USTUR Special Session
61st Annual Meeting of the Health Physics Society
Spokane, WA, July 19, 2016

Reanalysis of Radiation and Mesothelioma in the U.S. Transuranium and Uranium Registries

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"Learning from Plutonium and Uranium Workers"

Excess of mesothelioma deaths in the USTUR

Paper

CAUSES OF DEATH IN A COHORT OF 260 PLUTONIUM WORKERS

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Abstract—**The United States Transuranium and Uranium Registries (USTUR) is a unique postmortem research study of the biokinetics, dosimetry, and possible biological effects of actinide elements in persons with occupational exposure to these radioelements. Evaluation of the causes of death in the admittedly biased self-selected cohort of the first 260 deceased participants in the USTUR revealed, in general, no apparently elevated causes of death except for six cases of mesothelioma and six cases of astrocytoma glioblastoma multiforme. The mesothelioma cases had a documented occupational exposure to asbestos, and the six brain tumor deaths all occurred at a single work site and were not radiation related but rather are likely attributable to a factor specific to the work site or surrounding area. Incidental findings in this cohort did not suggest any radiation related illness or cause of death.**
Health Phys. 75(3):236–240; 1998

Key words: plutonium; exposure, occupational; mortality; tumors

INTRODUCTION

The United States Transuranium and Uranium Registries (USTUR) study the biokinetics, dosimetry, and possible biological effects of the actinide elements in humans, including thorium, uranium, plutonium, and americium. This is accomplished by collection of specific tissues at autopsy, or, in some cases the entire body, from volunteer donors with known exposures to one or more of these elements. Tissues thus obtained are examined histologically for pathology and analyzed radiochemically to determine their long-lived actinide content. These data are then used in conjunction with medical and occupational exposure histories to evaluate the biokinetics and possible biological effects of actinides that have been incorporated into the body. Detailed descriptions of the USTUR program and its historical development have been published elsewhere in the peer reviewed literature and in various annual reports (Kathren 1995a, 1995b; Kathren et al. 1993a).

Participants in the USTUR program are all volunteers and are typically persons with a history of occupational exposure to one or more actinide elements. The overwhelming majority of cases—more than 90%—have had documented occupational exposure to plutonium. A small fraction have been exposed primarily to americium or uranium. Thus, the cohort of participants is nearly exclusively plutonium workers who are by and large self selected with the majority enrolling many years prior to death and prior to diagnosis of terminal illnesses or curable malignancies and other diseases. Not all registrants, however, have been enrolled in advance of death. A few, most notably USTUR Case 102, a whole body donor with an americium contaminated wound, enrolled subsequent to a diagnosis of a terminal cancer (Breitenstein et al. 1985). Tissue donations from others, notably USTUR Case 0246 who suffered a massive intake of americium (Toohey and Kathren 1995), are sometimes made by next-of-kin at the time of death.

THE USTUR COHORT OF DECEASED REGISTRANTS

Since its inception in 1968, the USTUR has acquired data on more than 300 deceased individuals with known or possible intakes of the actinide elements. This cohort includes a group of about 50 British cases and a smaller group of Los Alamos cases that predated the establishment of the Registries and for whom limited data are available; the remaining 260 cases were individuals who had voluntarily enrolled in the USTUR and thus had been treated similarly with respect to data gathering and had been autopsied in accordance with the USTUR protocol (Kathren 1995a). Although this cohort of 260 cases is small and biased because it is self selected and includes a few registrants who enrolled after having being diagnosed with terminal cancer, it was nonetheless important to determine and evaluate the causes of death in the deceased registrant population to see if there were any obvious anomalies with respect to cause of death, recognizing that because of the inherent bias in the cohort, only very general and inferential conclusions might be drawn from the data.

The causes of death in the USTUR cohort of 260 deceased registrants who had enrolled in the USTUR

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(*Manuscript received* 18 *November* 1997; *revised manuscript received* 3 *March* 1998, *accepted* 15 *May* 1998)

0017-9078/98/$3.00/0

"In general, no apparently elevated causes of death except for six cases of mesothelioma….."
"The mesothelioma cases had a documented occupational exposure to asbestos,……"

Gold B, Kathren RL. Health Phys. 1998;75(3):236---240.

The Gibb study (Gibb et al. 2013, *Am J Public Health*. 103 (4): 710 -716) examines 7 mesothelioma deaths among 329 deceased registrants in the USTUR.

Analyses of Radiation and Mesothelioma in the US Transuranium and Uranium Registries

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Objectives. We examined the relationship between radiation and excess deaths from mesothelioma among deceased nuclear workers who were part of the US Transuranium and Uranium Registries.

Methods. We performed univariate analysis with SAS Version 9.1 software. We conducted proportionate mortality ratio (PMR) and proportionate cancer mortality ratio (PCMR) analyses using the National Institute for Occupational Safety and Health Life Table Analysis System with the referent group being all deaths in the United States.

Results. We found a PMR of 62.40 ($P < .05$) and a PCMR of 46.92 ($P < .05$) for mesothelioma. PMRs for the 4 cumulative external radiation dose quartiles were 61.83, 57.43, 74.46, and 83.31. PCMRs were 36.16, 47.07, 51.35, and 67.73. The PMR and PCMR for trachea, bronchus, and lung cancer were not significantly elevated.

Conclusions. The relationship between cumulative external radiation dose and the PMR and PCMR for mesothelioma suggests that external radiation at nuclear facilities is associated with an increased risk of mesothelioma. The lack of a significantly elevated PMR and PCMR for trachea, bronchus, and lung cancer suggests that asbestos did not confound this relationship. (*Am J Public Health.* 2013;103:710–716. doi:10.2105/AJPH.2012.300928)

Mesothelioma is a rare disease that accounts for approximately 0.10% of all deaths per year in the United States.[1] The age-adjusted incidence is approximately 2.1 per 100 000 among men and about 0.4 per 100 000 among women in the United States for the period 2000–2005.[2] Price and Ware[1] estimated that approximately 2400 new cases of mesothelioma were diagnosed in the United States in 2008. The risk factor most commonly associated with an increased risk of mesothelioma is asbestos. Smoking has not been identified as a risk factor for mesothelioma; neither does the combination of smoking and mesothelioma increase the risk of mesothelioma.[3,4] Spirtas et al.[5] estimated that among men, the attributable risk of asbestos for pleural mesothelioma and peritoneal mesothelioma was 88% and 58%, respectively. Among women, the attributable risk from asbestos for both sites combined (pleural and peritoneal) was only 23%.[5] Peto et al.[6] reported that among men the attributable risk from asbestos was 86%; among women, the attributable risk was only 38%. A variety of other agents including radiation, minerals, chemicals, viruses, and chronic inflammation have been implicated as causes of mesothelioma.[7–10] Ionizing radiation, such as x-rays, gamma rays, and alpha and beta particles, from both acute and long-term, low-level exposure is known to be associated with an increased risk of a variety of cancers. Exposure to radiation can cause mutations in the DNA and mutations can also occur during the body's attempt to repair damaged DNA. Such mutations can lead to cancer.[11]

Metz-Flamant et al.[12] reported that 15 of 17 studies of nuclear workers found an elevated risk of malignant pleural mesothelioma; all 17 studies provided exposure information. Eight studies reported that mesothelioma risks were higher for radiation-exposed workers than for other workers.[12] The authors claimed, however, that only 1 of 12 studies found a significant exposure–response relationship for cumulative external radiation dose but noted that with 1 exception, each study had few mesothelioma deaths.[12] Because of the lack of exposure–response and because asbestos could not be ruled out as a confounding agent, the authors concluded that studies of nuclear workers have not demonstrated an association between ionizing radiation exposure and malignant pleural mesothelioma.[12]

Gold and Kathren[13] reported an excess of mesothelioma deaths in the US Transuranium and Uranium Registries (USTUR). The USTUR, currently in its 44th year of operation, maintains whole and partial-body donations acquired postmortem from volunteer donors, most of whom worked at US Department of Energy nuclear facilities. These registrants worked with, and typically had a documented accidental intake of, 1 or more alpha-emitting radionuclides (e.g., uranium, plutonium, and americium). Intakes varied from background levels to substantial intakes. USTUR donors typically worked at government sites where plutonium, americium, or uranium were processed (e.g., Hanford, Rocky Flats, Los Alamos, Savannah River, Fernald, and Mound).[14] We examined the possible association of the excess of mesothelioma deaths in the USTUR with radiation exposure.

METHODS

Data recorded for all cases included nuclear facility of employment, dates of employment at the facility, date of birth, date of death, race, gender, date registered (agreed to be a donor), tobacco consumption (yes or no), dates of starting and stopping tobacco use, cumulative and yearly external radiation dose (mSv), and terminal dose rate (TDR) to the lung at time of death (mGy/year). Causes of death were coded to the *International Classification of Diseases, 10th Revision*.[15] For 2 individuals in the USTUR for whom death certificates were not available, we queried the National Death Index for cause of death. The National Death Index

The Gibb study error

- The Gibb study compares percentage of causes of deaths between the USTUR and the general population in the U.S., and suggests that external radiation at nuclear facilities is associated with an increased risk of mesothelioma.
- The study failed to recognize that the software performed calculations as if there were no mesothelioma deaths in the general population prior to 1999. (a new specific code for mesothelioma defined only in ICD-10).
- Six of seven mesothelioma cases were before 1999.
- The study made an error from the beginning, and its analysis on mesothelioma and radiation was wrong.

Letter to Editor: J. Zhou, Incorrect analyses of radiation and mesothelioma. American Journal of Public Health 104, E1-E1 (2014).

Reanalysis with a different approach

- Yes, there is an excess of mesothelioma cases in the USTUR and there are two more cases after the Gibb study (9 cases among 341 deceased registrants).
- Yes, the mean cumulative external radiation dose is higher for mesothelioma group than for other cancer and non-cancer groups.
- The reanalysis aims only to compare the group means statistically.

Study group descriptions:
LC/lung cancer, OC/other cancer, NC/non-cancer

	Meso	LC	OC	NC
Age at Death (range)	54 - 87	48 - 87	31 - 89	25 - 96
Employment Start (range)	1945 - 64	1942 - 82	1942 - 71	1941 - 83
Employment Duration (mean)	31.2	23.7	22.1	24.2
Cumulative External Dose [mSv] (mean)	173.9	105.1	109.7	152.5
Group Size	9	31	62	185

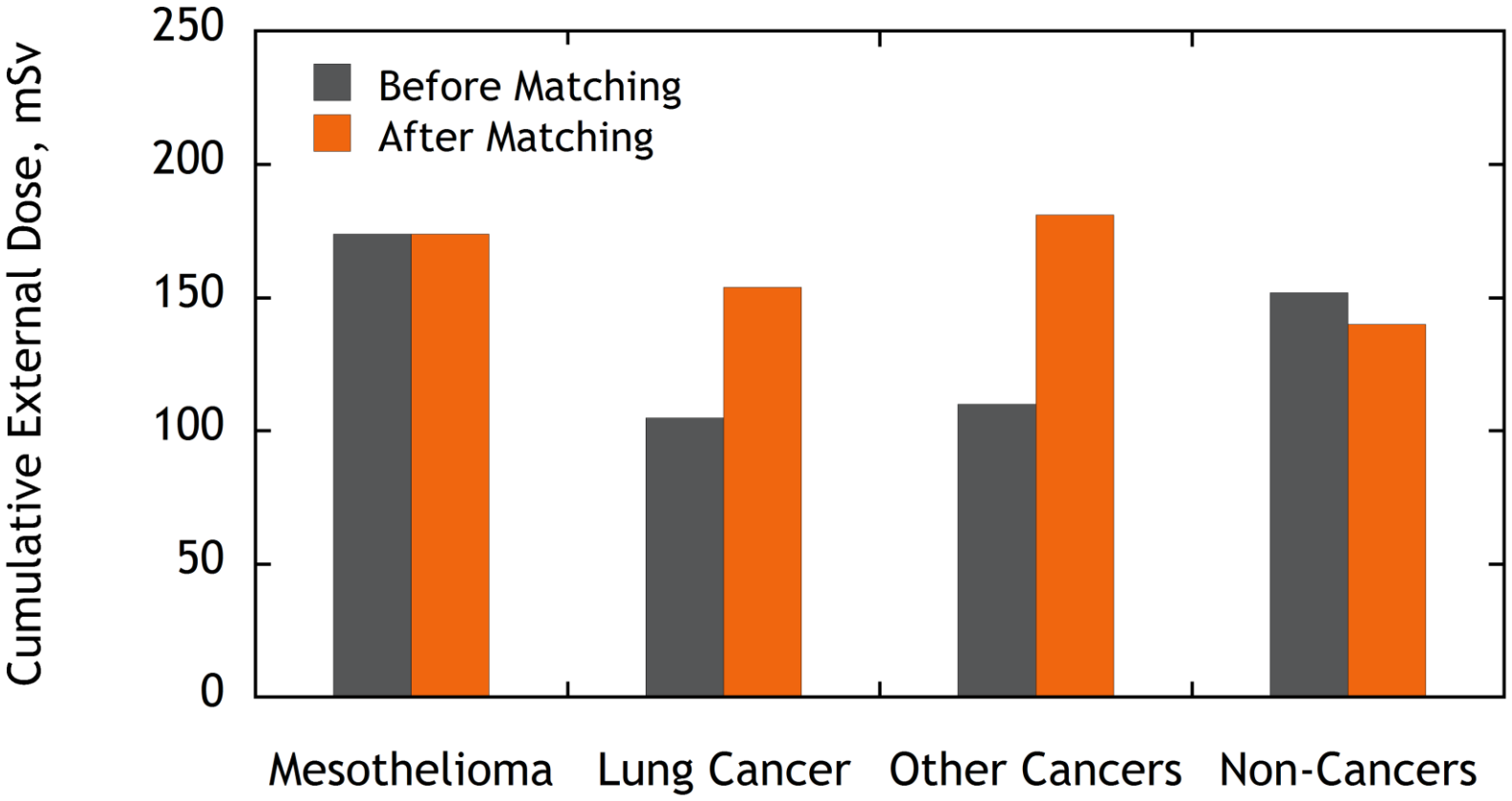
Different composition of the study groups

- Mesothelioma group has the largest cumulative external radiation dose.
- However, the mesothelioma group tends to be older at the age of death, hired earlier and employed longer than other groups.
- Therefore, age at death, employment start and employment duration are potential factors associated with cumulative external radiation dose.
- Take home message: control

A matched case "control" approach

- A matched case control approach is used to reduce the group differences, so that the mean external radiation doses among groups can be compared.
- For each case of mesothelioma, controls were identified in LC, OC and NC groups matching:
  - ✓ Employment duration (± 2.5 years)
  - ✓ Employment start(± 5 years)
  - ✓ Age at death (±5 years)
  - ✓ Birth year (±5 years)

Effect of matching



A permutation paired t-test (PPTT)

- For each paired t-test, one of multiple (4 ~5) matching controls for each case is randomly selected.
- Repeat the procedure 10,000 times, so the inference is based on a large number of paired t-tests.

	Dose to Meso cases and their matched NC controls, mSv								
Case #	1	2	3	4	5	6	7	8	9
Meso Cases	294.1	31.6	29.7	426.2	191.7	80.1	126.9	366.1	18.7
NC control 1	45.9	29.1	161.4	186.6	314.1	41.3	141.4	44.1	521.4
NC control 2	127.0	131.6	104.1	159.0	61.3	82.0	11.4	230.9	10.4
NC control 3	39.4	456.3	107.3	384.8	9.2	55.5	141.4	141.4	19.2
NC control 4	36.5	137.2	133.8	316.5	710.9	209.2	11.4	9.9	39.0
NC control 5					62.3	29.6		11.4	

- 5% of the significant paired t-tests ($p \geq 0.05$) is used as a critical level.

Results of PPTT

- PPTT was not significant
  - ✓ Meso vs. LC
  - ✓ Meso vs. OC
- PPTT was significant
  - ✓ Meso vs. NC

Cumulative External Radiation Dose (mSv)	% of significant Paired t-tests (10,000)
Meso vs. LC	0.0
Meso vs. OC	0.2
Meso vs. NC	9.0*

Conclusion

- The reanalysis finds that mean cumulative external radiation dose in mesothelioma group is statistically higher than non-cancer group.
- A follow-up conditional logistic regression for the mesothelioma and non-cancer groups shows no association between external radiation and mesothelioma. (results not presented here)
- The reanalysis makes no inference about the U.S. nuclear workers, as the Gibb study did, because the USTUR registrants are not representative of nuclear workers.

Key point of emphasis

- "It is to be emphasized that the present USTR is not an epidemiology study." (Observation and recommendation of the SAC in November 1979);
- The USTR "does not seek to measure mortality rates for specific diseases in transuranic workers." (USTR Annual Report, 1982);
- "The use of USTR data for this purpose is scientifically inappropriate and misleading." (USTR Annual Report, 1983)