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Mortality among a cohort of uranium mill workers: an update

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Aims: To evaluate the mortality experience of 1484 men employed in seven uranium mills in the Colorado Plateau for at least one year on or after 1 January 1940.

Methods: Vital status was updated through 1998, and life table analyses were conducted.

Results: Mortality from all causes and all cancers was less than expected based on US mortality rates. A statistically significant increase in non-malignant respiratory disease mortality and non-significant increases in mortality from lymphatic and haematopoietic malignancies other than leukaemia, lung cancer, and chronic renal disease were observed. The excess in lymphatic and haematopoietic cancer mortality was due to an increase in mortality from lymphosarcoma and reticulosarcoma and Hodgkin's disease. Within the category of non-malignant respiratory disease, mortality from emphysema and pneumoconioses and other respiratory disease was increased. Mortality from lung cancer and emphysema was higher among workers hired prior to 1955 when exposures to uranium, silica, and vanadium were presumably higher. Mortality from these causes of death did not increase with employment duration.

Conclusions: Although the observed excesses were consistent with our a priori hypotheses, positive trends with employment duration were not observed. Limitations included the small cohort size and limited power to detect a moderately increased risk for some outcomes of interest, the inability to estimate individual exposures, and the lack of smoking data. Because of these limitations, firm conclusions about the relation of the observed excesses in mortality and mill exposures are not possible.

In the United States, mining and milling of uranium ores to recover uranium for nuclear weapons began during World War II to support the Manhattan Project. Uranium bearing ores had been mined previously on a small scale, but mainly for the recovery of vanadium. Continued development and expansion of the industry after the war was promoted by a domestic uranium concentrate procurement programme that was established by the Atomic Energy Commission in 1947.[1] As early as 1949, health officials became concerned about the potential health risks associated with uranium mining and milling.[2]

The health risks associated with uranium mining have been extensively studied. Uranium miners have been found to have a substantially increased risk of death from lung cancer, which is associated with cumulative exposure to radon decay products.[3–5] Excess mortality from non-malignant respiratory diseases has also been found.[6] However, existing data concerning the health effects of uranium milling are limited. Waxweiler and colleagues reported a significantly increased risk of "other non-malignant respiratory disease" (standardised mortality ratio (SMR) = 2.50; observed (obs) = 39) among 2002 workers at seven uranium mills in the Colorado Plateau.[7] This category included emphysema, fibrosis, silicosis, and chronic obstructive pulmonary disease. Non-significant excesses were observed for lymphatic and haematopoietic malignancies other than leukaemia after 20 years latency (SMR = 2.3; obs = 6) and chronic renal disease (SMR = 1.67; obs = 6). In an earlier overlapping study of 662 uranium mill workers, Archer and colleagues observed an excess risk of mortality from lymphatic and haematopoietic malignancies other than leukaemia (SMR = 3.92; obs = 4).[8] Limited data from morbidity studies suggest that uranium millers may have an increased risk of pulmonary fibrosis[2] and renal tubular injury.[9]

The primary exposures of interest in uranium mills are uranium, silica, and vanadium containing dusts. Inhalation of uranium dust may pose an internal radiation hazard as well as the potential for chemical toxicity. High concentrations of radon and radon decay products, similar to the levels found in underground uranium mines, are not expected in the mills.

Because of continuing concern about the health effects of uranium milling, we extended the follow up of the cohort described by Waxweiler and colleagues.[7] The present report describes the mortality experience of the cohort through 21 additional years of observation. In addition, the risk of end stage renal disease was evaluated among the cohort.

Uranium milling process

The primary function of uranium mills is to extract and concentrate uranium from uranium containing ore to produce a semi-refined product known as yellowcake. Yellowcake is a chemically complex mixture of diuranates, basic uranyl sulphate, and hydrated uranium oxides that contains 80–96% uranium as U_3O_8, UO_3, and/or ammonium diuranate.[10] Yellowcake is used commercially to manufacture nuclear fuel for nuclear power and national defence purposes.

Conventional mills process uranium bearing ores from underground or open-pit mines. Until the mid-1970s, all yellowcake in the United States was produced at conventional uranium mills.[11] The main stages of the process in conventional mills involved: (1) ore handling and preparation; (2) extraction; (3) concentration and purification; and (4) precipitation, drying, and packaging. So-called "upgrader" facilities processed virgin ore that was initially too low in uranium content to process economically in a uranium mill. At an upgrader, a series of crushing, grinding, and chemical separation steps were employed to "upgrade" the percent

Main messages

- Potential exposures among uranium mill workers that may be associated with adverse health effects include uranium, silica, and vanadium containing dusts.
- We observed a statistically significant increase in mortality from non-malignant respiratory disease and non-significant increases in mortality from lymphatic and haematopoietic malignancies other than leukaemia, lung cancer, and chronic renal disease. These findings were consistent with our a priori hypotheses.
- The SMRs for lung cancer and emphysema among men hired before 1955, when exposures to uranium, silica, and vanadium were presumably higher, were significantly increased and greater than the SMRs observed among men hired in 1955 or later. However, mortality for causes of death observed to be in excess did not increase with employment duration.
- Limitations include a lack of smoking data, small cohort size and limited power to detect a moderately increased risk for some outcomes of interest, and the inability to estimate individual exposures to uranium, silica, and vanadium.

uranium contained in the final product, which was sent to a uranium mill for further processing. Unlike conventional uranium mills, upgrader facilities did not carry out concentration and purification of the uranium, and precipitation, drying, and packaging of yellowcake. In this paper, the term "mill" will be used in reference to both conventional uranium mills and upgrader facilities.

METHODS

Cohort description

The cohort was assembled from the personnel records obtained from the companies operating seven uranium mills (five conventional uranium mills and two upgraders). The original cohort described by Waxweiler and colleagues, which is referred to hereafter as the Waxweiler cohort, included 2002 men who had worked for at least one day after 1 January 1940, worked for at least one year in uranium mills, and never worked in underground uranium mines.[7] Because some of the work histories in the Waxweiler cohort were found to be coded inaccurately, we recoded all work histories. We also reviewed documentation from the original study to identify men who met the original cohort criteria, but had been omitted. Personnel records were obtained and work histories updated for cohort members who were still employed in 1971 when the personnel records were originally microfilmed. After re-coding the work histories, we limited the cohort to men who met the original cohort criteria, had never worked in an above-ground or underground uranium mine, and had worked for at least one year in the seven uranium mills before the personnel records were originally microfilmed in 1971 while the mills were operating to recover uranium and/or vanadium concentrates. The final cohort included 1485 men, 1438 (96.8%) of whom were in the Waxweiler cohort. Of the 564 workers not included in the current study, 103 (18.3%) worked in uranium mines, 318 (56.4%) never worked in one of the seven mills comprising the study, 141 (25.0%) worked for less than one year in the seven mills when they were operating, and one (0.2%) was excluded because the work history was incomplete. One woman whose gender was coded incorrectly in the Waxweiler cohort was also excluded.

Follow up

The vital status of all persons in the cohort was determined until 31 December 1998. Follow up included inquiry through the Social Security Administration, Internal Revenue Service, US Postal Service, National Death Index (NDI), and state bureaus of motor vehicles. Death certificates were obtained from state vital records offices for some deceased members of the cohort and coded by a trained nosologist according to the revision of the International Classification of Diseases in effect at the time of death. The causes of death for other deceased members of the cohort were obtained from the NDI.

To identify cohort members with treated end stage renal disease, the cohort was linked with the End Stage Renal Disease (ESRD) Program Management and Medical Information System (PMMIS) by name, social security number, and date of birth. The ESRD PMMIS is maintained by the Health Care Financing Administration (HCFA) and includes all individuals who received Medicare covered renal replacement therapy (dialysis or transplant) in 1977 or later. Approximately 93% of ESRD patients in the United States are included in the ESRD PMMIS.[12]

Analysis

The mortality experience of the cohort was analysed with the use of the National Institute for Occupational Safety and Health (NIOSH) modified life table analysis system (LTAS).[13 14] Each cohort member accumulated person-years at risk (PYAR) for each year of life after 1 January 1940 or completion of the one year eligibility period, whichever was later, until the date of death for deceased cohort members, the date last observed for persons lost to follow up, or the ending date of the study (31 December 1998) for cohort members known to be alive. Cohort members known to be alive after 1 January 1979 (the date that the NDI began) and not identified as deceased were assumed to be alive as of 31 December 1998. The PYAR were stratified into five year intervals by age and calendar time and were then multiplied by the appropriate US gender, race, and cause specific mortality rates to calculate the expected number of deaths for that stratum. The resulting expected numbers were summed across strata to obtain cause specific and total expected number of deaths. The ratio of observed to expected number of deaths was expressed as the standardised mortality ratio (SMR). Ninety five per cent confidence intervals (CI) were computed for the SMRs assuming a Poisson distribution for observed deaths. The mortality analysis was repeated using Colorado, New Mexico, Arizona, and Utah state mortality rates to generate expected numbers of deaths. In addition to analyses of underlying cause of death, all causes listed on the death certificate were analysed using multiple cause mortality methods described by Steenland and colleagues.[15] Multiple cause analyses are particularly important for diseases that may be prevalent at death but that are not the underlying cause of death.[15] In analyses using state or multiple cause mortality rates, person-years at risk started to accumulate on 1 January 1960, when the rates were first available, or completion of the one year eligibility period, whichever was later.

The end stage renal disease experience of the cohort was analysed using methods described by Calvert and colleagues.[16] Briefly, the modified life table analysis system was used to calculate PYAR, expected number of individuals developing ESRD, and standardised incidence ratios (SIRs) for ESRD. Since the ESRD PMMIS is considered incomplete prior to 1977, cohort members who died before this date were excluded from the ESRD analysis. PYAR for cohort members who were alive on 1 January 1977 began to accumulate on this date. Cohort members accumulated PYAR until the first service date for those with ESRD, the date of death for deceased cohort members, the date last observed for those lost to follow up, or the ending date of the study for those known to be alive. The first service date for ESRD, which generally represents the date on which renal replacement therapy began, was used as a surrogate for the date of onset of ESRD. After the PYAR were stratified into five year intervals by age and calendar time, the PYAR were multiplied by the appropriate US ESRD incidence rates to calculate the expected number of cases for that stratum. The US incidence rates were developed by NIOSH from the HCFA PMMIS data and US census data as described elsewhere.[16] The expected number of treated ESRD cases in all strata were summed to yield the total expected number. The ratio of the observed to expected number of treated ESRD cases was expressed as the standardised incidence ratio (SIR). The SIR for four major categories of ESRD (systemic, non-systemic, other, and unknown) were also calculated.

We stratified SMRs and SIRs by duration of employment (1–2, 3–9, 10+ years), time since first employment (latency) (0–9, 10–19, 20+ years), and year of first employment (<1955, 1955+). In general, the cut points for duration of employment and time since first employment were retained from the original study; however, we lowered the cut point between the lowest and middle duration of employment categories so that the number of deaths in each category would be more similar. The cut point for year first employed was selected a priori based on the assumption that exposures in the earlier years (when there was little emphasis on dust control) would be higher than in later years. Duration of employment was based on employment in the seven cohort mills while they were operating to produce uranium and/or vanadium concentrates and included employment that occurred prior to the start of the follow up period. The analyses were repeated restricting the cohort to those who had worked in a conventional mill and to those who had worked in a conventional mill that produced both vanadium and uranium concentrates. Because of the potential impact of exposures encountered during other employment in the uranium industry, SMRs and SIRs were also conducted restricting the cohort to those without such employment. All analyses were done using the PC version of the LTAS[17] (http://www.cdc.gov/niosh/ltindex.html). Testing for heterogeneity and trend in the SMRs used the methods of Breslow and Day.[18]

Based on previous studies and the known toxic effects of uranium and silica, the a priori outcomes of interest in this study included non-malignant respiratory disease, chronic renal disease, lung cancer, and lymphatic and haematopoietic cancer other than leukaemia. Within the major category of non-malignant respiratory disease, the minor category ''pneumoconiosis and other respiratory diseases'' was of a priori interest.

RESULTS

A total of 1484 men contributing 49 925 person-years were included in the study. Table 1 presents the distribution of the cohort by vital status, plant type (conventional mill, upgrader), duration of employment, time since first employment, and first year of employment. Race was unknown for 642 (43.3%) members of the cohort. Because all workers of known race were white, workers of unknown race were classified as white in the analysis. In the total cohort, 656 (44.2%) men were alive, 810 (54.6%) were deceased, and 18 (1.2%) were lost to follow up. Causes of death were obtained from death certificates or the NDI for 794 (98.0%) of the individuals known to be deceased. Deaths with missing causes of death were included in the other and unknown causes category. The duration of employment of the cohort is relatively short with a median of 3.6 (range 1–36.3) years. Over half of the cohort was first employed prior to 1955. The median time since first employment, based on employment in the seven mills while they were operating, is 37 years.

Table 1 Characteristics of the study population

No. of workers	1485
Excluded from analysis*	1
Person-years at risk	49925
Mill type	
Conventional mill only	1412 (95.1%)
Upgrader only	44 (3.0%)
Both	28 (1.9%)
Vital status as of 31 Dec 1998	
Alive	656 (44.2%)
Dead	810 (54.6%)
Unknown	18 (1.2%)
Year of birth	1921 median 1872–1951 range
Year of first employment†	
Prior to 1955	799 (53.8%)
1955 or later	685 (46.2%)
Duration of employment†	
1–2 years	634 (42.7%)
3–9 years	547 (36.9%)
10 + years	303 (20.4%)
Time since first employment†	
<10 years	76 (5.1%)
10–19 years	128 (8.6%)
20+ years	1280 (86.3%)

*Missing date of birth.
†Employment in the seven mills while operating to produce uranium and/or vanadium concentrates.

Almost all of the workers and person-years were from conventional uranium mills. Of the 1440 men who were employed at conventional mills, 1263 (87.7%) were employed at mills that recovered vanadium, 145 (10.1%) were employed at mills that did not recover vanadium, and 32 (2.2%) were employed both at mills that recovered vanadium and mills that did not recover vanadium. Among the entire cohort, 83 (5.6%) men had also been employed in other aspects of the uranium industry according to their employment application or other employment records.

Table 2 shows the results of the analysis for all causes of death. Mortality from all causes was less than expected, which is largely accounted for by fewer deaths from heart disease than expected. Mortality from all malignant neoplasms was also less than expected. Among the outcomes of a priori interest, a statistically significant increase in mortality from non-malignant respiratory disease (SMR = 1.43; 95% CI 1.16 to 1.73; obs = 100) and non-significant increases in mortality from trachea, bronchus, and lung cancer (SMR = 1.13; 95% CI 0.89 to 1.41; obs = 78), lymphatic and haematopoietic malignancies other than leukaemia (SMR = 1.44; 95% CI 0.83 to 2.35; obs = 16), and chronic renal disease (SMR = 1.35; 95% CI 0.58 to 2.67; obs = 8) were observed. The excess in mortality from lymphatic and haematopoietic malignancies was due to an excess in mortality from lymphosarcoma and reticulosarcoma (SMR = 1.74; 95% CI 0.48 to 4.46; obs = 4) and Hodgkin's disease (SMR = 3.30; 95% CI 0.90 to 8.43; obs = 4). Within the major category of non-malignant respiratory disease, mortality from emphysema (SMR = 1.96; 95% CI 1.21 to 2.99; obs = 21) and pneumoconioses and other respiratory disease (SMR = 1.68; 95% CI 1.26 to 2.21; obs = 52) was significantly increased. Among outcomes other than those of a priori interest, non-significant increases in mortality from other and unspecified cancers (SMR = 1.59; 95% CI 0.98 to 2.43; obs = 21) and accidents (SMR = 1.26; 95% CI 0.93 to 1.68;

Table 2 Uranium mill workers' mortality (since 1940, US referent rates): update of cohort to 1998

Underlying cause of death (ICD9 code)*	Obs	Exp	SMR	95% CI
All causes	810	877.66	0.92‡	0.86 to 0.99
All cancers (140–208)	184	204.12	0.90	0.78 to 1.04
Buccal and pharyngeal CA (140–149)	2	5.06	0.40	0.05 to 1.43
All digestive CA (150–159)	33	53.18	0.62§	0.43 to 0.87
Oesophagus (150)	1	5.06	0.20	0.01 to 1.10
Colon (152–153)	12	18.96	0.63	0.33 to 1.11
Rectal (154)	2	4.77	0.42	0.05 to 1.51
Liver and biliary (155–156)	4	5.04	0.79	0.22 to 2.03
Pancreas (157)	6	10.30	0.58	0.21 to 1.27
All respiratory CA (160–165)	78	72.29	1.08	0.85 to 1.35
Trachea, bronchus, and lung (162)	78	68.93	1.13	0.89 to 1.41
Male genital CA (185–187)	15	19.67	0.76	0.43 to 1.26
All urinary CA (188–189)	5	11.03	0.45	0.15 to 1.06
Kidney (189.0–189.2)	4	4.96	0.81	0.22 to 2.06
Leukaemia/aleukaemia (204–208)	5	7.62	0.66	0.21 to 1.53
Lymphatic and haematopoietic CA other than leukaemia (200–203)	16	11.08	1.44	0.83 to 2.35
Lymphosarcoma and reticulosarcoma (200)	4	2.29	1.74	0.48 to 4.46
Hodgkin's disease (201)	4	1.21	3.30	0.90 to 8.43
Other lymphatic and haematopoietic CA (202–203)	8	7.57	1.06	0.46 to 2.08
Other/unspecified CA (194–199)	21	13.20	1.59	0.98 to 2.43
Tuberculosis (001–008)	2	3.88	0.52	0.06 to 1.86
Diabetes mellitus (250)	10	14.60	0.68	0.33 to 1.26
Heart disease (390–398, 402, 404, 410–414, 420–429)	293	349.10	0.84§	0.75 to 0.94
Ischemic heart disease (410–414)	236	280.07	0.84§	0.74 to 0.96
Other circulatory disease (401, 403, 405, 415–417, 430–459)	69	83.06	0.83	0.65 to 1.05
Non-malignant respiratory disease (460–519)	100	70.16	1.43§	1.16 to 1.73
Pneumonia (480–486)	25	23.76	1.05	0.68 to 1.55
Chronic and unspecified bronchitis (490–491)	2	2.20	0.91	0.11 to 3.28
Emphysema (492)	21	10.72	1.96§	1.21 to 2.99
Pneumoconioses and other respiratory disease (470–478, 494–519)	52	30.87	1.68§	1.26 to 2.21
Non-malignant digestive disease (520–579)	23	36.91	0.62‡	0.39 to 0.94
Non-malignant genitourinary disease (580–629)	13	13.03	1.00	0.53 to 1.71
Acute renal disease (580–581, 584)	1	1.16	0.86	0.02 to 4.79
Chronic renal disease (582–583, 585–587)	8	5.91	1.35	0.58 to 2.67
Ill defined conditions (780–796, 798–799)	4	8.01	0.50	0.14 to 1.28
Accidents (E800–E949)	47	37.23	1.26	0.93 to 1.68
Violence (E950–E978)	18	17.73	1.02	0.60 to 1.60
Suicide (E950–E959)	15	14.19	1.06	0.59 to 1.74
Homicide (E960–E978)	3	3.54	0.85	0.18 to 2.48
Other and unknown causes	27†	14.04	1.92§	1.27 to 2.80

*International Classification of Disease codes, 9th revision.
†Includes 16 observed deaths with missing death certificates.
‡95% confidence interval excludes the null value (1.0).
§99% confidence interval excludes the null value (1.0).

obs = 47) were observed. The observed other and unspecified cancers were metastatic cancers of unknown primary site. Mortality from all digestive cancers was significantly less than expected (SMR = 0.62; 95% CI 0.43 to 0.87; obs = 33).

An analysis was also conducted (not shown) using US rate files for 1960 to 1999 which have 99 causes of death instead of 92 because these rate files include more detailed categories of non-malignant respiratory disease and slightly different categories of malignancies of the lymphatic and haematopoietic system. Of the 1484 cohort members, 89 (6.0%) were not included in this analysis because they had either died or were lost to follow up before 1960. Only one death from silicosis (SMR = 5.93; 95% CI 0.15 to 32.94) and two deaths from pneumoconioses other than silicosis and asbestosis (SMR = 2.29; 95% CI 0.28 to 8.25) were observed. The remainder of the excess in non-malignant respiratory disease mortality was due to a significant excess in mortality from emphysema (SMR = 1.83; 95% CI 1.10 to 2.86) and other respiratory diseases (SMR = 1.62; 95% CI 1.19 to 2.15). Most of the observed deaths from other respiratory diseases were due to chronic obstructive lung disease. In the category of malignancies of the lymphatic and haematopoietic system other than leukaemia, mortality was significantly increased for Hodgkin's disease (SMR = 4.01; 95% CI 1.09 to 10.25, obs = 4) and non-significantly increased for non-Hodgkin's lymphoma (SMR = 1.25; 95% CI 0.54 to 2.46; obs = 8).

In order to evaluate whether regional variations in mortality rates could explain the findings, analyses were conducted using state rates as the comparison population (table 3). State rates are not available before 1960 so men who had either died or were lost to follow up before 1960 were also excluded from this analysis. The excess in mortality from cancer of the trachea, bronchus, and lung (SMR = 1.51; 95% CI 1.19 to 1.89) based on state rates was statistically significant and greater than the excess based on US rates since 1960 (SMR = 1.13; 95% CI 0.89 to 1.42). In contrast, the excess in mortality from emphysema (SMR = 1.25; 95% CI 0.75 to 1.95) and other respiratory diseases (SMR = 1.35; 95% CI 0.99 to 1.79) was less than the excess based on US rates. Mortality from chronic renal disease was not increased based on state rates (SMR = 1.02; 95% CI 0.33 to 2.39; obs = 5) and was similar to that based on US rates since 1960 (SMR = 1.00; 95% CI 0.32 to 2.35). This is in contrast to the excess in mortality from chronic renal disease observed based on US rates since 1940.

Tables 4 and 5 show mortality according to duration of employment and time since first employment for selected causes of death based on US rates. Overall mortality was highest among those with the shortest duration of employment and lowest among those with the longest duration of employment. Similar trends with duration of employment were observed for mortality from lung cancer, non-malignant

Table 3 Uranium mill workers' mortality (since 1960) from selected causes of death (state referent rates): update of cohort to 1998

Underlying cause of death (ICD9 code)*	Obs	Exp	SMR	95% CI
All respiratory CA (160–165)	75	51.98	1.44‡	1.13 to 1.81
Trachea, bronchus, and lung (162)	75	49.73	1.51‡	1.19 to 1.89
Leukaemia/aleukaemia (204–208)	5	6.51	0.77	0.25 to 1.80
Lymphatic and haematopoietic CA other than leukaemia (200–203)	15	9.58	1.57	0.88 to 2.58
Non-Hodgkin's lymphoma (200, 202)	8	5.71	1.40	0.60 to 2.76
Hodgkin's disease (201)	4	0.94	4.24†	1.15 to 10.84
Myeloma (203)	3	2.93	1.02	0.21 to 3.00
Other/unspecified CA (187, 194–199)	22	11.93	1.84‡	1.16 to 2.79
Non-malignant respiratory diseases (460–519)	94	79.32	1.19	0.96 to 1.45
Chronic and unspecified bronchitis (490–491)	1	2.74	0.36	0.01 to 2.03
Emphysema (492)	19	15.22	1.25	0.75 to 1.95
Asbestosis (501)	0	0.12	0.00	0.00 to 30.62
Silicosis (502)	1	0.45	2.22	0.06 to 12.36
Other pneumoconioses (500, 503, 505)	2	0.40	5.04	0.61 to 18.19
Other respiratory diseases (470–478, 494–499, 504, 506–519)	47	34.86	1.35	0.99 to 1.79
Non-malignant genitourinary disease (580–629)	10	10.51	0.95	0.46 to 1.75
Acute renal disease (580–581, 584)	1	0.79	1.26	0.03 to 6.99
Chronic renal disease (582–583, 585–587)	5	4.89	1.02	0.33 to 2.39

*International Classification of Disease codes, 9th revision.
†95% confidence interval excludes the null value (1.0).
‡99% confidence interval excludes the null value (1.0).

respiratory disease, and emphysema. A positive trend between mortality and duration of employment was not observed for any of the selected causes of death except other and unspecified cancers. The excess in mortality from Hodgkin's disease was confined to 20 years or more since first employment. Mortality from Hodgkin's disease was significantly increased over sevenfold among this group, but the confidence interval around the point estimate was wide (95% CI 1.96 to 18.40).

Mortality was also examined (not shown) by date of hire (pre-1955 versus 1955 or later). There appeared to be a relation between an earlier date of hire and increased mortality from trachea, bronchus, and lung cancer (prior to 1955: SMR = 1.34, 95% CI 1.02 to 1.74; 1955 or later: SMR = 0.79, 95% CI 0.49 to 1.21). Mortality from emphysema was also higher among men hired prior to 1955 (SMR = 2.22; 95% CI 1.29 to 3.56; obs = 17) than among men hired in 1955 or later (SMR = 1.30; 95% CI 0.36 to 3.33; obs = 4), but mortality from pneumoconiosis and other respiratory disease was similar among men hired prior to 1955 (SMR = 1.69; 95% CI 1.17 to 2.36) and men hired in 1955 or later (SMR = 1.68; 95% CI 0.99 to 2.65).

Analyses of multiple causes of death and end stage renal disease incidence were conducted to further evaluate the risk of renal disease among the cohort. The risk of chronic renal disease mortality was not increased (SMR = 1.05; 95% CI 0.69 to 1.54, obs = 26) in the multiple causes of death analysis. The risk of treated end stage renal disease was less than expected overall (SIR = 0.71; 95% CI 0.26 to 1.55, obs = 6). The risk of treated end stage renal disease of unknown aetiology was increased (SIR = 2.73; 95% CI 0.56 to 7.98, obs = 3). This finding was based on three observed cases and the confidence interval was wide. The primary cause of renal failure was missing in the ESRD PMMIS for two of the three observed cases, raising the possibility that these cases were misclassified. Death certificates were available for these cases; renal disease was mentioned on the death certificate for both, but not a specific type or aetiology of renal disease.

Similar results were obtained when the cohort was restricted to men who were employed in conventional mills and when the cohort was restricted to men who were employed in conventional mills that produced both uranium and vanadium concentrates. Results were also similar when

Table 4 Uranium mill workers' mortality (since 1940) from selected causes of death by duration of employment (US referent rates): update of cohort to 1998

	Duration of employment (years)			
Underlying cause of death	1–2 SMR (obs)	3–9 SMR (obs)	⩾10 SMR (obs)	
All deaths	1.01 (352)	0.91 (295)	0.80 (163)†	‡
All cancers	0.94 (75)	0.91 (68)	0.83 (41)	
Trachea, bronchus, and lung CA	1.35 (36)	1.27 (32)	0.58 (10)	‡
Lymphatic and haematopoietic CA other than leukaemia	1.38 (6)	1.22 (5)	1.90 (5)	
Lymphosarcoma and reticulosarcoma	2.15 (2)	1.15 (1)	2.03 (1)	
Hodgkin's disease	1.91 (1)	4.25 (2)	4.57 (1)	
Other lymphatic and haematopoietic CA	1.03 (3)	0.73 (2)	1.56 (3)	
Other/unspecified CA	1.16 (6)	1.65 (8)	2.19 (7)	
Non-malignant respiratory disease	1.99 (53)†	1.12 (29)	1.02 (18)	‡
Emphysema	2.69 (11)†	1.79 (7)	1.11 (3)	
Pneumoconioses and other respiratory diseases	2.53 (29)†	1.07 (12)	1.35 (11)	
Chronic renal disease	1.27 (3)	1.33 (3)	1.53 (2)	

*95% confidence interval excludes the null value (1.0).
†99% confidence interval excludes the null value (1.0).
‡Test for trend p value <0.05.

Table 5 Uranium mill workers' mortality (since 1940) from selected causes of death by length of time since first employment (US referent rates): update of cohort to 1998

	Time since first employment (years)		
Underlying cause of death	**<10 SMR (obs)**	**10–19 SMR (obs)**	**≥20 SMR (obs)**
All deaths	0.95 (68)	0.87 (125)	0.93 (617)
All cancers	0.62 (7)	0.88 (25)	0.92 (152)
Trachea, bronchus, and lung CA	0.36 (1)	1.45 (13)	1.12 (64)
Lymphatic and haematopoietic CA other than leukaemia	1.35 (1)	0.00 (0)	1.72 (15)
Lymphosarcoma and reticulosarcoma	3.33 (1)	0.00 (0)	2.24 (3)
Hodgkin's disease	0.00 (0)	0.00 (0)	7.19 (4)**
Other lymphatic and haematopoietic CA	0.00 (0)	0.00 (0)	1.18 (8)
Other/unspecified CA	0.00 (0)	1.21 (2)	1.76 (19)*
Non-malignant respiratory disease	1.32 (4)	1.48 (11)	1.42 (85)**
Emphysema	2.39 (1)	2.21 (4)	1.89 (16)*
Pneumoconioses and other respiratory diseases	3.73 (2)	2.24 (4)	1.61 (46)**
Chronic renal disease	3.95 (3)	1.23 (1)	0.92 (4)

*95% confidence interval excludes the null value (1.0).
**99% confidence interval excludes the null value (1.0).

the cohort was restricted to men without known employment in other aspects of the uranium industry.

DISCUSSION

Uranium exposure presents both chemical and radiological hazard potentials. Both the chemical and radiological toxicity are influenced by the biological solubility of a given uranium compound. Poorly soluble uranium compounds are cleared slowly from the lungs and pose a potential internal radiation hazard. More soluble compounds are absorbed rapidly from the lungs, decreasing the radiation hazard, but increasing the potential for renal toxicity.[19 20] In the ore handling and preparation areas of the mills, the uranium in ore dusts consists mostly of insoluble uranium oxides with a relatively small fraction of the more soluble uranium compounds. The potential for exposure to the long lived alpha emitters (uranium-238, uranium-234, thorium-230, radium-226, and lead-210) is greatest in these areas of the mill. In the yellowcake drying and packaging areas of the mill, the uranium in yellowcake consists of a complex mixture of uranium compounds of varying solubility. The composition and solubility of the yellowcake product depends on the drying temperature employed.[19 21] In mills that dry the product at relatively low temperatures (100–150°C), the yellowcake product is high in ammonium diuranate $[(NH_4)_2U_2O_7]$ which is highly soluble in lung fluids; in mills that dry the product at relatively high temperatures (370–538°C), the yellowcake is high in uranium oxide (U_3O_8) which is mostly insoluble in lung fluids.[21 22] Based on available data on drying temperatures and drying equipment, four of the five conventional mills in this study used relatively high drying temperatures. The fifth mill did not prepare a dried yellowcake product; rather, it produced filter press cake or a uranium product liquor, depending on the year of operation. Accordingly, most mill workers in this study worked in mills that probably produced yellowcake of relatively low solubility.

Both human and animal data suggest that insoluble uranium compounds and thorium accumulate in the tracheobronchial lymph nodes.[23–26] Because of this, it has been suggested that studies of early uranium workers evaluate the effects on lymphatic tissues.[25] In the previous study of workers at the mills in this study, a significant increase in mortality from lymphatic and haematopoietic malignancies other than leukaemia was observed after 20 years latency, based on six deaths.[7] We also found an excess in mortality from lymphatic and haematopoietic malignancies other than leukaemia but the magnitude of the excess was less than the excess observed in the previous study. The observed excess was due to an excess in both Hodgkin's disease mortality and lymphosarcoma and reticulosarcoma mortality based on four observed deaths each. The ability to evaluate exposure response relations, using duration of employment as a surrogate of exposure, was limited by the small number of observed deaths from these cancers. Of the eight observed deaths due to Hodgkin's disease, lymphosarcoma, and reticulosarcoma in this study, three were observed in the previous study and one was observed in the study by Archer and colleagues.[8]

Hodgkin's disease and non-Hodgkin's lymphoma, a group of lymphomas which includes lymphosarcoma and reticulosarcoma, have not been clearly linked to radiation.[27 28] Data on the risk of death from Hodgkin's disease and non-Hodgkin's lymphoma among uranium or thorium workers are limited. An increased risk of Hodgkin's disease mortality and lymphosarcoma and reticulosarcoma mortality has been observed among uranium processing workers at the Fernald Feed Materials Production Center near Cincinnati, Ohio (SMR = 2.04, 95% CI 0.74 to 4.43, obs = 6; and SMR = 1.67, 95% CI 0.72 to 3.29, obs = 8, respectively)[29] and thorium processing workers (SMR = 1.64, 95% CI 0.33 to 4.79, obs = 3; and SMR = 1.14, 95% CI 0.23 to 3.34, obs = 3, respectively),[30] but not among uranium processing workers at the Y-12 plant at Oak Ridge, Tennessee[31] and Mallinckrodt Chemical Works in St Louis, Missouri[32] or among a combined cohort of uranium and other miners from 11 studies.[33] Hodgkin's disease mortality and incidence and non-Hodgkin's lymphoma incidence was associated with cumulative external radiation dose among workers at the Springsfield uranium production facility; the effects of internal exposures were not evaluated.[34] In general, these studies, like the current study, are limited by the small number of deaths from Hodgkin's disease and non-Hodgkin's lymphoma among exposed workers.

A new finding in this update not previously reported was a small increase in mortality from cancer of the trachea, bronchus, and lung, particularly relative to state rates. We also observed an increased risk of mortality from non-malignant respiratory disease. Mortality from lung cancer was higher based on state rates than US rates, whereas mortality from non-malignant respiratory disease was lower based on state rates than US rates. This is consistent with the relatively low smoking attributable mortality and relatively high chronic obstructive lung disease mortality in Arizona, Colorado, and New Mexico compared to other states.[35] The reason for the discrepancy in smoking-attributable mortality and chronic obstructive lung disease mortality in many inland western states is unknown. However, the results suggest that regional differences in mortality may explain, in part, the observed excess in non-malignant respiratory disease mortality based on US rates.

The excess in both lung cancer mortality and emphysema mortality was greater among workers hired prior to 1955, when there was little emphasis on dust control and exposures to uranium and silica containing dusts were presumably higher. However, mortality from lung cancer and non-malignant respiratory disease was inversely related to duration of employment. We found no evidence that workers who were hired prior to 1955 were more likely to be short term workers. The inverse relation between lung cancer and emphysema mortality and duration of employment in this study may be a reflection of the healthy worker survivor effect, in which individuals who remain in the workforce over time tend to be healthier than those who leave.[36] Duration of employment may also be a poor surrogate of exposure in this study since exposures are thought to have varied considerably by mill area and over time.

Some data suggest that uranium workers other than miners may be at increased risk of lung cancer[29 31] and non-malignant respiratory disease.[37] Uranium ore dust has been shown to induce pulmonary lesions in animals[23 38 39] and lung cancer in rats.[40] Silica exposure has been reported to lead to the development of silicosis, emphysema, obstructive airways disease, and lymph node fibrosis.[41] Although the carcinogenicity of silica continues to be debated in the scientific community, several investigators have showed an increased risk of lung cancer among workers exposed to silica.[42–44] Vanadium containing compounds have known acute respiratory effects,[45] but it is less clear whether exposure to vanadium can lead to chronic non-malignant respiratory disease.[45 46] In this study, we only observed three deaths from silicosis and unspecified pneumoconioses. The majority of the excess in non-malignant respiratory disease mortality was due to mortality from emphysema and other respiratory disease.

Other potential explanations also exist for the observed excesses in mortality from lung cancer and non-malignant respiratory disease mortality. Smoking data are not available for this cohort, and differences in smoking habits between the cohort and the general population may partially explain the excesses observed. White men in the Colorado Plateau uranium miners cohort were heavy smokers,[6 47] but it is unknown whether the smoking habits of uranium mill workers who never worked underground in uranium mines would be similar to these miners. Even if the mill workers in this study were more likely to smoke than the general population, other investigators have shown that smoking is unlikely to account for SMRs above 1.3 for lung cancer and other smoking related diseases.[48] Other potential factors that may contribute to these excesses include unknown employment in underground uranium mines and employment in other mines with increased levels of radon and radon decay products. It is unlikely that the cohort included many mill workers who also worked as uranium miners. Mill workers who also worked in uranium mines were identified by reviewing the work history records and by matching the cohort to a NIOSH file of over 18 000 uranium miners. All identified uranium miners were excluded from the final cohort. However, members of the cohort may have been more likely to work in other types of mines than the general population.

We found a small non-significant excess in chronic renal disease when using US rates as a comparison; this excess was not apparent when only deaths between 1960 and 1998 were analysed (both underlying cause and multiple cause). Renal effects have been observed among silica exposed workers. Goldminers and industrial sand workers exposed to silica have been found to be at excess risk of death from renal disease and to have increased renal disease incidence.[16 49 50] Low level β_2 microglobulinuria and aminoaciduria has been observed among uranium mill workers exposed to soluble uranium compounds at a mill not in the current study,[9] but little data on chronic renal disease mortality among uranium workers exist. An increase in mortality from chronic nephritis (SMR = 1.88; 95% CI 0.75 to 3.81) was observed among uranium processing workers at Mallinckrodt, based on six observed deaths.[32] An excess in chronic renal disease mortality has been observed among uranium miners (SMR = 1.6; 95% CI 0.7 to 3.0, obs = 9), but the observed excess was not related to duration of employment.[6]

This study may have underestimated the risk of ESRD and renal disease mortality associated with uranium milling. We observed an excess in chronic renal disease mortality during the follow up period 1940–59, but not during the follow up period 1960–98. This suggests that the exclusion of cohort members who died or were lost to follow up prior to 1960 may have been a significant limitation in our ability to evaluate the risk of ESRD and chronic renal disease mortality using multiple cause of death data. Because the cohort is relatively old, approximately 22% of the cohort was excluded from the analysis of ESRD because they died or were lost to follow up before the ESRD PMMIS is first considered complete, which also reduced the statistical power of the ESRD analysis. In addition, the majority of the mill workers in this study were probably exposed to relatively insoluble forms of uranium. The risk of renal disease may be higher in mills using relatively low drying temperatures where the potential for exposure to soluble forms of uranium is greater. The study evaluated chronic renal disease mortality and ESRD and was not able to evaluate the risk of less severe renal effects.

In conclusion, we observed an excess in mortality from haematopoietic and lymphatic malignancies other than leukaemia, trachea, bronchus, and lung cancer, non-malignant respiratory disease, and chronic renal disease. Some of these excesses were based on a small number of deaths and the confidence intervals around the point estimates were wide. Limitations include the lack of smoking data, small cohort size and limited power to detect a moderately increased risk of some of the a priori outcomes of interest, and the inability to evaluate exposure-response relations using individual estimates of exposure to uranium, silica, and vanadium. Because of these limitations and the lack of a positive trend between the observed excesses and duration of employment, firm conclusions about the relation of the observed excesses and mill exposures are not possible.

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