conditional logistic regression models were conducted in the statistical program *R* version 3.5.1 using the *survival* package (version 2.42.6) (30).

RESULTS

The study population consisted of 1,220 matched case-control pairs of male industrial workers, 651 from Sellafield and 569 from Springfields (Table 1). Cases were mostly comparable to controls but had a slightly higher BMI and blood pressure, and a slightly longer duration of employment. The reported prevalence of tobacco smoking at start of employment was approximately 8 percentage points higher in cases (55%) than controls (47%). Bivariate associations between radiation doses and potential confounding factors and IHD mortality are shown in Supple-

mentary Table S1 (<https://doi.org/10.1667/RADE-19-00007.1.S1>).

Of the workers included in this study, 87% were radiation workers monitored for external exposure (Table 1). External doses (unlagged) ranged from 0–1,655.8 mSv and were comparable between cases and controls, but not between sites (Fig. 1): whereas at Sellafield the median external doses for industrial workers were 69.1 and 64.8 mSv for cases and controls, respectively, these were only 7.1 and 8.6 mSv, respectively, at Springfields. Internal exposure was monitored for 48% of workers, higher in controls (51%) than cases (46%), and higher at Springfields (51%) than at Sellafield (41%) (Table 1). Unlagged internal doses ranged from 0–5,731.5 mSv and were much higher at Sellafield, with (for those monitored for internal exposure) median doses of 164.0 mSv for cases and 139.4 mSv for controls, compared to Springfields with 2.2 mSv and 2.7 mSv for cases and controls, respectively. Distributions for 15-year lagged external and internal doses are shown in Supplementary Fig. S2 (<https://doi.org/10.1667/RADE-19-00007.1.S1>).

External dose (unlagged), adjusted for age at death (or censoring), age and decade of start of employment, monitored for internal exposure, socio-economic status, and longest-held job (process/other worker), was associated with increased IHD mortality risk in a categorical analysis, although less so with a log-linear dose response (Table 2; model 5): increase in risk compared to the reference group (<2.6 mSv) reached conventional statistical significance in the highest dose group of 103+ mSv [OR_{quartile4} = 1.42; 95% confidence interval (CI): 1.04, 1.95] while the log linear increase in odds ratio (OR) per 100 mSv was 1.02 (95% CI: 0.96, 1.08). In Table 3, results are shown for 15-year lagged cumulative external doses, which showed (model 5) a lower IHD mortality risk estimate for the highest dose group (of 109+ mSv) of 1.35 (95% CI: 0.99, 1.84), but the log-linear trend in OR per 100 mSv was higher and close to conventional statistical significance, 1.05 (95% CI: 0.98, 1.12), and was the highest of the estimates for 0-, 5-, 10-, and 15-year dose lags (Supplementary Table S2).

An attenuating effect of employment duration was observed, especially in the highest external dose group, resulting from its correlation with cumulative dose (Tables 2 and 3; model 2). The confounding effects of pre-employment physiological traits (BMI and diastolic and systolic blood pressure), tobacco smoking, and shift work were small, although excessive occupational exposure to noise did have an attenuating effect in the highest quartile (OR_{quartile4} = 1.33; 95% CI: 0.95, 1.86) (Table 2, models 6–9). For a 15-year external dose lag, the effects of confounding from physiological traits, smoking and occupational exposures were smaller compared to those with unlagged external dose (Table 3, models 6–9). The size of the external dose excess risk estimates relied principally on whether workers were ever monitored for potential internal exposure during the relevant period (Tables 2 and 3; model 3).

TABLE 1
Demographics of Matched Case-Control Study Sample

Variable	No. of cases (%)	No. of controls (%)
Number	Total	n = 1,220
Site	Sellafield	651 (53.4)
	Non-radiation workers	77 (11.8)
	Radiation workers	574 (88.2)
	Monitored for internal exposure	268 (41.2)
	Censored occupational history ^a	0 (0%)
	Springfields	569 (46.6)
	Non-radiation workers	93 (16.3)
	Radiation workers	476 (83.7)
	Monitored for internal exposure	291 (51.1)
	Age at start of employment (years)	<20
20–29		295 (24.2)
30–39		427 (35.0)
40–49		442 (36.2)
50+		41 (3.4)
Employment start date (year) at either site		<1950
	1950–1959	809 (67.0)
	1960–1969	258 (21.1)
	1970 +	112 (8.8)
Employment duration (censored) (years)	<5	484 (42.4)
	5–9	164 (12.5)
	10–19	307 (24.0)
	20–29	211 (16.8)
	30+	54 (4.3)
Age at time of death (or censoring) (years)	<40	16 (1.2)
	40–49	135 (11.2)
	50–59	333 (27.0)
	60–69	501 (41.1)
	70+	235 (19.5)
	Socio-economic status (longest-held occupation)	1–2 (highest)
3		473 (38.8)
4		647 (53.0)
5 (lowest)		43 (3.5)
Missing		42 (3.4)
Main occupation (longest-held occupation)	Process worker	554 (45.4)
	Other	625 (51.2)
	Missing	41 (3.4)
Cumulative NIL ₈₅ exposure (dB(A)-years)	<85.0	445 (36.5)
	85.0–94.8	257 (21.1)
	94.9–99.7	270 (22.1)
	99.8+	243 (20.0)
	Missing	5 (0.4)
Shift work	Ever	688 (56.4)
	Never	447 (36.6)
	Missing	85 (7.0)
Pre-employment BMI	<18.5	28 (2.3)
	18.5–24.9	762 (62.5)
	25.0–29.9	344 (28.2)
	30+	50 (4.1)
Pre-employment smoking status	Current smoker	667 (54.7)
	Non/ex-smoker	207 (17.0)
	Missing	346 (28.4)
Pre-employment diastolic blood pressure (mmHg)	<70	26 (2.1)
	70–85	486 (39.8)
	86–99	444 (36.4)
	100+	198 (16.2)
	Missing	66 (5.4)
Pre-employment systolic blood pressure (mmHg)	<120	66 (5.4)
	120–138	453 (37.1)
	138–159	450 (36.9)
	160+	185 (15.2)
	Missing	66 (5.4)

^a Controls continued to work at Sellafield/Springfields after the death of the matched case.

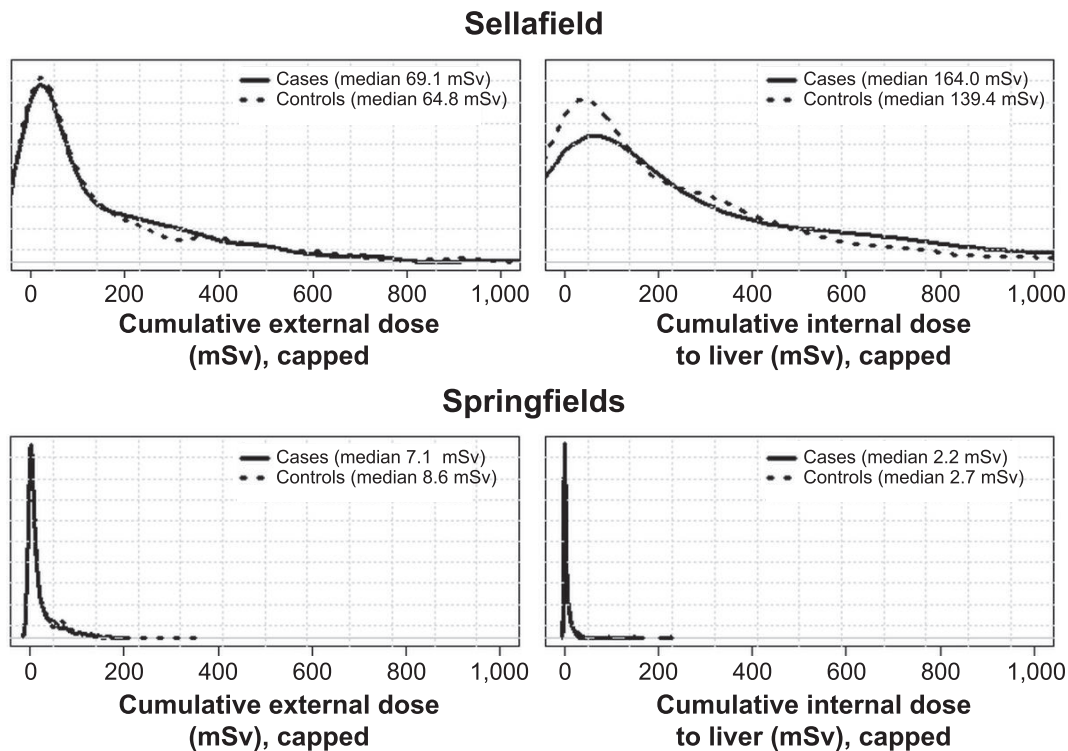


FIG. 1. Density plots of cumulative (unlagged) dose distributions for external and internal radiation exposures for cases and controls by nuclear site.

There is evidence of differences in dose-response associations between the Sellafield and Springfields sites for all industrial worker pairs, with associations much steeper at Springfields than at Sellafield (Table 4), and similarly when study subjects are restricted to just radiation worker pairs (with controls having complete occupational histories) (Fig. 2 and Supplementary Table S3; <https://doi.org/10.1667/RADE-19-00007.1.S1>) or when the Sellafield sample is limited to those cases and controls with cumulative external doses up to the maximum dose at the Springfields site (Supplementary Table S4). In this latter analysis, log-linear dose responses for the two nuclear sites combined are 1.16 (95% CI: 1.00, 1.35) and 1.15 (95% CI: 0.95, 1.40) per 100 mSv for unlagged and 15-year lagged cumulative external doses of <350 mSv and <267 mSv, respectively.

Restricting the analyses to 715 radiation worker pairs (with subgroup-specific quartiles), which excludes non-radiation workers from the external dose reference group, the association in the highest dose group using unlagged cumulative external doses was $OR_{\text{quartile4}} = 2.50$ (95% CI: 1.61, 3.89) and the log-linear trend in OR per 100 mSv was 1.09 (95% CI: 1.01, 1.17), while for 15-year lagged cumulative external doses an association in the highest dose group of $OR_{\text{quartile4}} = 1.54$ (95% CI: 1.01, 2.35) and a log-linear trend in OR per 100 mSv of 1.05 (95% CI: 0.97, 1.14) were observed (Supplementary Table S5; <https://doi.org/10.1667/RADE-19-00007.1.S1>). Unlagged dose-response associations were stronger for 152 radiation worker

pairs both monitored for external radiation exposure only [log-linear trend in OR = 1.56 (95% CI: 1.17, 2.07) per 100 mSv] than for 229 radiation worker pairs both monitored for external and internal radiation exposure [OR = 1.09 (95% CI: 0.93, 1.27) per 100 mSv], while for 15-year lagged external doses smaller differences were observed [OR = 1.10 (95% CI: 0.87, 1.38) vs. 1.04 (95% CI: 0.89, 1.21) per 100 mSv] for the two respective groups. These dose responses for 15-year lagged cumulative external dose are comparable to those observed in the full cohort of BNFL industrial radiation workers (5) (Fig. 3).

There was little evidence of an association between unlagged cumulative internal dose (to the liver) and IHD mortality risk, with excess risk of 25% (95% CI: -14%, 80%) for a dose of 52 mSv or greater when compared with the reference group of monitored workers with an internal dose of less than 2.89 mSv (Table 5; model 5). Workers who were not monitored for internal exposure, however, had a 48% (95% CI: 13%, 95%) increased risk of IHD mortality compared to the low internal dose reference group (Table 5), while workers monitored for internal exposure had a 20% (95% CI: -32%, -6%) decreased risk when compared to unmonitored workers (Supplementary Table S1; <https://doi.org/10.1667/RADE-19-00007.1.S1>). There was little evidence of confounding by employment duration, pre-employment physiological factors or tobacco smoking, shift work or occupational exposure to noise (Table 5).

Using 15-year lagged internal dose made little difference to the excess risks of IHD mortality: $OR_{\text{tertile3}} = 1.05$ (95%

TABLE 2
Cumulative Radiation Dose from External Sources (Unlagged Dose)

Model	Variables	Cumulative external radiation dose (mSv) ^a	Odds ratio	95% CI	<i>P</i> value
0	Bivariate	<2.6	1.00	Reference	
		2.6–21.4	0.97	0.77, 1.22	0.79
		21.4–102.8	0.94	0.75, 1.18	0.59
		102.8–1,655.8	1.04	0.81, 1.34	0.74
		Log-linear trend (per 100 mSv)	0.99	0.94, 1.05	0.72
1	Baseline model ^b	<2.6	1.00	Reference	
		2.6–21.4	1.00	0.79, 1.28	0.97
		21.4–102.8	0.95	0.75, 1.20	0.66
		102.8–1,655.8	1.04	0.80, 1.34	0.79
		Log-linear trend (per 100 mSv)	0.99	0.93, 1.04	0.63
2	Model 1 + employment duration	<2.6	1.00	Reference	
		2.6–21.4	0.99	0.78, 1.26	0.95
		21.4–102.8	0.91	0.71, 1.17	0.46
		102.8–1,655.8	0.95	0.68, 1.31	0.74
		Log-linear trend (per 100 mSv)	0.96	0.90, 1.03	0.24
3	Model 1 + monitored for internal exposure (yes/no)	<2.6	1.00	Reference	
		2.6–21.4	1.13	0.88, 1.45	0.34
		21.4–102.8	1.15	0.89, 1.49	0.28
		102.8–1,655.8	1.36	1.01, 1.84	0.04
		Log-linear trend (per 100 mSv)	1.02	0.96, 1.08	0.55
4	Model 3 + socio-economic status ^c	<2.6	1.00	Reference	
		2.6–21.4	1.15	0.90, 1.49	0.26
		21.4–102.8	1.18	0.91, 1.53	0.20
		102.8–1,655.8	1.38	1.02, 1.87	0.04
		Log-linear trend (per 100 mSv)	1.02	0.96, 1.08	0.59
5	Model 4 + process/other worker ^c	<2.6	1.00	Reference	
		2.6–21.4	1.17	0.91, 1.51	0.22
		21.4–102.8	1.20	0.92, 1.56	0.17
		102.8–1,655.8	1.42	1.04, 1.95	0.03
		Log-linear trend (per 100 mSv)	1.02	0.96, 1.08	0.54
6	Model 5 + physiological traits ^d	<2.6	1.00	Reference	
		2.6–21.4	1.18	0.91, 1.53	0.21
		21.4–102.8	1.21	0.93, 1.58	0.16
		102.8–1,655.8	1.43	1.04, 1.97	0.03
		Log-linear trend (per 100 mSv)	1.02	0.96, 1.08	0.54
7	Model 5 + smoking status	<2.6	1.00	Reference	
		2.6–21.4	1.17	0.91, 1.52	0.22
		21.4–102.8	1.19	0.91, 1.55	0.20
		102.8–1,655.8	1.38	0.99, 1.93	0.06
		Log-linear trend (per 100 mSv)	1.01	0.94, 1.07	0.86
8	Model 5 + shift work	<2.6	1.00	Reference	
		2.6–21.4	1.17	0.90, 1.51	0.23
		21.4–102.8	1.19	0.92, 1.56	0.19
		102.8–1,655.8	1.42	1.03, 1.95	0.03
		Log-linear trend (per 100 mSv)	1.02	0.96, 1.08	0.57
9	Model 5 + occupational noise	<2.6	1.00	Reference	
		2.6–21.4	1.13	0.87, 1.47	0.35
		21.4–102.8	1.13	0.86, 1.49	0.37
		102.8–1,655.8	1.33	0.95, 1.86	0.09
		Log-linear trend (per 100 mSv)	1.01	0.95, 1.08	0.75

^a Numbers of cases/controls in each cumulative dose quartile: 306/301 (<2.6 mSv); 304/307 (2.6–21.4 mSv); 305/321 (21.4–102.8 mSv); 305/219 (102.8–1,655.8 mSv). Industrial non-radiation workers are included in the reference groups.

^b Adjusted for age at death (or censoring), age at start of employment at either site, decade of start of employment.

^c Based on longest-held job.

^d Systolic and diastolic blood pressure and BMI.

TABLE 3
Cumulative Radiation Dose from External Sources (15-Year Lagged Dose)

Model	Variables	Cumulative external radiation dose (mSv) ^a	Odds ratio	95% CI	P value
0	Bivariate	<1.9	1.00	Reference	
		1.9–25.1	0.78	0.62, 0.98	0.04
		25.1–108.8	0.78	0.61, 1.00	0.05
		108.8–1,290.7	0.92	0.71, 1.20	0.53
		Log-linear trend (per 100 mSv)	0.99	0.93, 1.05	0.68
1	Baseline model ^b	<1.9	1.00	Reference	
		1.9–25.1	0.80	0.63, 1.01	0.06
		25.1–108.8	0.78	0.61, 0.99	0.04
		108.8–1,290.7	0.91	0.70, 1.19	0.49
		Log-linear trend (per 100 mSv)	0.99	0.93, 1.05	0.62
2	Model 1 + employment duration	<1.9	1.00	Reference	
		1.9–25.1	0.79	0.62, 1.00	0.05
		25.1–108.8	0.75	0.58, 0.96	0.02
		108.8–1,290.7	0.84	0.62, 1.14	0.26
		Log-linear trend (per 100 mSv)	0.97	0.90, 1.03	0.32
3	Model 1 + monitored for internal exposure ^c (yes/no)	<1.9	1.00	Reference	
		1.9–25.1	0.94	0.73, 1.21	0.63
		25.1–108.8	1.00	0.77, 1.30	1.00
		108.8–1,290.7	1.31	0.97, 1.77	0.08
		Log-linear trend (per 100 mSv)	1.05	0.98, 1.11	0.18
4	Model 3 + socio-economic status ^d	<1.9	1.00	Reference	
		1.9–25.1	0.97	0.75, 1.25	0.80
		25.1–108.8	1.02	0.78, 1.33	0.88
		108.8–1,290.7	1.33	0.99, 1.81	0.06
		Log-linear trend (per 100 mSv)	1.05	0.98, 1.12	0.18
5	Model 4 + process/other worker ^d	<1.9	1.00	Reference	
		1.9–25.1	0.97	0.76, 1.26	0.84
		25.1–108.8	1.03	0.79, 1.34	0.85
		108.8–1,290.7	1.35	0.99, 1.84	0.05
		Log-linear trend (per 100 mSv)	1.05	0.98, 1.12	0.17
6	Model 5 + physiological traits ^e	<1.9	1.00	Reference	
		1.9–25.1	0.98	0.76, 1.27	0.89
		25.1–108.8	1.02	0.77, 1.34	0.90
		108.8–1,290.7	1.38	1.00, 1.89	0.05
		Log-linear trend (per 100 mSv)	1.05	0.98, 1.12	0.14
7	Model 5 + smoking status	<1.9	1.00	Reference	
		1.9–25.1	0.98	0.75, 1.26	0.86
		25.1–108.8	1.02	0.78, 1.33	0.90
		108.8–1,290.7	1.34	0.97, 1.85	0.07
		Log-linear trend (per 100 mSv)	1.04	0.97, 1.11	0.30
8	Model 5 + shift work	<1.9	1.00	Reference	
		1.9–25.1	0.98	0.75, 1.25	0.80
		25.1–108.8	1.01	0.77, 1.33	0.93
		108.8–1,290.7	1.33	0.97, 1.81	0.08
		Log-linear trend (per 100 mSv)	1.04	0.98, 1.11	0.20
9	Model 5 + occupational noise	<1.9	1.00	Reference	
		1.9–25.1	0.94	0.72, 1.21	0.63
		25.1–108.8	0.96	0.73, 1.26	0.75
		108.8–1,290.7	1.27	0.93, 1.75	0.13
		Log-linear trend (per 100 mSv)	1.04	0.97, 1.11	0.23

^a Numbers of cases/controls in each 15-year lagged cumulative dose quartile: 306/301 (<1.9 mSv); 304/307 (1.9–25.1 mSv); 305/321 (25.1–108.8 mSv); 305/219 (108.8–1,290.78 mSv). Industrial non-radiation workers are included in the reference groups.

^b Adjusted for age at death (or censoring), age at start of employment at either site, decade of start of employment.

^c Monitored during the period more than 15 years before death or censoring.

^d Based on longest-held job.

^e Systolic and diastolic blood pressure and BMI.

TABLE 4
Subgroup Analysis by Nuclear Site, all Industrial Worker Pairs

		Sellafield (651 pairs)		Springfields (569 pairs)	
		OR ^a	95% CI	OR ^a	95% CI
Cumulative external dose, mSv (no dose lag)	<2.6	1.00	Reference	1.00	Reference
	2.6–21.4	1.17	0.77, 1.77	1.27	0.89, 1.79
	21.4–102.8	1.12	0.77, 1.63	1.37	0.91, 2.05
	102.8–1,655.8	1.20	0.82, 1.78	1.89	0.94, 3.78
	Log-linear trend (per 100 mSv)	0.98	0.92, 1.05	1.20	0.80, 1.80
Cumulative external dose, mSv (15-year dose lag)	<1.9	1.00	Reference	1.00	Reference
	1.9–25.1	0.98	0.64, 1.50	1.03	0.72, 1.45
	25.1–108.8	0.87	0.60, 1.27	1.28	0.85, 1.94
	108.8–1,290.7	1.23	0.85, 1.78	1.10	0.45, 2.69
	Log-linear trend (per 100 mSv)	1.02	0.95, 1.10	1.31	0.82, 2.07
		OR ^b	95% CI	OR ^b	95% CI
Cumulative internal dose, mSv (no dose lag)	0.01–2.89	1.00	Reference	1.00	Reference
	2.89–52.28	1.51	0.73, 3.16	0.67	0.46, 0.98
	>52.28	1.46	0.75, 2.83	0.40	0.03, 4.99
	Not monitored	1.58	0.83, 3.00	1.69	1.21, 2.37
Cumulative internal dose, mSv (15-year dose lag)	0.00–1.60	1.00	Reference	1.00	Reference
	1.60–35.06	1.30	0.59, 2.89	0.68	0.47, 0.98
	>35.06	1.50	0.73, 3.10	0.64	0.14, 3.06
	Not monitored	1.55	0.76, 3.15	1.24	0.87, 1.78

^a Odds ratio, adjusted for age at death (or censoring), monitored for internal radiation exposure (unlagged and lagged, respectively), decade of start of employment on site, age at start of employment, process worker (yes/no), socio-economic status. Industrial non-radiation workers are included in the reference groups.

^b Odds ratio, adjusted for age at death (or censoring), cumulative external radiation dose (unlagged and lagged, respectively), decade of start of employment on site, age at start of employment, process worker (yes/no), socio-economic status. Not monitored group includes industrial non-radiation workers.

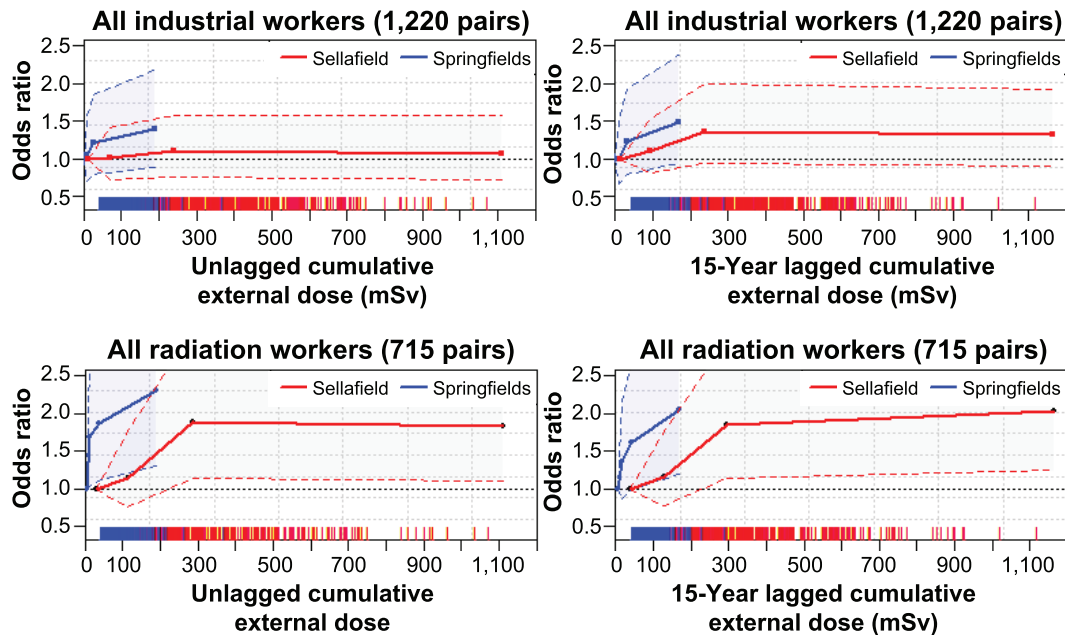


FIG. 2. Associations (solid lines) and 95% confidence intervals (shaded bands) between unlagged and 15-year lagged cumulative radiation dose from external sources by nuclear site. Cumulative dose categories are based on nuclear-site-specific quartiles of distribution in cases (quartile upper dose limits are used to plot odds ratios). Separate analyses are shown for all industrial workers (i.e., all case-control pairs in the study) in the top row and radiation workers (i.e., pairs monitored for external radiation and with complete occupational histories) in the bottom row (Supplementary Table S4; <https://doi.org/10.1667/RADE-19-00007.1.S1>). Cases are marked on the cumulative dose axis as vertical lines, with color indicating nuclear site.

Radiation worker case-control pairs

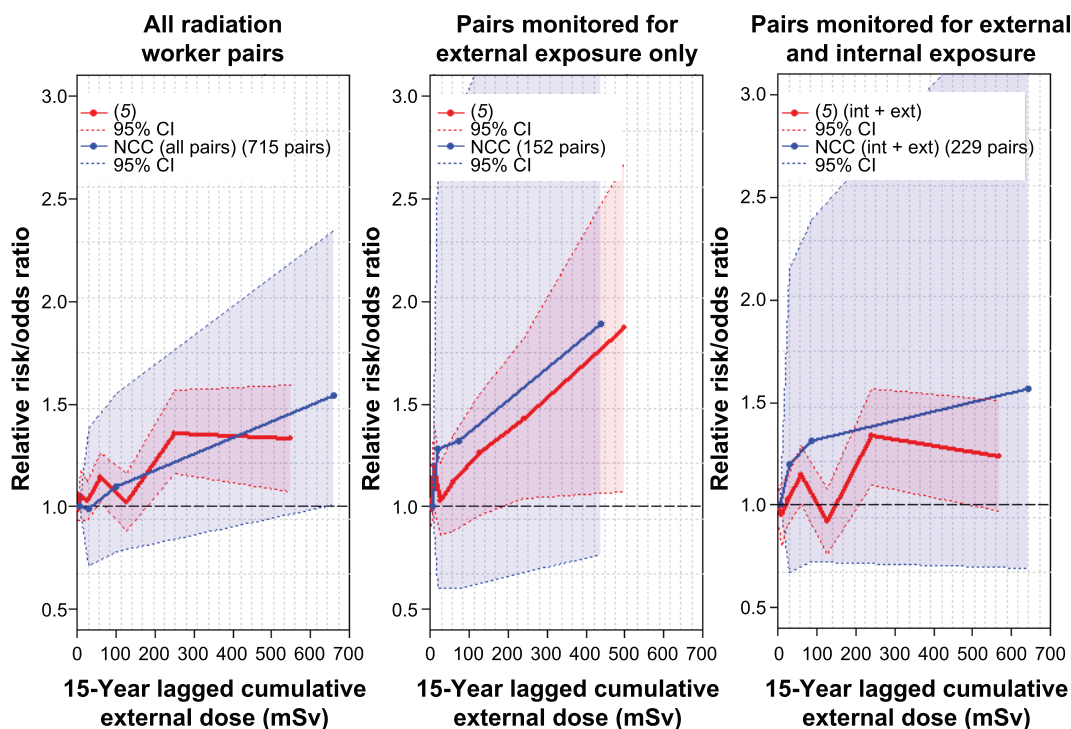


FIG. 3. Comparison of 15-year lagged cumulative external dose-response associations for IHD mortality for all matched case-control pairs of male industrial radiation workers with complete occupational histories from the nested case-control (NCC) study, pairs of radiation workers with complete occupational histories monitored for external exposure only, and pairs of radiation workers with complete occupational histories monitored for both external and internal exposures. These associations are compared with those for male industrial radiation workers in the BNFL cohort study (5).

CI: 0.70, 1.57) while the OR for the unmonitored group was 1.54 (95% CI: 1.14, 2.06) compared to the low internal dose reference group (<1.54 mSv) (Table 6; model 5). Analyses limited to (external) radiation worker pairs provided no evidence of excess risks associated with internal dose, but indicated a raised risk for workers not monitored for internal exposure, as for unlagged internal dose (Supplementary Table S5; <https://doi.org/10.1667/RADE-19-00007.1.S1>).

Analyses by employment duration indicated that whereas excess risks associated with unlagged external dose were solely suggested for worker pairs employed for more than 5 years, associations with internal dose appeared somewhat stronger for pairs employed for 5 years or less; the pattern of risks was reversed using 15-year lagged external dose, but remained much the same for 15-year lagged internal dose (Supplementary Table S6; <https://doi.org/10.1667/RADE-19-00007.1.S1>). External dose-response associations appeared to be more evident in “other workers” than in “process workers”, regardless of dose lag, but this was not apparent for internal dose (Supplementary Table S7).

DISCUSSION

This matched case-control study confirmed associations between cumulative 15-year lagged doses of radiation from

external sources and ischemic heart disease (IHD) mortality previously observed in the cohort of BNFL male industrial workers from which the current study subjects were drawn (5). In particular, the cohort study finding of a marked difference between workers monitored for external radiation exposure only, for whom a clear dose-response association was observed, and those workers monitored for both external and internal radiation exposure, where the external dose association is less evident, was confirmed in this study. Of note is that this difference in effect between these two radiation worker groups was also found for cancer mortality in the cohort of BNFL workers, in particular for digestive cancers (20). It remains unclear what the explanation for these findings could be, although are confounding, possibly involving dietary factors, must remain a possibility. However, in this case-control study there was little evidence for an effect of internal liver dose from plutonium and uranium on IHD mortality risk.

Patterns of monitoring for internal exposure are complex and differ over time, and probably also between nuclear sites. In the earlier years of operations, only those workers with the potential to receive internal doses from intakes of radioactive materials that were meaningful in terms of radiological protection tended to be monitored for the presence of internal emitters; but with time, workers who

TABLE 5
Cumulative Unlagged Radiation Dose (to the Liver) from Internally Deposited Plutonium and Uranium

Model	Variables	Cumulative internal radiation dose (mSv) ^a	Odds ratio	95% CI	<i>P</i> value
0.1	Bivariate	0.01–2.89	1.00	Reference	
		2.89–52.28	0.98	0.73, 1.31	0.90
		52.28–5,731.5	1.38	0.98, 1.96	0.07
		Not monitored	1.41	1.09, 1.81	0.01
0.2	Bivariate: Monitored case-control pairs only (n = 308 pairs) ^b	0.01–2.89	1.00	Reference	
		2.89–52.28	0.89	0.59, 1.34	0.58
		52.28–5,731.5	0.81	0.37, 1.77	0.59
		Not monitored	0.98	0.94, 1.03	0.39
1	Baseline model ^c	0.01–2.89	1.00	Reference	
		2.89–52.28	0.97	0.72, 1.30	0.83
		52.28–5,731.5	1.32	0.93, 1.88	0.12
		Not monitored	1.40	1.08, 1.81	0.01
2	Model 1 + employment duration	0.01–2.89	1.00	Reference	
		2.89–52.28	0.90	0.67, 1.22	0.51
		52.28–5,731.5	1.24	0.87, 1.77	0.24
		Not monitored	1.45	1.12, 1.88	0.00
3	Model 1 + cumulative unlagged external dose	0.01–2.89	1.00	Reference	
		2.89–52.28	0.93	0.68, 1.26	0.63
		52.28–5,731.5	1.28	0.89, 1.84	0.19
		Not monitored	1.52	1.16, 1.99	0.00
4	Model 3 + socio-economic status ^d	0.01–2.89	1.00	Reference	
		2.89–52.28	0.88	0.65, 1.20	0.42
		52.28–5,731.5	1.23	0.85, 1.78	0.28
		Not monitored	1.48	1.13, 1.95	0.00
5	Model 4 + process/other worker ^d	0.01–2.89	1.00	Reference	
		2.89–52.28	0.88	0.65, 1.20	0.42
		52.28–5,731.5	1.25	0.86, 1.80	0.24
		Not monitored	1.48	1.13, 1.95	0.00
6	Model 4 + physiological traits ^e	0.01–2.89	1.00	Reference	
		2.89–52.28	0.85	0.62, 1.16	0.30
		52.28–5,731.5	1.23	0.84, 1.78	0.28
		Not monitored	1.44	1.09, 1.91	0.01
7	Model 4 + smoking status	0.01–2.89	1.00	Reference	
		2.89–52.28	0.88	0.64, 1.21	0.42
		52.28–5,731.5	1.24	0.86, 1.80	0.25
		Not monitored	1.47	1.12, 1.94	0.01
8	Model 4 + shift work	0.01–2.89	1.00	Reference	
		2.89–52.28	0.89	0.65, 1.21	0.44
		52.28–5,731.5	1.26	0.87, 1.81	0.23
		Not monitored	1.48	1.13, 1.95	0.01
9	Model 5 + occupational noise	0.01–2.89	1.00	Reference	
		2.89–52.28	0.86	0.63, 1.17	0.33
		52.28–5,731.5	1.27	0.88, 1.84	0.20
		Not monitored	1.52	1.15, 2.00	0.00

^a Numbers of cases/controls in each cumulative dose tertile and unmonitored group: 187/218 (0.01–2.89 mSv); 187/224 (2.89–52.28 mSv); 188/185 (52.28–5,731.5 mSv); 658/593 (not monitored). The “not monitored” group includes industrial non-radiation workers.

^b The same model as model 0.1, but only includes matched case-control pairs where both the case and control were monitored for internal exposure at the index date.

^c Adjusted for age at death (or censoring), age at start of employment at either site, decade of start of employment.

^d Based on longest-held job.

^e Systolic and diastolic blood pressure and BMI.

were likely to have (much) lower intakes were also included in the monitoring program. Even if a worker provided just one urine sample for analysis that worker would fall into the internal exposure monitored group. However, the effect is consistent regardless of how this internal monitoring status

is defined in lagged external dose analyses. The effect of monitoring for internal emitters upon the external dose and IHD mortality association could be indicative of the influence of some non-radiation factor that is not accounted for in this study.

TABLE 6
Cumulative 15-Year Lagged Radiation Dose (to the Liver) from Internally Deposited Plutonium and Uranium

Model	Variables	Cumulative internal radiation dose (mSv) ^a	Odds ratio	95% CI	P value
0.1	Bivariate	0.00–1.54	1.00	Reference	
		1.54–33.01	0.72	0.52, 0.99	0.05
		33.01–3,642.47	1.25	0.85, 1.83	0.26
		Unmonitored	1.55	1.18, 2.04	0.00
0.2	Bivariate: Monitored case-control pairs only (n = 229 pairs) ^b	0.00–1.54	1.00	Reference	
		1.54–33.01	0.54	0.33, 0.88	0.01
		33.01–3,642.47	0.85	0.35, 2.09	0.72
		Unmonitored	1.53	1.16, 2.02	0.00
1	Baseline model ^c	0.00–1.54	1.00	Reference	
		1.54–33.01	0.69	0.49, 0.96	0.03
		33.01–3,642.47	1.19	0.80, 1.75	0.39
		Unmonitored	1.53	1.16, 2.02	0.00
2	Model 1 + employment duration	0.00–1.54	1.00	Reference	
		1.54–33.01	0.64	0.46, 0.90	0.01
		33.01–3,642.47	1.10	0.75, 1.63	0.63
		Unmonitored	1.64	1.24, 2.18	0.00
3	Model 1 + 15-year lagged cumulative external dose	0.00–1.54	1.00	Reference	
		1.54–33.01	0.66	0.47, 0.92	0.02
		33.01–3,642.47	1.07	0.71, 1.59	0.76
		Unmonitored	1.55	1.16, 2.08	0.00
4	Model 3 + socio-economic status ^d	0.00–1.54	1.00	Reference	
		1.54–33.01	0.64	0.46, 0.90	0.01
		33.01–3,642.47	1.05	0.70, 1.57	0.81
		Unmonitored	1.54	1.15, 2.06	0.00
5	Model 4 + process/other worker ^d	0.00–1.54	1.00	Reference	
		1.54–33.01	0.64	0.46, 0.90	0.01
		33.01–3,642.47	1.05	0.70, 1.57	0.81
		Unmonitored	1.54	1.14, 2.06	0.00
6	Model 4 + physiological traits ^e	0.00–1.54	1.00	Reference	
		1.54–33.01	0.62	0.44, 0.88	0.01
		33.01–3,642.47	1.07	0.71, 1.61	0.74
		Unmonitored	1.54	1.14, 2.08	0.01
7	Model 4 + smoking status	0.00–1.54	1.00	Reference	
		1.54–33.01	0.64	0.45, 0.90	0.01
		33.01–3,642.47	1.09	0.73, 1.64	0.68
		Unmonitored	1.62	1.20, 2.18	0.00
8	Model 4 + shift work	0.00–1.54	1.00	Reference	
		1.54–33.01	0.64	0.45, 0.90	0.01
		33.01–3,642.47	1.05	0.70, 1.58	0.80
		Unmonitored	1.56	1.16, 2.09	0.00
9	Model 5 + occupational noise	0.00–1.54	1.00	Reference	
		1.54–33.01	0.61	0.43, 0.86	0.01
		33.01–3,642.47	1.07	0.71, 1.61	0.74
		Unmonitored	1.61	1.19, 2.16	0.00

^a Numbers of cases/controls in each cumulative dose tertile and unmonitored group: 141/166 (0.00–1.54 mSv); 141/222 (1.54–33.01 mSv); 145/159 (33.01–3,642.47 mSv); 793/673 (unmonitored). Unmonitored group includes industrial non-radiation workers.

^b The same model as model 0.1, but only includes matched case-control pairs where both the case and control were monitored for internal exposure in longer than 15 years prior to death or censoring.

^c Adjusted for age at death (or censoring), age at start of employment at either site, decade of start of employment.

^d Based on longest-held job.

^e Systolic and diastolic blood pressure and BMI.

The BNFL cohort study (7) did not investigate the effect of doses from internal emitters, just the fact of monitoring or not, but the current study used (liver) doses from plutonium and uranium, which should take account of variations in the selection of radiation workers for monitoring for potential internal exposure. However, assessments of internal doses

using earlier monitoring data tend to be more uncertain than those using later data, but earlier internal doses were likely to have been higher. It should be noted that the BNFL cohort study included workers from two BNFL sites in addition to Sellafield and Springfields, although both external and internal doses in the BNFL cohort are

dominated by workers at the two sites included in this case-control study. Consistent with the results of studies of IHD in workers at the Russian Mayak nuclear site, many of whom were exposed to substantial amounts of plutonium (7, 8), little evidence of an influence of internal dose on IHD risk was found, with the possible exception of short-term employed workers. This last point suggests that risks may be associated with other factors specific to short-term employment, and raised risks were also found for those employed for less than 5 years who were not monitored for internal exposure. The results of this study were largely unaffected by the use of different dose lags. Heterogeneity in dose-response associations between sites was evident, but this was reduced when comparable external dose ranges for the two sites were used.

The main goal of this study was to assess whether the observed association between occupational external radiation dose and IHD mortality risk in the BNFL workforce (5) could (to some extent) be explained by selected confounding factors (for which individual-level information was not available in the cohort, but was in our nested case-control study). Specifically, in this study blood pressure, BMI and smoking status (all at the start of employment) were investigated, as well as socio-economic status, main occupation, shift work and exposure to excessive noise at work. However, with the possible exception of occupational noise exposure, none of these was an important confounder in this population. Although occupational noise exposure did attenuate associations between external dose and IHD mortality, patterns of findings indicated this was likely the result of some other unknown factor, a conclusion which echoes that of the original study (19).

An important strength of this study was that the inclusion of two nuclear sites resulted in a relatively large study sample of 1,220 matched pairs to examine associations in detail, which also enabled site-specific analyses to aid inferences and evaluations of radiation worker pairs with and without internal monitoring separately to directly compare the results with those from the cohort study. Another strength was the dose assessment using state-of-the-art algorithms which could be linked to all workers in this study. Furthermore, because of the incidence density sampling of the controls, the ORs can be interpreted as relative risks and directly compared to results from cohorts (31), and indeed, results are comparable (5). Reassuringly, this also indicates little evidence of over-matching, which had been highlighted as a possible problem (32). Finally, since blood pressure and BMI were measured at the start of employment they could not be on the causal pathway in relationship to occupational radiation exposure (33).

However, although pre-employment physiological traits, anthropometric measurements and tobacco smoking were used in this study, these are temporally variable. The study would have benefited from inclusions of longitudinal confounder information, but these data were not available. The possibility of residual confounding from changes in

these factors during employment therefore cannot be excluded. The study would have further benefited if IHD incidence rather than mortality could have been studied, but this information was also not available. Shift work was only classified as “having engaged in shift work for period of one month or more” (18), and evaluation of this factor would have been improved by more specific information on different characteristics of shift work, including “graveyard shifts”, “light at day”, “phase shifts” and “sleep disruption” (34). Heterogeneity in observed associations remains subject to residual confounding from some other, non-radiation, factor(s) not included in this study. This is particularly true for the marked difference in the association between external radiation dose and IHD mortality for workers monitored or not monitored for internal radiation exposure, despite the absence of an association with internal radiation dose. The similarity of this pattern with that for digestive cancer mortality in the BNFL worker cohort is intriguing. Finally, exploring different potential disease models, such as an additive model (35), was beyond the scope of this study, and should be evaluated in an appropriately powered occupational cohort with sufficient follow-up.

The heterogeneity in the external dose associations found in this case-control study of IHD mortality, and in the BNFL cohort study, has been observed in studies involving the wider British nuclear industry. Significant heterogeneity between nuclear sites or groups of sites has been reported from a recent study of IHD mortality rates and external radiation dose in the NRRW (4, 10, 36), and this was also observed in the International Nuclear Workers Study (INWORKS) that used an earlier NRRW dataset (6). These cohort studies also indicated higher risks among radiation workers not monitored for internal exposure. However, the studies included BNFL workers and so do not constitute independent findings. The authors advised caution in interpreting results until these heterogeneities are better understood.

In conclusion, this matched case-control study, nested in a cohort of British male industrial workers in the nuclear fuel cycle, confirmed associations between cumulative radiation doses from external sources and ischemic heart disease mortality, similar to those observed in a number of large national and international cohorts of radiation workers (5–8). Importantly, the study provided evidence that these associations were only to a small extent affected by confounding from pre-employment blood pressure, BMI and tobacco smoking status, or socio-economic status, main occupation or shift work and, to a lesser extent, noise exposure. However, the study confirmed the importance of whether or not a worker was monitored for internal radiation exposure, but found that internal dose itself had little effect upon the risk of IHD mortality. The explanation for this pattern of results remains unclear. Further research is required to explore in greater depth the heterogeneity in observed associations.

SUPPLEMENTARY INFORMATION

Table S1. Bivariate associations between population factors included in the study and IHD mortality.

Table S2. Associations between cumulative radiation dose from external sources and IHD mortality using different external dose lags.

Table S3. Subgroup analysis by nuclear site for all industrial workers and radiation worker pairs separately (results refer to Fig. 2).

Table S4. Subgroup analyses using truncated cumulative external and internal doses by nuclear site.

Table S5. Analyses of industrial radiation worker (cumulative external radiation dose >0 mSv) pairs only, including subgroup analyses for radiation worker pairs monitored for external exposure only and radiation worker pairs monitored for both external and internal exposure.

Table S6. Subgroup analyses of industrial worker case-control pairs by employment duration.

Table S7. Subgroup analyses of industrial worker case-control pairs by longest-held occupation.

Fig. S1. Density plots of cumulative unlagged external doses (mSv) in the four dose quartiles (note that in the figure, but not in the categorization itself, these overlap because of how densities are plotted).

Fig. S2. Density plots of cumulative 15-year lagged dose distributions for external and internal radiation exposures by nuclear site. Industrial non-radiation workers are included.

ACKNOWLEDGMENTS

We thank Les Scott [Public Health England, Centre for Radiation, Chemical and Environmental Hazards (CRCE)] for his help with exposure assessment and linkage of datasets, Will Atkinson (Nuvia) for his help with the SES-occupation coding scheme, and Prof. McNamee (University of Manchester) for her help with data identification, management and linkage. This work was supported by the National Institute for Health Research (Policy Research Programme, Occupational Exposure to Ionising Radiation and Mortality from Ischaemic Heart Disease, PR-R14-0915-23004). The views expressed in this publication are those of the author(s) and not necessarily those of the NHS, the National Institute for Health Research or the Department of Health and Social Care. RW is a member of the Technical Working Party of the UK Compensation Scheme for Radiation-Linked Diseases. Otherwise, the authors declare no actual or potential competing financial interests.

Received: December 4, 2019; accepted: July 13, 2020; published online: August 27, 2020

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