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A Nested Case-Control Study of Multiple Myeloma Risk and Uranium Exposure among Workers at the Oak Ridge Gaseous Diffusion Plant

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The primary risk factors of multiple myeloma are age, race and sex, but several studies have found an association between radiological hazards and multiple myeloma. The purpose of this nested case-control study was to investigate whether workers with chronic low-level exposure to internally deposited uranium at the Oak Ridge Gaseous Diffusion Plant in eastern Tennessee were at higher risk of dying of multiple myeloma than those without occupational exposure to uranium, with the consideration of potential confounders of external ionizing radiation and occupational chemical hazards such as mercury, nickel and trichloroethylene. The main analyses were carried out using conditional logistic regression on 98 cases and 490 controls (five controls matched to each case on gender, race and age at risk). Our study showed a weak association between internal uranium dose estimated from urinalysis results and multiple myeloma risk: OR = 1.04 (95% CI 1.00–1.09) at 10 μGy with the inclusion of other risk factors. The parameter estimates and the corresponding odds ratios were very similar when internal doses were imputed for subjects without urine samples. Further studies that include updating this cohort and combining with workers from other gaseous diffusion plants are needed to investigate the relationship between multiple myeloma risk and radiation or other chemical exposures.

INTRODUCTION

Multiple myeloma is a plasma cell neoplasm that is characterized by multiple destructive masses of plasma cells distributed randomly throughout the skeletal system and sometimes in soft tissue, crowding out normal blood cells. The primary risk factors are age, race and sex (*1*). Exposure to ionizing radiation has been investigated as a potential risk factor for multiple myeloma (*2*). Studies examining the risk of multiple myeloma in atomic bomb survivors, who received short-term, high-dose-rate exposures, reported increased risks and incidence of the disease among the exposed (*3–5*). However, a more recent study of cancer incidence adding 12 years of follow-up found no evidence of an excess risk for multiple myeloma (*6*). Studies of radiologists and veterinarians, who received relatively long-term, low-dose external exposures, showed evidence of excess mortality due to multiple myeloma (*7–9*). With regard to internal exposure, radium dial painters (*10, 11*) and Thorotrast patients (*12–14*) were found to have excess mortality from multiple myeloma. Studies of uranium miners and millers did not show statistically significant increases in mortality due to multiple myeloma (*15, 16*).

The Oak Ridge Gaseous Diffusion Plant (K-25) in eastern Tennessee was constructed in 1943 and began operation in 1945. There were approximately 48,000 workers involved in construction and operation between 1945 and 1985. The plant's main function was the enrichment of uranium using the gaseous diffusion process in support of the U.S. atomic weapons program and for use in naval, research and commercial power reactors. During the facility's operation, a variety of radiological and chemical hazards existed, including uranium (as an internal exposure hazard mainly from soluble UF_6 and UO_2F_2, but also other soluble and insoluble uranium compounds), mercury, nickel and trichloroethylene (TCE).

In reviewing the causes of deaths among K-25 workers, a relatively large number of deaths due to multiple myeloma were observed. The purpose of this nested case-control study was to investigate whether workers with chronic low-level exposure to internally deposited uranium at K-25 were at higher risk of dying of multiple myeloma than those without occupational exposure to uranium, with the consideration of potential confounders of external ionizing radiation and occupational chemical hazards such as mercury, nickel and TCE. Mercury, nickel and TCE were chosen for assessment because they were used in large quantities

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TABLE 1
Distribution of Cases and Non-duplicate Controls in Three Internal Dose Groups

	Cases (n = 98)			Controls (n = 483)		
Internal dose	Exposed[a]	Unexposed[b]	Imputed[c]	Exposed	Unexposed	Imputed
Group I	28	70	—	86	397	—
Group II	72	26	44	309	174	223
Group III	74	24	2	329	154	20

[a] Uranium intake and bone marrow absorbed dose estimated for 114, 381 and 403 exposed subjects in Groups I, II and III, respectively, based on urinalysis results and from imputation.
[b] Subjects without urine samples or imputed doses in each group were considered unexposed to uranium and were assigned zero dose.
[c] Number of subjects with imputation from job titles and department numbers (Group II) or department number alone (Group III).

at the site, because they were used throughout much of the tenure of the workers being studied, because industrial hygiene air monitoring results were available during most of the decades of interest, and because information regarding their association with multiple myeloma is lacking. Benzene, which was associated with multiple myeloma risk in a meta-analysis (*17*), was not chosen for assessment because its use was not widespread at K-25 and because available industrial hygiene data did not support such an assessment.

MATERIALS AND METHODS

Study Subjects

Cases and controls were drawn from a computerized roster of 47,941 workers hired prior to January 1, 1985 and employed for at least 30 days at K-25. Vital status for these workers was ascertained through December 31, 1998. The protocol was approved and reviewed annually by the Centers for Disease Control and Prevention (CDC) Institutional Review Board to ensure that the research project was conducted in an ethical manner and was consistent with CDC's policies and procedures for protection of human research participants. Cases with multiple myeloma (ICD-8 203) listed on the death certificate as underlying or contributory cause of death and date of death prior to January 1, 1999 were included in the study. Five controls matched to each case on gender, race and age at risk were randomly selected with replacement from the population based on incidence density sampling, where a risk set for each case was developed that was comprised of all workers who were at risk of dying from multiple myeloma and who lived to at least the age attained by the index case at the time of death (*18*).

Internal Dose

Absorbed bone marrow doses from occupational exposure to uranium were estimated using a novel approach based on individual median and departmental average median uranium urinalysis results and the historical bioassay monitoring practices at K-25. A detailed description of the methods used for dose estimation is provided elsewhere (*19*).

Briefly, health monitoring records from K-25 used for the dose estimation included results of worker medical examinations, area and personnel radiation exposure monitoring reports, and measurement results of uranium mass and radioactivity excreted in urine dating back to 1948. Fluorometric analysis results (uranium mass) were available for 118 study subjects and uranium gross α-particle analysis results (radioactivity) were available for 115 study subjects. The monitored study subjects submitted an average of 15 urine samples (range from 1 to 154) during their employment. The exposure assessor was blinded to the case status in estimating the exposures. A detailed description and an analysis of these data are provided elsewhere (*19, 20*).

Three exposed groups were constructed based on the availability of urine samples and other surrogates of exposure. Group I exposed consisted of 114 study subjects who were monitored and whose individual urinalysis results could be found in the historical records. Estimates of uranium intake and bone marrow absorbed dose for these workers were determined directly from the urinalysis results. One subject with a single urinalysis result was considered unlikely to be exposed and was assigned a dose of zero. Group II exposed included all Group I exposed plus an additional 267 study subjects who were not monitored by urinalysis but for whom annual absorbed doses could be imputed based on job titles and department numbers. In Group III exposed, doses were also imputed based on department number alone for an additional 22 non-monitored subjects for whom job title information was unavailable. A total of 403 Group III subjects (including 381 exposed subjects from Group II) were considered exposed based on bone marrow dose estimates. Subjects without urine samples or imputed doses in each group were considered unexposed to uranium and were assigned a dose of zero. The total numbers of cases and controls were the same in each group, but their exposure classifications could be different. Table 1 shows the distribution of cases and non-duplicate controls by exposure status in these internal dose groups.

External Radiation Exposure

Researchers conducting the exposure assessment were blinded to case status. The full study roster was used for all data collection and subsequent reconstruction of doses. Occupational radiation exposures from external sources were estimated using information obtained primarily from available site exposure records. Doses received at other nuclear facilities were also estimated using information from data maintained from previous studies and from other exposure databases, such as the Radiation Exposure Information and Reporting System (REIRS) maintained by the U.S. Nuclear Regulatory Commission (NRC) and the Radiation Exposure Monitoring System (REMS) of the U.S. Department of Energy (DOE). External occupational radiation exposure was evaluated as equivalent dose to the bone marrow resulting from whole-body irradiation by X-ray and γ-ray sources. Recorded doses were adjusted for measurement biases arising from exposure to heterogeneous radiation fields, calibration methods, dosimeter design, dosimeter energy response, and geometry of the critical organ (*21*). Equivalent dose (mSv) was converted to absorbed dose (mGy) assuming a radiation weighting factor of 1 for X, γ and β-particle radiation.

Workers at K-25 were exposed primarily to radiation types and energies associated with natural and recycled uranium enrichment processes. Personnel dosimeter records were available for some K-25 workers beginning in 1945. However, the number of individuals assigned dosimeters varied over the years. During the early years, only workers entering radiation-controlled areas and deemed likely to receive measurable dose were monitored. Beginning in 1951,

dosimeters were issued to the entire work force as part of the security badge, although only those likely to receive a measurable dose were processed. Because of the policies in effect, data were not available for the majority of exposed workers until 1975 (*22*). For periods where monitoring data were not available, separate methods were developed for dose estimation similar to those suggested by Watson *et al.* (*23*) and Richardson *et al.* (*24*) using employment and facility histories and the monitoring results of nearby workers and periods.

Available work histories were used to identify job title and department assignments for each unmonitored work year for each potentially exposed worker prior to 1975. Annual dose distributions were developed for each job class and department. The dose to the worker was then estimated based on the year of potential exposure and one of the following three criteria listed in order of preference: (1) the average annual dose for workers with the same job class and department, (2) the average annual dose for workers in the same department, and (3) the average annual dose for the job class. If none of the criteria were met, exposure was considered unlikely or minimal.

Medical X-Ray Dose

Annual absorbed bone marrow doses due to work-related medical X-ray examinations were estimated. Only absorbed doses to the active bone marrow from photofluorographic chest X-ray examinations were estimated because they were routinely administered and required as a condition of employment and delivered a relatively large amount of bone marrow dose compared to other direct radiographic procedures (*25, 26*). PCXMC (Personal Computer program for X-ray Monte Carlo), a computer program developed by the Finnish Centre for Radiation and Nuclear Safety (*27*), was used for dose calculations.

The methods used for X-ray examination parameter selection and dose assignment were similar to those described by Anderson and Daniels (*28*). X-ray examination parameters such as focus-to-skin distance (FSD), entrance skin exposure (ESE), and quantity of beam filtration were taken from a 1956 study of medical X-ray examination doses at Oak Ridge area medical facilities.[2]

Chemical Exposure Assessment

A modified job-exposure matrix approach that incorporated available industrial hygiene records to link K-25 study subjects with historic mercury, nickel and TCE exposure levels was the basis of the chemical exposure assessment for this study. An algorithm was developed to calculate annual and cumulative exposure scores for each of the three chemicals for every study subject.

Historic air monitoring results and employment history information were obtained during site visits to K-25. Employee identifiers were not available for the monitoring results, and building/work locations were not available in the work histories, making it impossible to link workers directly with air monitoring results. Instead, researchers relied on available site records regarding the organizational units, materials, methods, locations and nature of the work carried out at the K-25 site to identify four mutually exclusive exposure activities for each of the three study chemicals. A mean airborne exposure level was estimated for each exposure activity by decade for the three chemicals using the historic industrial hygiene air monitoring data (mercury, $n = 8102$; nickel, $n = 5441$; and TCE, $n = 2728$).

Information about workforce organization and work responsibilities at K-25 was used to associate departments with exposure activities for the three chemicals. Department names were available for 99.2% of the work histories of the study subjects. Researchers associated departments with chemical exposure activities on the basis of department name, building/location, site reports, chemical urinalysis frequency data, accident data and other available documents.

Workers not employed in an exposure-associated department during their tenure at K-25 were considered unexposed.

The cumulative exposure score per chemical for a study subject was calculated as follows:

$$\text{Cumulative Exposure Score (CES)} = \Sigma_i \Sigma_j C_{ij} \times D_{ij} \times f_{ij},$$

where C represents the estimated mean airborne level of the chemical present in the exposure activity work area *i*, during work history period *j*; D is the number of days the subject worked in a department associated with an exposure activity work area *i*, during work history period *j*; *f* is a factor representing the relative fraction of time/day the subject spent in the exposure activity work area *i*, during work history period *j*.

Factor assignments were made in consensus meetings by a team of NIOSH industrial hygienists. The assignments were based on job titles using professional judgment of work activity, work location and the chemical.

For this study the cumulative exposure score provided a relative measure of exposure to mercury, nickel and TCE for each study subject being evaluated. As a semi-quantitative estimate, these scores are not comparable to any absolute exposure values or occupational health limits.

Statistical Analysis

Conditional logistic regression was used to evaluate any dose–response relationship between multiple myeloma mortality and internal ionizing radiation dose (Groups I, II and III), with adjustment for potential confounders such as external ionizing radiation exposure, medical X-ray dose (analyzed as a separate term or in combination with external ionizing radiation), and chemical agents (mercury, nickel and TCE). A lag of 15 years was used for radiological and chemical exposures in the main analyses because of the potentially long latency of multiple myeloma. Models with other lags (0, 5, 10 and 20 years) were tested, but the differences in terms of deviances were negligible. Some exposed subjects became unexposed with zero exposure due to the lags. It was reported that workers hired during the World War II era were older at the time of hiring, while at other times the plants tended to hire younger men (*29*). To explore a possible wartime-era worker effect (i.e., males hired during World War II at an older age possibly had their entire exposure history excluded in the 15-year lag), birth cohort and age at hire were included separately in the analysis to investigate the impact on the coefficient of internal ionizing radiation dose. Birth cohort was grouped according to quartiles of birth year ($<$1910, 1910–1916, 1917–1922 and $\geq$1923) as well as a binary variable ($<$1917 and $\geq$1917). Age at hire was treated as a continuous variable. All the exposure terms were modeled log-linearly using PECAN in Epicure (*30*). Odds ratios (ORs) and the corresponding 95% profile likelihood-based confidence intervals (CIs) were derived from parameter estimates and the associated standard errors of the regression model. Point estimates for dose–response analyses were scaled according to the observed range of exposure for cases and controls.

RESULTS

Demographics

A total of 98 workers died from multiple myeloma (82 as underlying cause of death and 16 as contributory cause of death) as of December 31, 1998. There were 72

[2] E. Gupton, T. Tuck and T. Lincoln, Exposure data—Diagnostic radiography—K-25 (1956), unpublished document.

TABLE 2
Year of Birth among Cases and Controls

		Cases count (%)	Controls count (%)	Total	Odds ratio (95% CI)[a]
Birth year (Quartiles)	<1910	24 (24%)	118 (24%)	142	Baseline
	1910–1916	19 (19%)	115 (23%)	134	0.88 (0.29, 2.68)
	1917–1922	29 (30%)	130 (27%)	159	1.80 (0.43, 8.03)
	>=1923	26 (26%)	127 (26%)	153	1.95 (0.37, 10.60)
Birth year (Binary)	<1917	43 (44%)	233 (48%)	276	Baseline
	>=1917	55 (56%)	257 (52%)	312	2.05 (0.78, 5.87)

[a] Profile likelihood-based confidence intervals.

white males, 23 white females, one non-white male, and two non-white females among these deceased cases. Five controls matched to each case on gender, race and age at risk were selected, for a total of 490 (219 deceased). Because of sampling with replacement, seven controls were selected more than once for different cases. Cases and controls had very similar averages for year of birth (both 1916) and age at hire (31.7 and 30.9 years). Cases on average were employed longer (10.3 years) than the controls (7.4 years). Increased multiple myeloma risks were seen in the later two quartiles of birth cohort (Table 2).

Exposures

The average cumulative internal dose estimates with a 15-year lag for Group I (including the exposed with urinalysis data and the unexposed with assigned zero exposure) were 0.026 mGy for cases and 0.012 mGy for controls. With imputation for workers in Groups II and III, these averages increased (Table 3). The higher average cumulative doses for Group II and Group III compared to Group I were expected because doses were imputed for some study subjects who were not monitored by urinalysis; i.e., fewer subjects were assigned zero doses.

Out of 581 cases and non-duplicate controls (selected with replacement), 309 study subjects had records of chest X-ray examinations. An additional 75 study subjects assumed to have chest X-ray examinations were assigned doses using an algorithm based on work history, job title and information on the frequency and period of use of photofluorography at K-25. Estimated external radiation exposures with a 15-year lag were relatively small (0.8 mGy for cases and 1.3 mGy for controls) compared to exposure from work-related medical X-ray examinations (8.8 and 7.8 mGy for cases and controls, respectively). The estimated mercury and nickel exposures were similar between cases and controls. The cases had more TCE exposure than the controls, but the differences were not statistically significant due to the large variations in exposure (Table 3).

Univariate Analysis

The univariate associations of radiological and chemical exposures with multiple myeloma are listed in Table 4. Each of the three internal dose estimates was weakly associated with multiple myeloma risk. Without considering any potential confounders, multiple myeloma risks increased slightly with increased internal doses in any of the three groups in the univariate analysis (OR = 1.04 at 10 μGy). External radiation exposure, medical X-ray doses, or chemical exposures were not associated with multiple myeloma risks.

TABLE 3
Summary Statistics of Cumulative Exposure with a 15-Year Lag among Cases and Controls

	Cases (n = 98)				Controls (n = 490)			
	Mean	Std	Median	Range	Mean	Std	Median	Range
Internal Group I (mGy)[a]	0.026	0.09	0	0–0.7	0.012	0.04	0	0–0.4
Internal Group II (mGy)[a]	0.031	0.09	0.01	0–0.7	0.018	0.05	0	0–0.4
Internal Group III (mGy)[a]	0.031	0.09	0.01	0–0.7	0.019	0.05	0.01	0–0.4
External (mGy)[b]	0.8	1.7	0	0–8.6	1.3	12.2	0	0–266.3
Medical X ray (mGy)[c]	8.8	12.7	4.8	0–43.4	7.8	11.1	4.8	0–43.4
External + X ray (mGy)	9.5	13.6	4.8	0–52.0	9.1	17.2	4.8	0–280.7
Mercury	4.2	21.4	0	0–190.5	4.8	28.4	0	0–353.3
Nickel	1.0	3.5	0	0–27.5	0.8	3.4	0	0–33.2
Trichloroethylene (TCE)	183.8	668.2	0	0–5304.4	113.4	558.3	0	0–6047.2

[a] Uranium intake and bone marrow absorbed dose estimated based on urinalysis results and from imputation; zero dose assigned to the unexposed in each group.

[b] External occupational radiation exposure evaluated as equivalent dose to the bone marrow resulting from whole-body irradiation by X- and γ-radiation sources.

[c] Annual absorbed bone marrow doses due to work-related medical X-ray examinations.

TABLE 4
Univariate Analysis: Conditional Logistic Regression of Multiple Myeloma Risk and Exposures (with a 15-year lag) at the Oak Ridge Gaseous Diffusion Plant (K-25)

Factor	Parameter estimate	Standard error	Odds ratio	95% profile likelihood-based confidence intervals
Internal dose[a] (at 10 μGy)				
Group I	0.037	0.017	1.04	(1.00, 1.08)
Group II	0.034	0.017	1.04	(1.00, 1.07)
Group III	0.034	0.017	1.04	(1.00, 1.07)
Other radiation dose (at 1 mGy)				
External[b]	−0.008	0.022	0.99	(0.90, 1.01)
Medical X-ray examinations[c]	0.008	0.010	1.01	(0.99, 1.03)
External + X ray	0.002	0.006	1.00	(0.99, 1.01)
Chemical exposure				
Mercury	−0.001	0.004	1.00	(0.99, 1.01)
Nickel	0.009	0.031	1.01	(0.94, 1.07)
Trichloroethylene (TCE/100)	0.017	0.016	1.02	(0.98, 1.05)

[a] Uranium intake and bone marrow absorbed dose estimated based on urinalysis results and from imputation; zero dose assigned to the unexposed in each group.
[b] External occupational radiation exposure evaluated as equivalent dose to the bone marrow resulting from whole-body irradiation by X-ray and gamma-radiation sources.
[c] Annual absorbed bone marrow doses due to work-related medical X-ray examinations.

Multivariate Analysis

Table 5 shows multivariate analyses of multiple myeloma risk with Group I internal dose from urinalysis results and all potential confounders (birth year quartiles, external radiation exposure, medical X-ray doses, and chemical exposures). The dose–response relationship between internal dose and multiple myeloma risk was weakly positive (OR = 1.04 at 10 μGy). Combining external radiation exposure and medical X-ray doses and further collapsing birth year into a binary indicator had minimal impact on the risks (~4% increase in the parameter estimate; OR = 1.04 at 10 μGy). This reduced model was used in further analyses. Using imputed internal dose for the exposed in Group II or III, the odds ratio remained the same although the parameter estimate reduced slightly (a 4% drop). The odds ratios for other risk factors except birth year effect were essentially unchanged (Table 5). The changes in parameter estimates for internal doses are negligible, because the odds ratios remain 1.04 in all scenarios.

Dropping the risk factors one at a time from the full model had minimal impact on the internal dose (Group I) risk estimate, because the changes were within 10% of the original estimate. Substituting the birth year indicator with age at hire did not improve the model fit, because the deviance changed from 343.21 to 342.47, and the increase in risk estimate was within 10% of the estimate with birth year.

The relationship between internal radiation dose and multiple myeloma risk was also tested using a linear excess relative rate (ERR) model (Table 6), commonly used in radiation research, as well as a categorical model where exposures were classified dichotomously as zero and non-zero (results not shown). Neither of these models fit the data better than the log-linear model in terms of deviance, but the differences are negligible. The direction or significance of the risk estimates did not change with different models. Further dividing the subjects into categories based upon the 50th (median), 75th, and 90th percentiles of the exposure distribution among cases did not show a clear increasing trend with increased dose categories (Table 7). Observations were similar, except with wider confidence intervals, when using only cases with multiple myeloma as underlying cause of death (n = 82) and 410 matched controls (results not shown).

DISCUSSION

Multiple myeloma is a rare and fatal disease that accounts for about 2% of all cancer deaths in the U.S (*1*). It is a disease that primarily afflicts the elderly and is rarely diagnosed prior to age 40 (*1, 2*). The etiology of multiple myeloma is largely unknown. Within a sparse list of environmental risk factors, there is some evidence of a modest relationship between the disease and exposure to ionizing radiation (*7–14*). The main exposure in our study is long-term low internal dose in workers, which is different from studies of A-bomb survivors with short-term, high-dose-rate exposures (*3–6*), radiologists and veterinarians with external exposures (*7–9*), or patients who received relatively high internal dose (*12–14*). A threefold excess risk of multiple myeloma deaths, much higher than our findings, was observed in a study of female radium workers. However, the excess was more closely correlated with employment duration than with radium intake (*11*). In our study, we observed a weak association between multiple myeloma

TABLE 5
Multivariate Analysis: Conditional Logistic Regression of Multiple Myeloma Risk with Internal Dose (with a 15-year lag) and Other Risk Factors at the Oak Ridge Gaseous Diffusion Plant (K-25)

Factor	Parameter estimate	Standard error	Odds ratio	95% profile likelihood-based confidence intervals
Birth year 1910–1916[a]	−0.109	0.567	0.90	(0.29, 2.77)
Birth year 1917–1922	0.561	0.757	1.75	(0.41, 8.03)
Birth year >=1923	0.646	0.861	1.91	(0.36, 10.63)
External[b]	−0.013	0.037	0.99	(0.87, 1.01)
Medical X-ray examinations[c]	−0.003	0.012	1.00	(0.97, 1.02)
Mercury	−0.004	0.005	1.00	(0.98, 1.01)
Nickel	−0.012	0.037	0.99	(0.91, 1.06)
Trichloroethylene/100	0.021	0.021	1.02	(0.98, 1.06)
Internal Group I	0.040	0.021	1.04	(1.00, 1.09)
Birth year[e]	0.666	0.524	1.95	(0.72, 5.76)
External + X ray	−0.005	0.010	1.00	(0.97, 1.01)
Mercury	−0.004	0.005	1.00	(0.98, 1.01)
Nickel	−0.013	0.037	0.99	(0.91, 1.06)
Trichloroethylene/100	0.021	0.021	1.02	(0.98, 1.06)
Internal Group I[d]	0.042	0.021	1.04	(1.00, 1.09)
Birth year[e]	0.692	0.523	2.00	(0.74, 5.90)
External + X ray	−0.005	0.010	1.00	(0.97, 1.01)
Mercury	−0.005	0.005	1.00	(0.98, 1.01)
Nickel	−0.014	0.037	0.99	(0.91, 1.05)
Trichloroethylene/100	0.022	0.021	1.02	(0.98, 1.07)
Internal Group II[d]	0.040	0.021	1.04	(1.00, 1.09)
Birth year[e]	0.690	0.523	1.99	(0.74, 5.89)
External + X ray	−0.005	0.010	1.00	(0.97, 1.01)
Mercury	−0.005	0.005	1.00	(0.98, 1.01)
Nickel	−0.014	0.037	0.99	(0.91, 1.05)
Trichloroethylene/100	0.022	0.021	1.02	(0.98, 1.07)
Internal Group III[d]	0.040	0.021	1.04	(1.00, 1.09)

[a] Grouped based on quartiles of birth year, with workers born before 1910 as baseline.
[b] External occupational radiation exposure (at 1 mGy).
[c] Annual absorbed bone marrow doses (at 1 mGy) due to work-related medical X-ray examinations.
[d] Uranium intake and bone marrow absorbed dose (at 10 μGy) estimated based on urinalysis results and from imputation; zero dose assigned to the unexposed in each group.
[e] Workers born in 1917 or after compared to those born before 1917.

mortality and ionizing radiation exposure, quantified as absorbed dose to bone marrow from the uptake of soluble uranium compounds. This weak association persisted after adjustment for important confounders such as co-exposure to external radiation and other carcinogenic chemicals. The risk estimates were presented in μGy because, as shown in Table 3, no subjects had estimated internal exposures over 0.7 mGy. Presenting risk estimates in the same unit as those for external exposures or medical X rays (mGy) would potentially give the false impression of extremely high risk instead of a weak association among these workers.

Among notable strengths, this study examined 98 cases drawn from a cohort of 47,941 nuclear workers; thus it is among the largest studies of multiple myeloma and occupational exposure to ionizing radiation. Second, detailed work history information and uranium exposure data were available. The study design enabled the use of these data for a rigorous analysis of individual ionizing radiation exposures and co-exposures to prevalent carcinogenic chemicals. Therefore, exposure misclassification, although inevitable in the absence of complete exposure information, was minimized to the extent practical.

TABLE 6
Linear Excess Relative Rate (ERR) Model: Conditional Logistic Regression of Multiple Myeloma Risk and Internal Dose (with a 15-year lag) at the Oak Ridge Gaseous Diffusion Plant (K-25)

Internal dose	Parameter estimate	Standard error	ERR per 10 μGy	95% profile likelihood-based confidence intervals
Group I	0.06	0.05	0.06	(0.00, 0.19)
Group II	0.05	0.04	0.05	(0.00, 0.18)
Group III	0.05	0.04	0.05	(0.00, 0.17)

TABLE 7
Categorical Model: Conditional Logistic Regression of Multiple Myeloma Risk and Internal Dose (with a 15-year lag) at the Oak Ridge Gaseous Diffusion Plant (K-25)

Internal dose	Exposure distribution[a]	Cases (n = 98)	Controls (n = 490)	Odds ratio	95% CI[b]
Group I[c]	Unexposed	73	409	—	—
	>0–90th	16	53	1.72	(0.90, 3.15)
	>90th	9	28	1.87	(0.79, 4.08)
Group II	Unexposed	31	192	—	—
	>0–50th	18	62	1.91	(0.96, 3.77)
	>50th–75th	24	136	1.14	(0.62, 2.11)
	>75th–90th	16	69	1.54	(0.74, 3.14)
	>90th	9	31	1.92	(0.77, 4.48)
Group III	Unexposed	29	173	—	—
	>0–50th	20	76	1.62	(0.84, 3.10)
	>50th–75th	25	143	1.06	(0.57, 1.95)
	>75th–90th	15	67	1.38	(0.66, 2.84)
	>90th	9	31	1.80	(0.73, 4.21)

[a] Based on the 50th (median), 75th and 90th percentiles of the exposure distribution among cases.
[b] 95% profile likelihood-based confidence intervals.
[c] In Group I, there was no exposed case with exposure <75th percentile among all cases; therefore, (>0–50th), (>50th–75th) and (>75th–90th) exposures were combined.

Controls were matched to each case on gender, race and age at risk to make them comparable with respect to these factors and to avoid potential confounding. The wartime-era worker effect was not apparent in our study because the risk estimates in each birth year category (Table 2) are not significantly different. In a case-control study at four nuclear facilities, multiple myeloma was not associated with lifetime cumulative whole-body ionizing radiation dose (*31*). Similarly, our study did not show association between multiple myeloma mortality and external radiation dose, medical X-ray dose, or the combination of these two doses (Table 4).

There are a number of important limitations that must be considered when interpreting these results. First, the dose response is influenced by the choice of affected tissue. The target organ used for exposure assessment was the active red bone marrow, which was assumed to be the critical organ in terms of multiple myeloma pathogenesis. However, the origin of multiple myeloma in terms of site of transformation is not known. Because multiple myeloma is a B-cell malignancy, a current model of pathogenesis assumes the mutation occurs at the level of memory B cells undergoing antigen or T-cell stimulation with the resulting plasmablasts migrating through the blood and depositing in the marrow, where differentiation to mature plasma cells occurs. This model suggests that pathogenesis of myeloma could occur in lymphoid follicles (*32*). B cells and tertiary lymphoid neogenesis are associated with chronic inflammation in various organs, including the kidney (*33, 34*). Renal inflammation could result from chemical toxicity or radiotoxicity of soluble uranium; renal inflammation and histological damage have been demonstrated in workers chronically exposed to soluble forms of uranium (*35, 36*). Thus the site of malignant transformation in multiple myeloma could be another organ such as the kidney. The kidneys, along with bone surfaces and liver, receive higher (by a factor of 3.5 or more) doses than the bone marrow from internal exposure to soluble uranium.

There is sparse information on the radiogenicity of multiple myeloma in humans and the relative biological effectiveness (RBE) of uranium α particles for induction of hematopoietic malignancies. A study of leukemia and other related hematological disorders among Thorotrast patients suggested an RBE of less than 20 for thorium α particles (*37*). If the target organ for multiple myeloma is indeed the bone marrow, then the RBE for uranium α particles is likely much lower than 20. The International Agency for Research on Cancer (IARC) estimated an RBE between 1 and 2 for induction of leukemia by α particles (*38*). This is apparently because uranium deposits primarily on the bone surface and, because of the relatively short range of α particles, most of the target cells escape irradiation (*39*).

The uranium found in excreta used to assess ''dose'' may be a marker for some other (unknown) contaminant that is also present. The strength of the association may not be solely attributable to the effects of ionizing radiation and may result from a correlated chemical exposure that is indistinguishable from the bioassay information. Surrogates were used for exposure assessment that relied on employment duration. As such, duration of employment could not be examined appropriately as a separate covariate because it was significantly correlated with each of the exposure metrics. Although cases worked longer than controls and employment duration was highly and positively correlated with exposure metrics, the estimated doses for cases were not always higher than the controls. As

shown in Table 3, with a 15-year lag, cases had higher mean doses from uranium uptake, medical X rays, TCE and nickel, but they also had less exposure to external radiation and mercury.

Urinalysis data were available for approximately 20% of the study subjects. Internal dose estimates were imputed based on work histories for workers not monitored by urinalysis to reduce the number of workers with assigned zero doses. These methods yielded slightly reduced risk parameter estimates, but the resulting odds ratios and the corresponding 95% confidence intervals were very similar.

Variations in dosimetry practices, equipment and exposure conditions over the years may result in uncertainty in the recorded whole-body radiation doses and subsequently in the estimation of the worker's equivalent dose to the bone marrow. Larger dose uncertainties are also likely from exposures during medical X-ray examinations because X-ray procedures and equipment changed over time. We made great effort to reduce sources of dose uncertainty, but bias in dose estimates may be present due to the differences between actual values and reference values used for dose reconstruction. In addition, the exposure assessors were blinded to case status, so any exposure misclassification is likely to be non-differential. Consequently, any potential association of external radiation exposure and multiple myeloma mortality may have been biased toward the null.

CONCLUSION

Our study showed a weak association between internal radiation dose estimated from urinalysis results and multiple myeloma risk (OR = 1.04 at 10 μGy, 95% CI 1.00–1.08) without the inclusion of other risk factors. The odds ratio remained 1.04 (95% CI 1.00–1.09) with adjustment for birth year, combination of external radiation exposure and medical X-ray doses, and chemical exposures. The odds ratios and the corresponding 95% confidence intervals were very close when the estimated internal doses were imputed. We did not observe a birth cohort/year or age-at-hire effect within our study subjects. In fact, no other occupational risk factors investigated had an association with multiple myeloma risk, and their influence on the internal dose estimates was minimal. Further studies that include updating this cohort and combining with workers from other gaseous diffusion plants are needed to investigate the relationship between multiple myeloma risk and radiation or other chemical exposures.

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