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Ischemic Heart and Cerebrovascular Disease Mortality in Uranium Enrichment Workers

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Abstract

Objective: Linear and non-linear dose-response relationships between radiation absorbed dose to the lung from internally deposited uranium and external sources and circulatory system disease (CSD) mortality were examined in a cohort of 23,731 male and 5552 female U.S. uranium enrichment workers.

Methods: Rate ratios (RRs) for categories of lung dose and linear excess relative rates (ERRs) per unit lung dose were estimated to evaluate associations between lung absorbed dose and death from ischemic heart disease (IHD) and cerebrovascular disease (CeVD).

Results: There was a suggestion of modestly increased IHD risk in workers with internal uranium lung dose above 1 milligray (mGy) (RR = 1.4; 95% CI: 0.76, 2.3) and a statistically significant increased IHD risk with external dose exceeding 150 mGy (RR = 1.3; 95% CI: 1.1, 1.6) compared to the lowest exposed groups. ERRs per mGy were positive for IHD and uranium internal dose and for both outcomes per Gy external dose, although confidence intervals generally included the null.

Conclusions: Non-linear dose-response models using restricted cubic splines revealed sublinear responses at lower internal doses, suggesting that linear models that are common in radioepidemiological cancer studies may poorly describe the association between uranium internal dose and CSD mortality.

Keywords

Uranium; radiation absorbed dose; dose-response; ischemic heart disease; cerebrovascular disease

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CONTRIBUTORSHIP

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COMPETING INTERESTS

The authors report no competing interests.

CONFLICT OF INTEREST

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INTRODUCTION

A recent study of cause-specific mortality in a pooled cohort of U.S. gaseous diffusion plant workers showed positive associations between absorbed dose from internal uranium exposure and mortality from kidney cancer, chronic renal diseases, and multiple myeloma.[12] Although gaseous diffusion plant workers have lower mortality from circulatory system diseases (CSDs, i.e., ischemic heart and cerebrovascular disease) compared to the general population,[1] recent interest in the relationship between CSD and low-dose chronic exposure to radiation warrants a study of the variation in risk with level of radiation exposure.

Several studies demonstrate that exposure to high levels of external ionizing radiation at high dose rates increases CSD mortality. CSD mortality is associated with external radiation exposures in atomic bomb survivors above 0.5 Gy[3] and among radiotherapy patients.[4,5] CSD risks at lower levels of exposure are not as well understood. However, a meta-analysis examining risk of CSD from low-level ionizing radiation exposure found associations with ischemic heart disease (IHD) (excess relative rate per sievert [ERR Sv^{-1}] = 0.10, 95% CI: 0.04, 0.15) and cerebrovascular disease (CeVD) (ERR Sv^{-1} = 0.21, 95% CI: 0.02, 0.39).[6] The International Nuclear Workers Study (INWORKS) examined CSD mortality among workers with protracted low-level exposure to ionizing radiation and reported a positive association between external radiation and all CSD mortality (ERR Sv^{-1} = 0.22, 90%CI: 0.08, 0.37).[7]

A study of Mayak workers exposed to both external ionizing radiation and internally deposited plutonium found significant increased risk of CSD (IHD and CeVD) with external dose (ERR Gy^{-1} = 0.05, 95% CI: >0, 0.11) and separately for absorbed dose to the liver from internally deposited plutonium (ERR Gy^{-1} = 0.27; 95% CI: 0.12, 0.48). However, the risk estimate for internal dose decreased and became non-significant when adjusted for external ionizing radiation dose.[8] Another study of Mayak nuclear workers with both internal and external radiation exposure reported a linear association between external radiation exposure and IHD among males. Associations between absorbed dose to the liver from internal exposure to plutonium and IHD incidence and mortality were also observed.[9] Evaluation of CeVD in the Mayak worker cohort found significant increased incidence with external dose (ERR Gy^{-1} = 0.46; 95% CI: 0.37, 0.57) and absorbed dose to the liver from internally deposited plutonium (ERR Gy^{-1} = 0.28; 95% CI: 0.16, 0.42).[10] This same study also found a significant increased risk of CeVD mortality for workers with absorbed dose to the liver > 0.1 Gy. A study of both the Mayak worker cohort and the UK Sellafield cohort found little evidence of a dose-response relationship between CSD, IHD, or CeVD mortality and internal dose from plutonium when the cohorts were evaluated separately or when the plutonium workers from each cohort were pooled. However, the ERRs were significantly elevated with respect to external dose for both cohorts for CSD and IHD, but not for CeVD.[11]

Few studies of large cohorts with internal exposure to uranium exist. A recent nested case-control study of French nuclear fuel cycle workers exposed to uranium found a 20% increase in CSD mortality per milligray (mGy) uranium lung dose (adjusted excess odds ratio = 0.2, 95% CI: 0.004, 0.5).[12] A study of nuclear fuel cycle workers with internal and

external dosimetry found some positive but non-statistically significant associations between external dose and CSD, but no consistent associations between internal dose and CSD were found.[13]

The purpose of this study is to examine the dose-response relationships between absorbed ionizing radiation dose to the lung from internal exposure to uranium and external ionizing radiation and deaths from IHD and CeVD among a previously studied cohort of US uranium enrichment workers. Individual organ doses from internal exposure to uranium and external ionizing radiation were available for the cohort, as well as potential confounding exposures such as organ doses from internal exposure to contaminant radionuclides and non-radiological agents.

METHODS

Cohort

The cohort definition is described elsewhere.[1] In brief, the cohort included previously studied workers from three U.S. gaseous diffusion plants: the Oak Ridge Gaseous Diffusion Plant (K-25) in Oak Ridge, Tennessee, the Portsmouth Gaseous Diffusion Plant (PORTS) in Piketon, Ohio, and the Paducah Gaseous Diffusion Plant (PGDP) in Paducah, Kentucky. Eligible workers were required to have worked for at least one continuous year at K-25 during January 1, 1948 – December 31, 1985, at PORTS during March 1, 1956 – May 31, 2001, or at PGDP during September 1, 1952 – December 31, 2003. These dates represent the operational periods at all three facilities, except for K-25, for which the begin date was set to minimize the inclusion of short-term construction workers.

Vital status was ascertained through 2011 using information from previous studies,[14–16] the National Death Index (NDI) Plus, the Social Security Administration (SSA) mortality database, and Internal Revenue Service (IRS) records, LexisNexis, and death certificates from state vital records. Only 17 workers were lost to follow up. Person-time at risk began after one year of continuous employment and ended at the earliest of the worker's death date, the date last observed, or end of study (December 31, 2011). Mortality outcomes examined were IHD and CeVD, as coded by the International Classification of Diseases (ICD) revision in effect at the time of death. The specific codes are available online (http://links.lww.com/JOM/A10) and in Supplemental Table S-1. The study was approved by the Institutional Review Board (IRB) of the National Institute for Occupational Safety and Health (NIOSH).

Exposure Assessment

The dose assessment for this cohort from internal exposure to uranium and recycled uranium contaminants was described in detail in previous publications.[17,18] Intakes were estimated using facility bioassay records containing urinalysis data on uranium gravimetric and radioactivity concentrations, and technetium-99 (^{99}Tc) and plutonium-239 (^{239}Pu) concentrations. Chronic exposure was assumed to occur from the first date through the last date of employment. Bioassay data were imputed for workers with no recorded data using department-specific uranium, ^{99}Tc, and ^{239}Pu concentrations averaged from reported

bioassay data. Absorbed lung doses were calculated from intakes as part of a previous dose-response analysis.[17]

Absorbed dose from occupational sources of external ionizing radiation, consisting of both recorded badge dose and work-related medical X-rays examinations (WRX) were estimated using data obtained from facility records and from the U.S. Department of Energy Radiation Exposure Monitoring System (REMS) and the U.S. Nuclear Regulatory Commission Radiation Exposure Information and Reporting System (REIRS).[1] The dose from WRX was estimated using employment histories and information on facility procedures.[19] WRX dose estimates were limited to photofluorographic chest X-rays conducted only at K25 as part of routine physical examinations administered to workers from mid-1945 through 1956.

Socioeconomic Status

Lifestyle factors, such as smoking history, alcohol use, diet, and exercise are associated with IHD and CeVD and may confound dose-response relationships. No specific information on these factors was available for the subjects, however, low socioeconomic status (SES) has been shown to be a suitable proxy for predicting CSD mortality.[20] In this study, SES was approximated by collapsing job titles into one of five categories in increasing level of SES: unskilled worker, skilled worker, administrative support, student, and professional/technical. The first job title was chosen to represent lifestyle behaviors that may be related to cancer risk (e.g., smoking alcohol use) that are usually established in adolescence and early adulthood. For the analyses, study subjects assigned to the student were combined with professional/technical and those with missing SES were assigned to the unskilled worker category.

Statistical Analysis

The dose-response association between absorbed dose to the lung from internal exposure to uranium and CSD mortality was evaluated using Cox proportional hazards regression. Risk sets for each case of IHD and CeVD included all study subjects who were considered at risk as of the age of death of the index case. As done in previous studies, the risk sets were also matched on sex, race, birth date (within five years), facility (i.e., K-25, PORTS, PGDP), and socio-economic status (SES).[12] General relative rate models were fit using methods described by Langholz and Richardson.[21] The model form is $h(t, x) = h_0(t)*\varphi(x)$, where $h(t, x)$ is the expected hazard at attained age, t, and specified dose, x, and $\varphi(x)$ is the effect of dose on the baseline hazard, h_0. Linear excess relative rates (ERR), where $\varphi(x) = 1 + ERR*x$, were evaluated for comparison to other radiation studies. Since the distribution of lung absorbed doses was highly positively skewed, the ERR was evaluated for the full cohort, for the cohort excluding person-time with lung dose greater than 10 mGy, and for the cohort excluding person-time with lung dose greater than 1 mGy to examine the effect of this skewed dose distribution on the ERR estimate. To examine potential departure of the dose-response from linearity, a categorical model was used as well as restricted cubic splines (RCS) with three knots at equally spaced points. Model fit was assessed using the Akaike Information Criterion (AIC). Models were evaluated with lags of 0 and 10 years. Adjustment for potential confounding exposures such as external ionizing radiation, and internal dose

from ^{239}Pu and ^{99}Tc was done by including one potential confounding variable at a time in the model. Confounding was suspected if the parameter estimate changed by ±20%.

The effect of absorbed dose to the lung from external ionizing radiation on CSD mortality was also evaluated using similar methods described above for absorbed lung dose from internally deposited uranium. In this case, RRs were generated for four categories of lung dose and linear ERRs were generated for the full cohort and by excluding person-time above various cut-points of external dose to allow for comparison to the literature. All statistical analyses were conducted using SAS software (Version 9.4, SAS Institute, Cary, NC. ©2002-2012).

RESULTS

The full cohort consisted of 29,303 workers. By primary facility, there were 16,978 workers at K-25, 6,935 workers at PORTS, and 5,390 workers at PGDP. As of December 31, 2011, 45% of the cohort were deceased, including 3,488 deaths from IHD and 746 deaths from CeVD. Less than 0.07% of the person-time from 17 workers was lost to follow-up. The demographics of the full cohort and cases are provided in Table 1.

The distribution by demographics of cumulative absorbed dose to lungs from internally deposited uranium and external ionizing radiation is shown in Table 2.

Bioassay data on internal uranium exposure were available for 58% of the cohort and imputed for an additional 33%. The remaining 9% of workers were assumed to be unexposed based on job titles and/or department titles that indicated low exposure potential (e.g., administrative staff). Workers exposed to uranium were also assumed to be exposed to contaminant radionuclides. Lung absorbed dose from internal exposure to the recycled uranium contaminant ^{99}Tc was highly skewed with a median of 0.030 mGy and a 95th percentile of 0.30 mGy. Lung absorbed dose from exposure to ^{239}Pu was only available for the K-25 cohort and averaged 6.5 mGy, with a median of 2.2 mGy and a 95th percentile of 24 mGy.

Table 3 shows the estimated RRs adjusted for age, sex, race, birth date, facility, and SES for both IHD and CeVD of absorbed organ dose from internally deposited uranium at three categories of dose compared to non-exposed workers. Separate results for males and females are provided in the online supplement (Tables S-2 and S-3).

Adjusting for external dose or contaminant radionuclides (^{239}Pu and ^{99}Tc) did not appreciably change results (within ±20%). Estimation of ERR per mGy of dose is also shown in Table 3. In general, risk estimates were imprecise and varied widely by person-time dose restrictions. The ERRs for IHD were positive but confidence intervals were wide and included the null. There was no evidence of a linear association between absorbed lung dose from internally deposited uranium and CeVD risk.

Categorical, linear, and spline models estimating the association between lung absorbed dose from internal uranium with no exposure lag and IHD and CeVD are displayed graphically in Fig. 1A and 1B, respectively. There was no noticeable difference when models were fit using

a 10-year exposure lag. Based on AIC values for each of the models (Supplemental Table S-4), the spline model provided the best fit with lung dose for IHD (Fig. 1A) and the linear model provided the best fit for CeVD (Fig. 1B). The evidence of a nonlinear dose-response association for both outcomes was apparent in RCS models, which generally show a positive slope for exposures above 1 mGy and attenuation of risk at higher doses (~3+ mGy).

Table 4 shows RRs adjusted for age, sex, race, birth date, facility, and SES by category of absorbed lung dose from external ionizing radiation. Separate results for males and females are provided in the online supplement (Tables S-5 and S-6).

A positive dose-response association was indicated for IHD but not for CeVD in the categorical model. There was indication of excess IHD risk with increasing dose; however, statistical significance was achieved only after excluding person-time with lung absorbed dose from external ionizing radiation exposure ≥100 mGy.

The fit for the three models with no lag (categorical, linear, spline) evaluated for lung absorbed dose from external ionizing radiation exposure with no exposure lag is displayed graphically in Fig. 1C and 1D, for IHD and CeVD, respectively. There was also no noticeable difference for external dose when models were fit using a 10-year exposure lag. Based on AIC values (Supplemental Table S-4) for each of the models, the categorical model provided the best fit with lung dose for IHD (Fig. 1C) and the linear model provided the best fit for CeVD (Fig. 1D).

DISCUSSION

There was little evidence of a linear dose-response trend between internal dose and CSD outcomes. Categorical models suggested an association between IHD and internal dose that was restricted to the highest dose category, although confidence intervals were wide and included the null. The AIC values indicated that the spline model provided the best fit with lung absorbed dose. The decreased risk above 2 mGy of lung dose in the RCS model was due to fewer cases with cumulative lung absorbed dose above that level. Additionally, the increase in the ERR (Table 3 and Figs. 1A and 1B) including only lung dose <10 mGy (which excluded person-time of 12 study subjects) and including only lung dose < 1 mGy (which excluded person-time of 111 study subjects) showed how sensitive the ERR is to person-time in the far right tail of the positively skewed dose distribution (see Table 2).

After exclusion of person-time of workers who had lung dose above 1 mGy, the results of this study are similar to a recent nested case-control study by Zhivin et al.[12] in which it was reported an adjusted linear excess odds ratio (EOR) of 0.2 (95% CI: −0.01, 1) per mGy of lung dose for IHD and 0.7 (95% CI: 0.1, 3) per mGy lung dose for CeVD from exposure to uranium compounds with a mixture of solubilities.[12] Overall, the rate ratios for the categorical model in this study (RRs) and the Zhivin et al. study (ORs) suggest that the dose-response may be sublinear at low dose (<1 mGy), although this study lacks adequate power to observe the dose-response in this range.

As in the Zhivin et al. study,[12] no change in estimate was observed in this study with the adjustment for external ionizing radiation dose. In this study, when external dose was

evaluated separately, risk estimates (ERR per mGy) were several magnitudes lower than those found for internal dose and non-statistically significant except when restricted to lung dose <100 mGy, but similar to the ERRs reported in the INWORKS study.[7]

Risk estimates for males and females evaluated separately in this study reflect the findings in the INWORKS study[7] with females having higher risk estimates as opposed to the Mayak studies,[8] which showed higher risk for males, although the risk estimates for this uranium cohort are not precise. Internal dose for Mayak workers was due primarily to plutonium body burden and dose estimates for both external ionizing radiation and internal dose to the liver were much higher than dose estimates in this uranium-exposed cohort or for the INWORKS cohort, which only included workers with primarily external exposure. Sex differences could also be attributed to other non-radiation factors specific to the cohorts.

The selection of target organ for evaluating the relationship between internal exposure to uranium and cardiovascular or cerebrovascular disease is not straightforward. The site of pathogenesis in CSD is thought to be the blood vessels which current biokinetic models do not include as a compartment. In this study, lung dose from rapidly soluble uranyl fluoride (UO_2F_2) was estimated as the primary exposure of interest. Other studies have looked at heart wall and kidney dose, in addition to lung dose and found positive associations between internal uranium exposure and CSD mortality.[12] In this study, lung and heart wall doses estimated for a subset of workers were nearly perfectly correlated and equivalent, so it is assumed that use of heart wall dose would have resulted in similar risk estimates. Because the chemical form of the uranium is highly soluble, and kidney is one of the primary target organs for uranium, there was less correlation between kidney doses and heart or lung doses.

For study subjects without bioassay data, lung doses were imputed by assigning department-specific urine uranium concentrations according to an individual's work history. These department-specific urine uranium concentrations were derived by averaging all urine samples associated with a specific department. This likely introduced significant shared error in the individual dose estimates which could cause attenuation of the dose-response relationship.[22]

The biological mechanisms of radiation induction of ischemic heart and cerebrovascular disease are not well-characterized. It is speculated that the soluble uranium compounds may induce a systemic inflammatory response in the blood vessels initiating atherosclerosis and resulting in disease.[23] Other studies have suggested that there is a strong association between exposure to heavy metals and coronary artery disease.[24] A recent study of Navajo communities located near abandoned uranium mines showed significant serum inflammatory potential for chronically exposed persons. This observed change in serum composition, which may be caused by chronic toxic exposures to uranium or other metals, could promote vascular inflammatory responses.[25] The elevated rates observed in this study could also be due do a combination of metal toxicity and radiation damage, or an interaction between the two co-exposures.

It is possible that the elevated risk of IHD is due to exposure to fluoride, as the uranium compound of concern is UO_2F_2. However, it is difficult to separate the effects of uranium

from fluoride. Fluoride was analyzed in about 5% of urine samples at the Portsmouth facility as part of the bioassay program, however determination of occupational fluoride exposure by urinalysis was complicated by exposure from other non-occupational sources. All samples with fluoride concentrations were either below the detectable level or within the range expected from intake of soft drinks, tea, ground water, and/or fluoridated water. Exposure to nickel and trichloroethylene (TCE) was evaluated in the mortality study,[1] however there were too few workers with exposure to evaluate confounding in this study. There is also the possibility that other unknown chemicals were present in the cascade that moved with the UO_2F_2 which would be a potential co-exposure. Other potential confounding exposures relevant to CSD outcomes include noise exposure and shift work, which were not evaluated in this study.

A strength of this study is the large cohort with relatively homogeneous exposure among the three facilities, the number of IHD and CeVD cases, and the individualized lung dose assessed from bioassay records. Among limitations common to observational studies, this study lacks information on lifestyle and physiological risk factors for CSD such as smoking, obesity, hypertension, cholesterol, and glycemia. However, Zhivin et al.'s nested case control study of uranium workers[12] found no change in estimate when adjusting for these potential confounders. Another source of potential bias is outcome misclassification. Validation studies show that death certificates over-report coronary heart disease by up to 20%.[26,27] However, strong bias from this source is unlikely as there is no evidence that ascertainment error varies by exposure level.

CONCLUSIONS

This study is among the largest to examine CSD risk in workers from ionizing radiation absorbed dose resulting from their uranium exposure. There was some evidence of an association between radiation dose and CSD mortality in this cohort that was consistent with previous reports; however, most risk estimates lacked statistical precision. The evidence was strongest for IHD, which showed positive associations with both external and internal ionizing radiation exposure, although poorer statistical precision was observed in internal dose models. Linear models differed markedly from RCS models, the latter generally indicated sublinear responses at low dose levels, followed by dose-range of increasing risk with attenuated responses at higher doses. This pattern was most evident for IHD and internal exposure. Point estimates in linear models increased with increasing exclusion of person-time with dose. Together, these findings suggest that linear excess relative risk models that are widely used in radioepidemiology may poorly describe the dose-risk relationship between ionizing radiation and CSD. Risk from uranium metal exposure (i.e., chemical toxicity) should also be investigated to evaluate potential chemotoxic response.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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What this paper adds:

What is already known about this subject?

- Recent research suggests a relationship between exposure to ionizing radiation and circulatory system disease, however few studies have found a significant association with exposure from internally deposited radionuclides such as uranium.

What are the new findings?

- There was a significant association between ischemic heart disease and external ionizing radiation as has been found in previous studies.
- The relationship with internal exposure to uranium was positive but not significant and risk estimates for internal dose were several magnitudes higher when internal and external dose-response were evaluated separately.
- The relationship between cerebrovascular disease and external dose was positive, but not statistically significant, and there does not appear to be a relationship with internal dose.

How might this impact on policy or clinical practice in the foreseeable future?

- This study adds to the understanding of non-malignant health effects from low dose ionizing radiation needed to inform risk management decisions.
- This study suggests that the use of linear excess relative risk models widely used in radioepidemiological cancer studies may not adequately describe the dose-response relationship between ionizing radiation and circulatory system disease, but further investigation is needed.
- The risk of circulatory system disease due to the chemotoxicity of uranium as a heavy metal should be further evaluated.

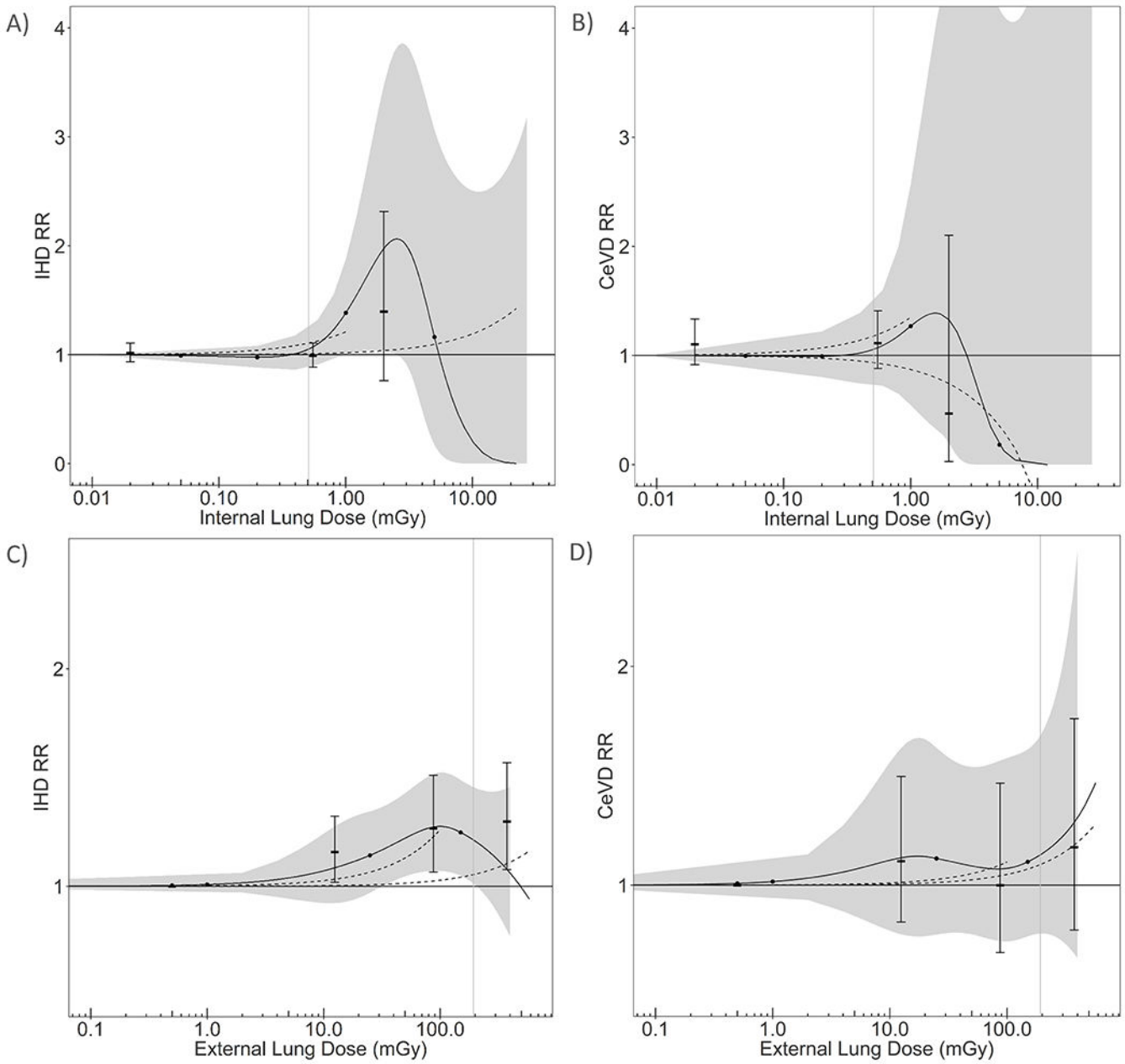

Fig. 1.

Relative rates (RR) versus absorbed lung dose from internal uranium exposure (A and B) and external ionizing radiation exposure (C and D). Linear model: dashed lines with dose limited to <10 mGy and < 1 mGy for internal dose and dose limited to <500 mGy and <100 mGy for external dose; Categorical model: vertical lines at midpoint of dose categories; Spline model: solid line with equally-spaced knots; 95% confidence interval for spline model: gray shaded area; 99th percentile of dose: light gray vertical line. External ionizing radiation exposure includes exposure from work-related photofluorographic X-ray

examinations administered at the K-25 facility. RRs were evaluated with no lag and adjusted for matching variables: age, sex, race, birth date, facility, and socio-economic status (SES).

Table 1.

Characteristics of the cohort and IHD (n=3488) and CeVD (n=746) cases.

Characteristics	Cohort N (%)	IHD Cases N (%)	CeVD Cases N (%)
Sex			
Male	23751 (81)	3221 (92)	638 (86)
Female	5552 (19)	267 (8)	108 (14)
Race			
White[a]	27287 (93)	3354 (96)	702 (94)
Other	2016 (7)	134 (4)	44 (6)
Birth cohort			
<1930	12931 (44)	2976 (85)	643 (86)
1930-1939	4639 (16)	336 (10)	68 (9)
1940-1949	5368 (18)	123 (4)	25 (3)
1950-1959	5364 (18)	51 (1)	10 (1)
1960+	1001 (3)	2 (0)	0 (0)
Age at hire (years)			
<25	11364 (39)	680 (19)	135 (18)
25-<35	11608 (40)	1479 (42)	297 (40)
35-<45	4571 (16)	897 (26)	189 (25)
45+	1760 (6)	432 (12)	125 (17)
Year of hire			
<1950	5718 (20)	1515 (43)	351 (47)
1950-1959	9022 (31)	1544 (44)	301 (40)
1960-1969	2463 (8)	115 (3)	26 (3)
1970-1979	9133 (31)	288 (8)	63 (8)
1980+	2967 (10)	26 (1)	5 (1)
Age at last follow-up (years)[b]			
<45	732 (2)	104 (3)	11 (1)
45-<55	2941 (10)	359 (10)	49 (7)
55-<65	8194 (28)	726 (21)	89 (12)
65-<75	7221 (25)	983 (28)	188 (25)
75+	10215 (35)	1316 (38)	409 (55)
Socio-economic status			
Student	610 (2)	10 (>1)	2 (>1)
Unskilled worker	3583 (12)	402 (12)	97 (13)
Skilled worker	14539 (50)	2215 (64)	430 (58)
Professional/technical	5724 (20)	479 (14)	102 (14)
Administrative support	4489 (15)	360 (10)	106 (14)
Unknown	358 (1)	22 (1)	9 (1)
Facility			
K-25	16978 (58)	2378 (68)	540 (72)
PORTS	6935 (24)	637 (18)	100 (13)

Characteristics	Cohort N (%)	IHD Cases N (%)	CeVD Cases N (%)
PGDP	5390 (18)	473 (14)	106 (14)

K-25: Oak Ridge Gaseous Diffusion Plant, Tennessee; PORTS: Portsmouth Gaseous Diffusion Plant in Piketon, Ohio; PGDP: Paducah Gaseous Diffusion Plant, Kentucky; IHD: ischemic heart disease; CeVD: cerebrovascular disease.

[a] White includes 6 workers with unknown race.

[b] Age at lost to follow-up, death, or study end, whichever is the earliest.

Table 2.

Cumulative absorbed lung dose (mGy) from internal exposure to uranium and external ionizing radiation for workers with non-zero dose.

	No. with non-zero dose	Mean (S.D.)	Median	95th percentile	Maximum
Internal exposure to uranium					
Full Cohort	20626	0.10 (0.71)	0.042	0.26	60
Sex					
Male	17304	0.10 (0.60)	0.043	0.26	36
Female	3322	0.10 (1.1)	0.039	0.25	60
Race					
White	19142	0.10 (0.59)	0.043	0.27	36
Other	2016	0.12 (1.6)	0.036	0.19	60
Facility					
K-25	13523	0.12 (0.87)	0.050	0.30	60
PORTS	3159	0.052 (0.17)	0.020	0.18	5.6
PGDP	3944	0.065 (0.13)	0.037	0.20	4.8
External ionizing radiation[a]					
Full Cohort	26896	44 (66)	3.7	185	592
Sex					
Male	22228	46 (67)	4.6	185	592
Female	4668	32 (55)	1.2	181	205
Race					
White	25127	46 (66)	4.2	185	592
Other	1763	16 (43)	1.4	158	274
Facility					
K-25	16037	71 (73)	60	186	592
PORTS	6424	2.9 (5.4)	1.0	11	86
PGDP	4435	7.0 (16)	1.7	31	214

K-25: Oak Ridge Gaseous Diffusion Plant, Tennessee; PORTS: Portsmouth Gaseous Diffusion Plant, Piketon, Ohio; PGDP: Paducah Gaseous Diffusion Plant, Kentucky.

[a]External ionizing radiation includes work-related photofluorographic X-ray examinations administered at the K-25 facility.

Table 3.

Rate ratios (RRs) by category of lung absorbed dose and linear excess relative rate (ERR) per mGy of lung absorbed dose from internal exposure to uranium.

		IHD		CeVD	
Model	**Lung Dose (mGy)**	**Cases**	**RR (95% CI)**	**Cases**	**RR (95% CI)**
Categorical	0	832	1.0 (ref)	164	1.0 (ref)
	> 0 - 0.1	2073	1.0 (0.94, 1.1)	434	1.1 (0.92, 1.3)
	> 0.1 - 1	570	0.99 (0.89, 1.1)	147	1.1 (0.88, 1.4)
	>1	13	1.4 (0.76, 2.3)		
	Restriction by lung dose (mGy)		**ERR mGy^{-1} (95% CI)**		**ERR mGy^{-1} (95% CI)**
Linear ERR	Full cohort	3488	0.019 (−0.077, 0.26)	746	−0.13 (−0.42, 0.44)
	< 10[a]	3488	0.15 (−0.076, 0.44)	746	−0.0076 (−0.045, 0.65)
	<1[b]	3475	0.21 (−0.18, 0.66)	745	0.35 (−0.37, 1.3)

IHD: Ischemic heart disease; CeVD: Cerebrovascular disease.

RRs were evaluated with no lag controlling for age, sex, race, birth date, facility, and socio-economic status (SES).

[a]Person-time was truncated for 12 study subjects who had lung dose above 10 mGy.

[b]Person-time was truncated for 111 study subjects who had lung dose above 1 mGy.

Table 4.

Relative rate (RR) by category of lung absorbed dose and linear excess relative rate (ERR) per Gy of lung absorbed dose from external ionizing radiation exposure.

		IHD		CeVD	
Model	**Lung Dose (mGy)**	**Cases**	**RR (95% CI)**	**Cases**	**RR (95% CI)**
Categorical	0 – 1	353	1.0 (ref)	77	1.0 (ref)
	> 1 – 25	978	1.2 (1.0, 1.3)	182	1.1 (0.83, 1.5)
	> 25 – 150	1143	1.3 (1.1, 1.5)	236	1.0 (0.69, 1.5)
	>150	1014	1.3 (1.1, 1.6)	251	1.2 (0.80, 1.8)
	Restriction by lung dose (mGy)		**ERR Gy^{-1} (95% CI)**		**ERR Gy^{-1} (95% CI)**
Linear ERR	Full cohort	3488	0.28 (−0.45, 1.1)	746	0.49 (−0.94, 2.5)
	<500	3488	0.26 (−0.48, 1.1)	746	0.53 (−0.91, 2.6)
	<400	3487	0.38 (−0.37, 1.3)	746	0.66 (−0.82, 2.8)
	<300	3485	0.54 (−0.24, 1.5)	745	0.75 (−0.77, 2.9)
	<200	3455	0.84 (−0.0047, 1.9)	738	1.0 (−0.58, 3.4)
	<100	2211	2.6 (0.2, 5.5)	447	1.1 (−3.0, 7.3)

IHD: Ischemic heart disease; CeVD: Cerebrovascular disease.

External ionizing radiation exposure includes exposure from work-related photofluorographic X-ray examinations administered at the K-25 facility.

RRs were evaluated with no lag and adjusted for matching variables: age, sex, race, birth date, facility, and socio-economic status (SES).