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

Joey Zhou, Ph.D.

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A recently published paper, “Analysis of Radiation and Mesothelioma in the U.S. Transuranium and Uranium Registries”, (Gibb et al. 2013, *Am J Public Health*. 103 (4): 710 -716) examines 7 mesothelioma deaths among a small population of 329 deceased registrants in the USTUR.

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

Herman Gibb, PhD, Keri Fulcher, MS, Sumitha Nagarajan, MPH, Stacey McCord, MS, Naz Afarin Fallahian, PhD, Heather J. Hoffman, PhD, Cary Haver, MPH, Sergei Tolmachev, PhD

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 United States Transuranium and Uranium Registries (USTUR)

USTUR Registrants are volunteer body donors, who are typically former nuclear workers of the U.S. Department of Energy with a history of accidental occupational exposure to ionizing radiation. The main purpose of these donations has been for radiochemical analysis of the postmortem tissues and biokinetic modeling studies of radionuclides.

Mesothelioma

- A rare form of cancer that develops from cells of the mesothelium
- Accounts for only 0.1% of all deaths per year in the U.S.
- Most commonly caused by exposure to asbestos.
- Occurs more often in men than in women and risk increases with age

Mesothelioma and Radiation

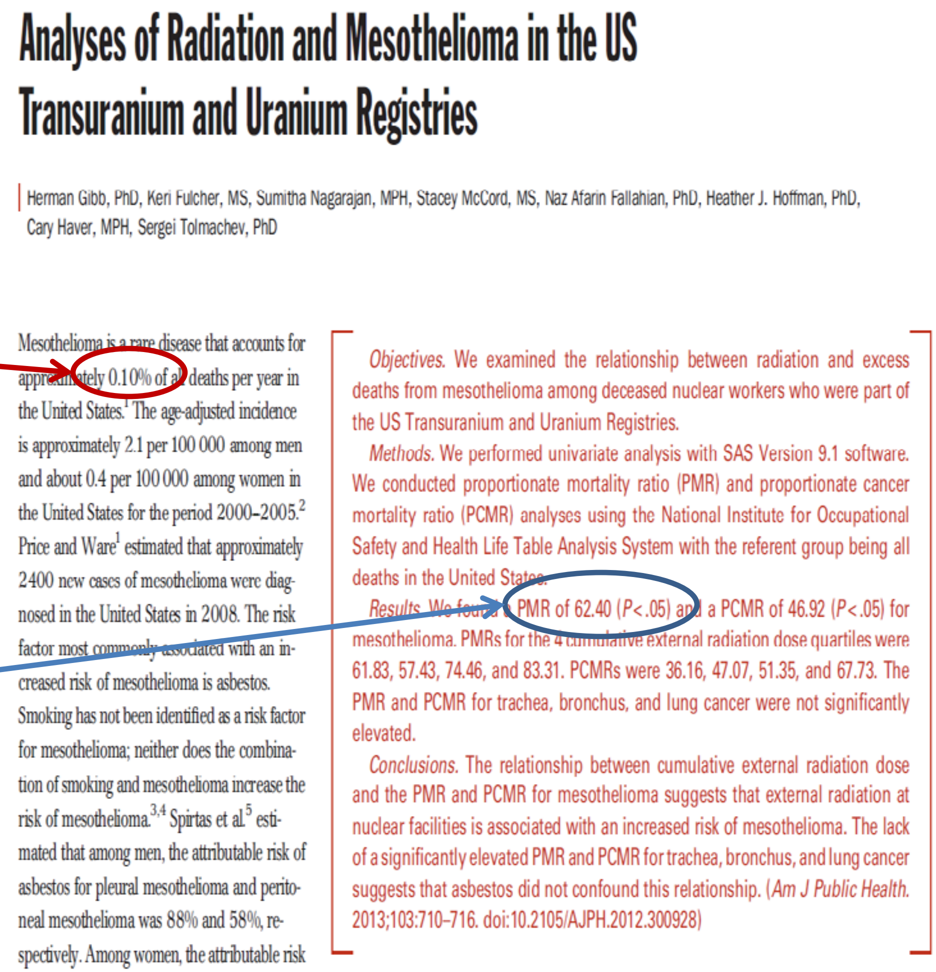
- Studies of patients treated by radiotherapy for primary cancers have suggested that radiation contributes to the development of secondary mesothelioma.
- Studies of nuclear workers have not demonstrated an association between ionizing radiation exposure and mesothelioma (Metz-Flamant et al. 2011).

- The Gibb study finds a proportionate mortality ratio (PMR) of 62.4 for mesothelioma, and as cumulative external radiation dose increases, PMR increases.
- The Gibb study suggests that cumulative external radiation at nuclear facilities is associated with an increased risk of mesothelioma.
- PMR definition: the proportion of observed deaths from a given cause in a study population divided by the proportion of deaths expected from this cause in a standard population.

$$PMR = P_{obs} / P_{exp}$$

- Mesothelioma accounts for 2.1% (7/329) of all USTUR deaths.
- Mesothelioma accounts for approximately 0.1% of all deaths in the U.S.
- Crude PMR estimate:

$$PMR = P_{obs} / P_{exp}$$
$$= 2.1\%/0.1\% = 21$$



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- Since mesothelioma is primarily an occupational disease and the USTUR registrants were overwhelmingly adult male Caucasians,

$$PMR = P_{obs} / P_{exp}$$

$$=2.1\%/0.1\% = 21$$

- The reported PMR of 62.4 for mesothelioma is strikingly large, and does not add up by quick examination.

Concern with the Small Sample Size in the Gibb Study

- Intuitively there are many causes of deaths in the U.S. population and much less causes (some causes with no observed deaths) of 329 deaths in the USTUR.
- Therefore, the cause-specific proportion of death in the Gibb study and the corresponding cause-specific proportion of death in the U.S. population are based on different numbers of causes of deaths.
- The cause-specific proportion in the Gibb study is inflated because it is based on fewer causes of deaths. As a result, the PMR is overestimated and therefore biased.

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informa healthcare

Bias in the proportionate mortality ratio analysis of small study populations: A case on analyses of radiation and mesothelioma

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Abstract

Purpose: To quantify bias in the proportionate mortality ratio (PMR) analysis of small study populations and develop a bias correction methodology.
Materials and methods: Bias in the PMR analysis of small study populations is quantified through algebraic derivation. A simulation procedure is developed to evaluate the relationship between bias and study population size. A recently published PMR analysis of radiation and mesothelioma among 329 deceased registrants in the United States Transuranium and Uranium Registries (USTUR) is used as an illustrated example.
Results: The proportionate mortality ratios are biased and overestimated in small population studies; the smaller the study population, the larger the overestimation. As such, the average overestimation of PMR for mesothelioma in the analyses of radiation and mesothelioma in USTUR is 7.2% (95% confidence interval = 5.1%, 9.7%); the PMR overestimation is 22.5% (95% confidence interval = 16.8%, 29.1%) when stratified by quartiles of radiation doses.
Conclusions: The degree of PMR small sample bias is mainly determined by the sample size ratio, which is defined as the ratio of the sample size to the number of disease categories in the reference population. Correction for the bias is recommended when the sample size ratio is less than 5. The quantification and correction algorithm of the PMR small sample bias developed in this research supplements the PMR methodology.

Keywords: Radiation health effect, mesothelioma, proportionate mortality ratio, small sample bias

Introduction

A recently published study, *Analysis of Radiation and Mesothelioma in the United States Transuranium and Uranium Registries* (Gibb et al. 2013) examines seven the United States (LTAS 2010, LTAS Manual 2010. Schubauer-Berigan et al. 2011), the study (referred as the Gibb study hereafter) finds a proportionate mortality ratio (PMR) of 62.40 for mesothelioma. The Gibb study suggests that cumulative external radiation is associated with an increased risk of mesothelioma.

The reported PMR of 62.4 for mesothelioma is strikingly large, and does not add up by quick examination. A PMR is defined as the proportion of observed deaths from a given cause in a study population divided by the proportion of deaths expected from this cause in a standard population. The proportion of observed deaths from mesothelioma among all USTUR deaths is 2.1% (7/329), while the proportion of deaths from mesothelioma among all U.S. deaths is approximately 0.1% (Price and Ware 2009) as cited by the Gibb study. Therefore, a crude estimate of the PMR for mesothelioma is only 21.0 (2.1% / 0.1%). Furthermore, mesothelioma is primarily an occupational disease and the USTUR registrants were overwhelmingly adult male Caucasians. Since mesothelioma accounts for over 0.16% of all deaths in the population of American male Caucasians over age 30 (LTAS 2010, 119 Underlying Cause U.S. Death Proportions 1960–2007), a better estimate of the PMR for mesothelioma is 13.1 (2.1% / 0.16%). Thus, the PMR for mesothelioma was largely overestimated in the Gibb study. As detailed in the letter to the editor (Zhou 2014), the Gibb study fails to consider the disease coding change for mesothelioma over the timeframe of the study.

The PMR analysis using a sample size of only 329 deaths in the Gibb study is also problematic. In practice, PMR are often computed for large study populations (in which more than thousands of cases are considered) over a broad number of disease categories. When PMR analysis is applied to a small study population over a large number of disease categories, the small number of deaths is likely distributed over

National Institute for Occupational Safety and Health/Life Table Analysis System (LTAS)

- The Gibb study applies LTAS, a software used to analyze a study population to determine if disease incidence or mortality among the study population is higher or lower than expected compared to a referent population.
- LTAS translates the causes of death from the World Health Organization International Classification of Diseases (ICD) codes to 119 disease categories and provides the baseline U.S. death proportions.

Mesothelioma ICD coding history

- Since 1999 when ICD-10 was implemented, mesothelioma has been coded as a separate underlying cause of death (C45.0-C45.9)
- Pre-1999, mesothelioma was coded as,

  Malignant neoplasm of pleura, unspecified (ICD-9:163.9)

  Malignant neoplasm of bronchus and lung, unspecified (ICD-9:162.9)

  Malignant neoplasm without specification of site (ICD-9:199-)

NIOSH-119 ICD Codes by Category, 1960-2007

Major ID	Minor ID	Minor Description	Revision 7	Revision 8	Revision 9	Revision 10
1		TUBERCULOSIS & HIV RELATED DISEASE (MAJOR)*				
1	1	Respiratory tuberculosis	001-008	010-012	010-012	A16#, A16.2-A16.5, A16.7-A16.9, B90#, B90.9, J65#, O98.0
1	2	Other tuberculosis	010-019	013-019	013-018	A17#, A17.0-A17.1, A17.8-A17.9, A18#, A18.0-A18.8, A19#, A19.0-A19.2, A19.8-A19.9, B90.0-B90.2, B90.8
1	3	HIV-related †	No codes	No codes	042-044	B20, B21#, B21.0-B21.3, B21.7-B21.9, B22#, B22.0-B22.2, B22.7, B23#, B23.0-B23.2, B23.8, B24#
2		MALIGNANT NEOPLASMS OF BUCCAL CAVITY & PHARYNX (MAJOR)				
2	4	MN of lip	140	140	140	C00#, C00.0-C00.6, C00.8-C00.9
2	5	MN of tongue	141	141	141	C01#, C02#, C02.0-C02.4, C02.8-C02.9
2	6	MN of other parts of buccal cavity	142-144	142-145	142-145	C03#, C03.0-C03.1, C03.9, C04#, C04.0-C04.1, C04.8-C04.9, C05#, C05.0-C05.2, C05.8-C05.9, C06#, C06.0-C06.2, C06.8-C06.9, C07#, C08#, C08.0-C08.1, C08.8-C08.9, C46.2
2	7	MN of pharynx	145-148	146-149	146-149	C09#, C09.0-C09.1, C09.8-C09.9, C10#, C10.0-C10.4, C10.8-C10.9, C11#, C11.0-C11.3, C11.8-C11.9, C12#, C13#, C13.0-C13.2, C13.8-C13.9, C14#, C14.0, C14.2, C14.8

9		MALIGNANT NEOPLASMS OF OTHER & UNSPECIFIED SITES (MAJOR)				
9	28	MN of bone	196	170	170	C40#, C40.0-C40.3, C40.8-C40.9, C41#, C41.0-C41.4, C41.8-C41.9
9	29	Melanoma	190	172#, 172.0-172.4, 172.6-172.9	172	C43
9	30	Other MN of skin	191	173#, 173.0-173.4, 173.6-173.9	173	C44, C46#, C46.0, C46.9
9	31	Mesothelioma ‡	No codes	No codes	No codes	C45#, C45.0-C45.2, C45.7, C45.9
9	32	MN of connective tissue	197	171	171	C46.1, C49#, C49.0-C49.6, C49.8-C49.9

NIOSH/LTAS has no mesothelioma death data pre-1999

Example: White males, age 70 to 74

Age	Calendar Period	Proportion
70-74	1960-1964	0
70-74	1965-1969	0
70-74	1970-1974	0
70-74	1975-1979	0
70-74	1980-1984	0
70-74	1985-1989	0
70-74	1990-1994	0
70-74	1995-1999	0.000544
70-74	2000-2004	0.002813
70-74	2005-2009	0.002926
70-74	2010+	0.002926

- LTAS:proportions for mesothelioma (minor 31) are all zeros pre-1999
- More than 80% of USTUR deaths occurred before 1999 including 6 of 7 USTUR mesothelioma cases

LTAS calculates PMR as a ratio of weighted sums of the proportion of deaths from a specific cause in a study population vs. the comparable weighted sum in the U.S. population deaths (stratified by age, race, sex, and calendar year)

$$PMR = \sum W_i * P_{obs,\, i} \,/\, \sum W_i * P_{exp,\, i}$$

Where,

$P_{obs,\, i}$ = the i^{th} stratum-specific proportion in the study population

$P_{exp,\, i}$ = the i^{th} stratum-specific proportion in the U.S. population

W_i = the i^{th} stratum-specific number of observed deaths in the study population.

Conclusions

- The USTUR death data are not compatible and therefore should have not been compared with the LTAS U.S. death data in the PMR analysis for mesothelioma because there is no specific code for it pre-1999.
- The analyses of the Gibb study were conducted incorrectly from the beginning, resulting in false findings and conclusions on mesothelioma and radiation.
- Caution should be exercised when using LTAS, or similar analytic software, for mortality studies where the rules for coding cause of death are different over the time frame of a study.

INCORRECT ANALYSES OF RADIATION AND MESOTHELIOMA

The recent article, "Analyses of Radiation and Mesothelioma in the US Transuranium and Uranium Registries," by Gibb et al.[1] examines seven mesothelioma deaths among a small population of 329 deceased registrants in the US Transuranium and Uranium Registries (USTUR). Using the National Institute for Occupational Safety and Health's Life Table Analysis System with the referent group being all deaths in the United States,[2,3] the study finds a proportionate mortality ratio (PMR) of 62.40 ($P < .05$) for mesothelioma, the highest PMR ever observed and more than an order of magnitude higher than any other published studies.[1]

Mesothelioma has been coded as a separate underlying cause of death (C45.0-C45.9) since 1999 when *International Classification of Diseases, 10th revision* (*ICD-10*)[4] was implemented. Before 1999, mesothelioma was coded as malignant neoplasm of pleura, unspecified (*ICD-9*:163.9); malignant neoplasm of bronchus and lung, unspecified (*ICD-9*:162.9); malignant neoplasm without specification of site (*ICD-9*:199); and so on. Life Table Analysis System has no death data in the mesothelioma disease category for the United States before 1999[2,5] and therefore does not support PMR analysis for mesothelioma deaths before 1999. More than 80% of USTUR deaths occurred before 1999 including six of seven USTUR mesothelioma cases.[6,7]

Life Table Analysis System calculates PMR as a ratio of weighted sums of the proportion of deaths from a specific cause in the exposed versus the comparable weighted sum in the unexposed (often the US population deaths). Adjustment for age, race, gender, and calendar time is accomplished by stratification and indirect standardization.[2,3] The formula to calculate the PMR is presented below.

$$(1)\quad PMR = \Sigma W_i * P_{i1} / \Sigma W_i * P_{i0}$$

where the variables are defined as follows:

- P_{i1} = the i^{th} stratum-specific proportion in the observed cohort (the exposed cohort)
- P_{i0} = the i^{th} stratum-specific proportion in the reference population (unexposed population)
- W_i = the i^{th} stratum-specific number of observed deaths in the exposed cohort.

Because all strata before 1999 have zero P_{i0} and only 20% (one fifth) of USTUR deaths contribute the weighted sum of the denominator in the formula, the PMR for mesothelioma by Gibb et al. is greatly overestimated. If one assumes that the age distributions of deceased registrants (who were overwhelmingly White and male) are similar before and after 1999, and the stratum-specific proportions for mesothelioma in the reference populations are the same before and after 1999, the PMR for mesothelioma is a five-fold overestimate.

The USTUR death data are not compatible and therefore should have not been compared with the Life Table Analysis System US death data in the PMR analysis for mesothelioma because there is no specific code for it before 1999. The analyses were conducted incorrectly from the beginning, resulting in an artificially high–reported PMR for mesothelioma. Caution should be exercised when using Life Table Analysis System or similar analytic software for mortality studies in which the rules for coding cause of death are different over the time frame of a study. ■

Joey Zhou, PhD, MPH

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GIBB ET AL. RESPOND

We thank Zhou for his interest in our study; however, his letter misquotes our article. He states that we reported that our proportionate mortality ratio (PMR) for mesothelioma was "the highest PMR ever observed and more than an order of magnitude higher than any other

Proportionate mortality ratio explained

- Proportionate mortality ratio (PMR):the proportion of observed deaths from a given cause in a study population divided by the proportion of deaths expected from this cause in a standard population.

$$PMR = P_{obs} / P_{exp}$$

A PMR greater than 1.0 (statistical significance is determined by assuming Poisson distribution) indicates that a particular cause accounts for a greater proportion of deaths in the population of interest compared to the standard population.