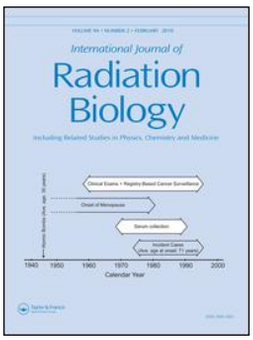

International Journal of Radiation Biology

ISSN: 0955-3002 (Print) 1362-3095 (Online) Journal homepage: https://www.tandfonline.com/loi/irab20

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To cite this article: Michael T. Mumma, Jennifer L. Sirko, John D. Boice Jr. & William J. Blot (2019): Mesothelioma mortality within two radiation monitored occupational cohorts, International Journal of Radiation Biology, DOI: 10.1080/09553002.2019.1642540

To link to this article: https://doi.org/10.1080/09553002.2019.1642540

Accepted author version posted online: 10 Jul 2019.
Published online: 22 Jul 2019.

INTERNATIONAL JOURNAL OF RADIATION BIOLOGY
https://doi.org/10.1080/09553002.2019.1642540

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ORIGINAL ARTICLE

Mesothelioma mortality within two radiation monitored occupational cohorts

Michael T. Mumma[a,b], Jennifer L. Sirko[a], John D. Boice, Jr.[c,d], and William J. Blot[a,d,e]

[a]International Epidemiology Institute, Rockville, MD, USA; [b]Vanderbilt Institute for Clinical and Translational Research, Vanderbilt University Medical Center, Nashville, TN, USA; [c]National Council on Radiation Protection and Measurements, Bethesda, MD, USA; [d]Vanderbilt Epidemiology Center, Division of Epidemiology, Department of Medicine, Vanderbilt-Ingram Cancer Center, Vanderbilt University Medical Center, Nashville, TN, USA; [e]Vanderbilt-Ingram Cancer Center, Vanderbilt University School of Medicine, Nashville, TN, USA

ABSTRACT

Purpose: The risk of mesothelioma, including cancers of the pleura and peritoneum, was examined within two large cohorts of workers monitored for exposure to ionizing radiation.

Methods and materials: Mortality was assessed among 253,632 workers routinely monitored for external radiation, including 30,724 industrial radiographers (IR) at shipyards, 142,583 workers at nuclear power plants (NPP), and 83,441 IR who had not worked at an NPP or shipyard. Follow-up was from 1969 through 2011. Standardized mortality ratios (SMRs) and 95% confidence intervals (CIs) were computed; observed numbers of deaths from mesothelioma (including cancers of the pleura and peritoneum) and asbestosis were compared with numbers expected based on age-, sex-, and calendar year-specific national mortality rates. Job history and quantitative asbestos exposure data were unavailable, but work at a shipyard was taken as a surrogate for the likelihood of exposure. Cox proportional hazards models were used to estimate hazard ratios (HRs) for mesothelioma in relation to estimated cumulative radiation exposure to the lung.

Results: The mean duration of follow-up was 25.3 years (max 42 years). The mean cumulative lung dose was 28.6 mGy (7.3% > 250 mGy). Nearly 20% of the workers had died by 2011. A total of 421 mesothelioma deaths were found (75% occurring after 1999) with increased SMRs among workers monitored in shipyards (SMR 9.97; 95% CI 8.50–11.63) and for NPP workers (SMR 5.55; 95% CI 4.88–6.29), but not for IR who had not worked in shipyards (SMR 1.15; 95% CI 0.53–2.19). Likewise, deaths from asbestosis ($n = 189$) were also increased for shipyard and NPP workers (SMR = 18.1 and 9.2, respectively), but not among workers who never worked at a shipyard or NPP (SMR = 0.70; $n = 1$). Radiation dose to the lung was not associated with a statistically meaningful dose-response trend for mesothelioma in the combined cohorts (HR at 100 mGy = 1.10; 95% CI 0.96–1.27; $p = .18$), nor was mesothelioma risk associated with radiation exposure among IR who had not worked in a shipyard and assumed minimally exposed to asbestos.

Conclusions: An elevated rate of death from mesothelioma was observed in two radiation-exposed occupational groups with potential for asbestos exposure. The increased risk of death from asbestosis, combined with little evidence of a rising trend in mesothelioma mortality with increasing radiation exposure, suggests that the mesothelioma (and asbestosis) excess in these workers was due to asbestos exposure in shipyards and power plants and not to occupational low-dose radiation.

ARTICLE HISTORY
Received 28 January 2019
Revised 17 May 2019
Accepted 29 May 2019

KEYWORDS
Mesothelioma; asbestos; cohort; epidemiology

Introduction

Mesothelioma is a rare and highly lethal cancer originating in the mesothelial cells that line the pleura, peritoneal, heart, and other cavities. Most cases (81%) of mesothelioma arise in the pleural lining of the lung and chest cavity, while 9% arise in the peritoneal lining of the abdominal cavity and a smaller percentage in the pericardium (ACS 2017). Asbestos exposure in the workplace is the major cause of mesothelioma, accounting for up to 80% of cases (Crew et al. 2005; Boffetta and Stayner 2006; International Agency for Research on Cancer (IARC) 2012; Carbone et al. 2012; Carbone and Yang 2017). Asbestos was widely used in heat-resistant materials and insulation from the 1940s through the 1970s in the United States, primarily in the construction, textile, auto, aircraft and shipbuilding industries, and in electric power plants including nuclear power plants (NPP) (Selikoff and Seidman 1991). Incidence rates of mesothelioma in the United States increased until the mid-1990s, remained level for several years, and began to decline in 2005 in men while remaining stable in women (ACS 2017). These trends and sex-specific differences reflect in large part the reduction in workplace exposure to asbestos in jobs that were traditionally male-oriented professions.

Suspected non-asbestos risk factors for malignant mesothelioma include ionizing radiation (high-dose radiotherapy and Thorotrast (i.e. radioactive thorium dioxide that emits alpha particles)), viral infections (e.g. SV40), genetic predisposition (e.g. germline mutations of the BRCA1-associated protein 1), chronic pleural inflammation, and erionite

CONTACT Michael T. Mumma mike.mumma@iei.us International Epidemiology Institute, 1455 Research Blvd, Suite 550, Rockville, MD 20850, USA

(a naturally occurring fibrous material similar to asbestos). These factors may act alone or as co-factors together with asbestos or with 'naturally occurring asbestos-like material' such as erionite, to cause mesothelioma (Crew et al. 2005; Carbone et al. 2012, 2016; Attanoos et al. 2018). Animal experiments have shown the co-carcinogenic properties of high-dose radiation with asbestos (Warren et al. 1981). The polyomavirus simian virus 40 (SV40) has been reported to induce mesothelioma and to be a co-factor for asbestos carcinogenesis in experimental animals; however, the evidence for a causal relationship between SV40 and mesothelioma in humans is lacking (Carbone et al. 2012). Chronic inflammation appears to promote the occurrence of asbestos-related mesothelioma (Carbone and Yang 2017). Mesothelioma may thus be a multifactorial disease and not all non-asbestos causes may have been identified nor have all co-factor mechanisms.

Low-dose ionization radiation has been suggested as a possible risk factor for mesothelioma (Goodman et al. 2009), but the evidence is limited (Metz-Flammant et al. 2011). Practically all worker studies of low-dose radiation are unable to rule out asbestos used in thermal insulation at the worksite or used in shipyards as a contributing causal factor. Studies with information on potential asbestos exposure (e.g. based on job category and work environment, shipyard work, and clinical examinations) discount a radiation association (Schubauer-Berigan et al. 2005, 2015; Richardson et al. 2007; Till et al. 2018). It has been suggested that exposure to asbestos may have been positively correlated with radiation dose within a pooled analysis of five U.S. cohorts (Schubauer-Berigan et al. 2005), suggesting that any radiation association with mesothelioma may be confounded by unknown or uncontrolled exposure to asbestos. That is, jobs linked with asbestos work also have a high potential for radiation exposure. Furthermore, there is no evidence that cancer of the pleura or peritoneum is increased among Japanese atomic bomb survivors (Grant et al. 2017).

There have been few if any occupational studies of radiation-exposed groups with large enough size, duration of follow-up, and assessment of asbestos to evaluate convincingly any association between radiation exposure and mesothelioma (Metz-Flammant et al. 2011). Accordingly, we evaluated the risk of mesothelioma, including cancer of the pleura and peritoneum, by combining two large occupational cohorts monitored for external radiation, that is, NPP workers and industrial radiographers (IR). We sought to evaluate (1) the risk of mesothelioma overall; (2) the risk of mesothelioma among the subgroups of these workers who had been employed in shipyards and/or power plants, where there is high potential for asbestos exposure (Selikoff and Hammond 1978; Selikoff et al. 1979); (3) the risk of asbestosis, due entirely to asbestos exposure, to help assess confounding between asbestos and radiation exposures; and (4) any association between mesothelioma and cumulative low-dose radiation exposure overall and specifically among IRs not known to have worked at a shipyard.

Methods

Population identification. The study population was formed by combining two occupational cohorts: NPP workers ($n = 135{,}193$) and IRs ($n = 123{,}510$) within the Million Person Study of Low-Dose Health Effects (MPS) (NCRP 2018; Boice et al. 2019). Both cohorts were drawn from either the U.S. Nuclear Regulatory Commission (NRC) Radiation Exposure Information and Reporting System (REIRS) database or the electronic records of Landauer, Inc. (Hagemeyer et al. 2018). The NPP workers were identified by selecting workers monitored for radiation exposure between 1969 and 31 December 1984 at an NPP. Because of the very large numbers of NPP workers with a career badge dose of less than 10 mSv, a 10% random sample was selected for cost efficiency with minimal loss of statistical power. All NPP workers with career badge dose greater than 10 mSv were included in the cohort. Individuals were considered eligible for study if sufficient personal identifiers (either a Social Security Number or name and date of birth) were available to allow for vital status follow-up and had at least 30 days of radiation monitoring as an IR or at an NPP facility. There were 5071 workers in both the IR and NPP cohorts, resulting in a combined study population of 253,632.

Mortality follow-up. Mortality status as of 31 December 2011 as well as cause of death were determined from various mortality databases, including the National Death Index, the Social Security Administration (Death Master File and Service for Epidemiologic Researchers), and death certificates provided by state departments of health (Mumma et al. 2018). Underlying cause of death was coded according to the International Classification of Diseases (ICD) revision in effect at the time of death. An ICD code specific to malignant mesothelioma (C45) did not appear until 1999 when the 10th revision of the ICD was issued (ICD10). For earlier years we combined deaths from malignant cancers of the pleura (ICD8 163.0; ICD9 163) and peritoneum (ICD8 158.9; ICD9 158.8–158.9). Asbestosis mortality was indicated by the following codes: ICD8 515.2, ICD9 501, and ICD10 J61.

Radiation dose estimation. Estimation of occupational career radiation dose to the lung followed the procedures outlined by Boice et al. (2006), and described more fully in NCRP (2018) and by Dauer et al. (2018). Briefly, radiation doses from all places of employment were sought by linking the study population to the U.S. Department of Energy Radiation Exposure Monitoring Systems dosimetry database, historical DOE study databases as well as U.S. military service dosimetry databases. These doses, in addition to the doses from the REIRS and Landauer databases, were combined to create annual dose estimates of all occupational external radiation. There were minimal intakes of radionuclides in these occupations studied and thus no radiation from internal emitters was included in the annual dose estimates. Cumulative doses were obtained by summing the annual doses across all years monitored for radiation exposure. The procedures outlined in NCRP (2018) were then used to convert the measured personal dose equivalents

Table 1. Characteristics of the combined industrial radiographer (IR) and nuclear power plant (NPP) worker study populations ($n = 253,632$).

Characteristic	*n*	%
Total	253,632	100.0
Sex		
Female	17,312	6.8
Male	236,320	93.2
Occupational category		
Only monitored for radiation in shipyard	27,608	10.9
Only monitored for radiation at NPP	139,467	55.0
Monitored at both at shipyard and NPP	3116	1.2
Never monitored at shipyard or NPP (IR workers only)	83,441	32.9
Year of Birth		
1904–1929	26,280	10.4
1930–1939	25,629	10.1
1940–1949	59,038	23.3
1950–1959	78,507	31.0
1960–1993	64,178	25.3
Mean YOB	*1951*	
Start of follow-up		
1969–1979	103,760	40.9
1980–1989	88,251	34.8
1990–2011	61,621	24.3
Mean year at start of follow-up	*1983*	
Mean age at start of follow-up	*31.8*	
Years of follow-up		
0–9	28,736	11.3
10–19	42,058	16.6
20–29	73,798	29.1
30–39	93,168	36.7
40–42	15,872	6.3
Mean duration of follow-up (years)	*25.3*	
Career badge dose		
Less than 1 mSv	73,418	28.9
1–<10 mSv	41,635	16.4
10–<50 mSv	86,355	34.0
50–<100 mSv	27,542	10.9
100–<250 mSv	20,126	7.9
250 mSv or greater	4556	1.8
Mean career badge dose (mSv)	*35.4*	
Mean number of years monitored	*9.80*	
Vital status as of 31 December 2011		
Alive	204,206	80.5
Dead	49,426	19.5
Mean age at end of follow-up	*57.7*	

[Hp (10)] into individual lung doses using the appropriate dose conversion factors for the incident gamma ray energies. The primary source of exposure at NPPs was to radioactive cobalt (^{60}Co and ^{58}Co) and to some extent radioactive cesium (^{137}Cs). The primary source of exposure to IRs was to radioactive iridium (^{192}Ir) and to some extent radioactive cobalt (^{60}Co).

Asbestos exposure. Personal or work area measurements on asbestos exposures were not available. To investigate the potential of occupational asbestos exposure, each worker's exposure history within the REIRS and Landauer dosimetry databases was used to determine if they were ever monitored for radiation at either a shipyard or a U.S. naval facility (for IRs) or at an NPP, occupational settings with increased likelihood of asbestos exposure (Boffetta and Stayner 2006; IARC 2012). Keyword searches of the employer name (within REIRS) and account name (within Landauer) were used to identify shipyards, marinas, dry docks, and naval facilities. NRC license codes and Landauer account names were used to identify nuclear power facilities. Employment at a shipyard carried a strong potential for asbestos exposure (Selikoff and Hammond 1978; Selikoff et al. 1979; Tagnon et al. 1980; Matanoski 1991; Matanoski et al. 2008). Within nuclear and other power plants, asbestos was used for insulation of pipes, boilers, generators, and electric wirings (Boffetta et al. 1991). Individual workers within NPPs, however, could not be identified as to their potential for asbestos exposure. To address confounding by potential asbestos exposure, we created three non-overlapping groups of workers among whom risk of mesothelioma and asbestosis were assessed: (1) those ever monitored at shipyards (predominantly IR); (2) those who worked only at NPP but not at a shipyard; and (3) IR who had not been monitored at a shipyard or NPP.

Statistical analysis. Standardized mortality ratios (SMRs) were computed comparing the numbers of deaths observed from mesothelioma, asbestosis, and other causes among the workers with the numbers expected based on mortality rates in the general U.S. population. U.S. mortality rates by age, calendar year, and sex were applied to the corresponding person-years of follow-up to obtain the expected number of deaths (overall and for other conditions, including mesothelioma and asbestosis). The end of follow-up was taken as the date of death, the 95th birthday, or 31 December 2011, whichever came first. Observed and expected numbers of deaths were examined by sex, potential occupation exposure to asbestos (as judged by ever being monitored at a shipyard and/or a NPP), year of first radiation monitoring, time since first monitoring, and duration of follow-up. Confidence intervals (CI) for the SMRs were computed assuming that the observed number of deaths followed a Poisson distribution (Bailar and Ederer 1964). A 95% CI that excluded 1.0 was considered statistically significant at the two-sided significance level of .05.

Within-cohort (internal) analyses were conducted using Cox proportional hazards models to compute hazard ratios (HRs) and corresponding 95% CI. Age at follow-up was used as the underlying timescale for the analysis. Covariates in the models included sex, year of birth, potential occupational exposure to asbestos (ever monitored at a shipyard), year of first radiation monitoring, and socioeconomic status (SES), with the exposure variable of interest being cumulative radiation exposure to the lung. Direct measures of individual-level SES were not available; thus, to derive a surrogate measure for missing smoking and individual-level SES data, we obtained and geocoded residential address histories for all workers, linked them to area-level SES measures from the United States Census, and used the mean educational attainment within the Census Block Group as a measure of SES (Cohen et al. 2018). For the internal analyses, radiation exposure was lagged 10 years to be consistent with observations from reports of radiation therapy and secondary mesothelioma, where mesotheliomas occurred an average of 18 years (range 5–>40 years) after high-dose radiation treatment (Cavazza et al. 1996; Crew et al. 2005; Hodgson et al. 2007; Goodman et al. 2009; Carbone et al. 2012; Farioli et al. 2016) and with the estimated minimum latency period between initial asbestos exposure and mesothelioma onset (Boffetta and Stayner 2006). Furthermore, radiation studies that include workers potentially exposed to asbestos have reported latencies up to 40 years (Schubauer-

Table 2. Standardized mortality ratios (SMR) and 95% confidence intervals (CIs) for all causes of death and deaths due to mesothelioma and asbestosis among the combined industrial radiographer (IR) and nuclear power plant (NPP) worker cohorts ($n = 253,632$), 1969–2011.

	All causes of death			Mesothelioma[a]			Asbestosis		
	N	SMR	95% C.I.	*N*	SMR	95% C.I.	*N*	SMR	95% CI
Total	49,275	0.88*	0.88–0.89	421	6.10*	5.53–6.71	189	11.4*	9.85–13.2
Sex									
Male	48,338	0.88*	0.87–0.89	421	6.15*	5.58–6.77	87	9.15*	7.34–11.3
Female	937	0.97	0.91–1.04	0	0.00	0.00–6.53	103	14.0*	11.4–16.9
Occupational category									
Ever monitored at shipyard	13,474	0.86*	0.85–0.88	163	9.97*	8.50–11.6	100	18.1*	14.8–22.1
Only monitored at NPP	29,535	0.89*	0.88–0.90	249	5.55*	4.88–6.29	88	9.16*	7.35–11.3
Never at shipyard or NPP	6266	0.91*	0.89–0.93	9	1.15	0.53–2.19	1	0.70	0.01–3.89
Socioeconomic status									
Low	17,040	1.04*	1.03–1.06	108	5.48*	4.50–6.62	84	16.5*	13.2–20.4
Medium	25,178	0.91*	0.90–0.92	236	6.90*	6.05–7.84	90	11.0*	8.84–13.5
High	7057	0.60*	0.58–0.61	77	5.10*	4.02–6.37	15	4.60*	2.58–7.60
Year first monitored									
1940–1959	24,351	0.88*	0.87–0.89	276	8.37*	7.42–9.42	135	14.0*	11.7–16.5
1960–1990	23,185	0.89*	0.88–0.90	141	4.18*	3.52–4.93	54	8.19*	6.15–10.7
1991–2011	1739	0.81*	0.47–4.47	4	1.75	0.47–4.48	0	0	0.00–13.5
Time since first monitor									
Less than 10 years	5,175	0.67*	0.65–0.69	17	4.88*	2.84–7.81	4	6.79*	1.83–17.4
10–19 years	10,614	0.85*	0.84–0.87	34	3.66*	2.53–5.11	21	8.97*	5.55–13.7
20–29 years	16,779	0.95*	0.93–0.96	129	4.86*	4.06–5.78	65	11.7*	9.00–14.9
30 years or more	16,707	0.94*	0.92–0.95	241	8.12*	7.13–9.21	99	12.3*	10.0–15.0
Time period of follow-up									
1969–1979	1861	0.56*	0.53–0.59	4	2.73	0.73–6.99	4	20.9*	5.63–53.5
1980–1999	20,744	0.85*	0.84–0.86	102	7.47*	6.09–9.07	89	16.2*	13.0–20.0
2000–2011	26,670	0.95*	0.94–0.96	315	5.85*	5.22–6.53	96	8.84*	7.16–10.8

*$p < .05$.
[a]Pleura and peritoneum (ICD8: 158.9,163.0; ICD9: 158.8-158.9,) and mesothelioma (ICD10 C45).

Berigan et al. 2015; Yiin et al. 2017). Analyses showed an SMR of 4.9 ($n = 17$) within the first 10 years of first radiation monitoring (suggestive of asbestos exposure prior to radiation monitoring); therefore, follow-up within the first 10 years of radiation exposure were excluded in the internal Cox analyses. For consistency and comparisons with other cohorts, we also computed HRs adjusting for duration of monitoring at an IR or NPP facility (<1, 1–4, 5–9, 10–19, 20–29, ≥30 years). Special attention was paid to IR who had not worked in shipyards, a group with low likelihood of asbestos exposure, but small numbers of mesotheliomas ($n = 9$) among this group precluded informative Cox analyses.

Analyses were conducted with SAS/STAT software (version 9.4 of the SAS System for Windows, SAS Institute Inc., Cary, NC). Human subjects research approval was received from Vanderbilt University Institutional Review Board.

Results

Demographic and occupational characteristics of the combined study cohorts are shown in Table 1. Among 253,632 workers, 12% had ever worked in shipyards or naval facilities (90% as IR), 55% were NPP workers only, and 33% were IR who had not been monitored at shipyards or NPP. Most workers (93%) were male, the mean year of birth was 1951, and the mean duration of follow-up was 25 years. Over 49,000 workers, or 20%, had died as of 31 December 2011. The mean career badge dose was 35 mSv. The mean career lung dose was 28.6 mGy. During nearly 6,500,000 person-years of follow-up there were 421 deaths from mesothelioma and 189 deaths from asbestosis, all among men.

Total mortality was significantly below expectation in the combined study population (SMR 0.88), consistent with a healthy worker effect (Table 2). The numbers of total cancers (SMR 1.02; CI 1.00–1.03, $n = 15,105$) and smoking-related cancers (SMR 1.03; CI 1.01–1.05, $n = 7826$) were close to those expected (not shown). However, there were large and significant excesses of mesothelioma among shipyard workers (SMR 9.97; $n = 163$) and NPP workers (SMR 5.55; $n = 249$). The 83,441 IR workers who never worked at a shipyard did not show a significant increased rate of mesothelioma (SMR = 1.15; 95% CI 0.53–2.19; $n = 9$). Parallel findings were seen for deaths from asbestosis, with SMRs reaching 18.14 (95% CI 14.8–22.1) and 9.16 (95% CI 7.50–11.4) for shipyard and NPP workers, respectively, but 0.70 for IR workers not employed at shipyards (95% CI 0.01–3.89). Increasing SMRs from high to low SES were seen for total mortality and asbestosis but not for mesothelioma, possibly due to higher smoking prevalence among those in lower socioeconomic groups. SMRs were higher for mesothelioma prior to 2000, but the increased rates persisted beyond 2000 (SMR = 5.85) with 315 deaths (75% of all mesothelioma deaths) observed during the latest follow-up time period. SMRs also were highest when follow-up time exceeded 30 or more years from first radiation monitoring.

Table 3 shows the HRs and 95% CI derived from the Cox models for mesothelioma mortality in the combined cohorts by cumulative lung dose categories (including a lag of 10 years for all radiation doses as well as exclusion of the first 10 years of follow-up for all individuals) adjusted for sex, year of first monitoring, year of birth, ever monitored at a shipyard and SES. Because workers with <1 mGy cumulative dose included disproportionate numbers of office and other workers with characteristics different from the

Table 3. Hazard ratios (HR) and 95% confidence intervals (CI) derived from Cox proportional hazards models for mesothelioma mortality, follow-up starting 10 years after first radiation monitoring and dose lagged 10 years for the combined IR and NPP cohorts ($n = 157{,}855$ workers), 1969–2011.

			Not adjusted for duration of radiation monitoring		Adjusted for duration of radiation monitoring	
Lung dose (mGy)	Number of workers	Number of cases	HR[a]	95% CI	HR[a]	95% CI
1–<10	40,739	81	1.00	REF	1.00	REF
10–<50	78,819	172	1.22	0.92–1.60	1.21	0.92–1.59
50–<100	22,123	37	0.98	0.66–1.46	0.96	0.64–1.44
≥100	1	40	1.36	0.92–2.00	1.31	0.89–1.95
	p for trend[b]		*.18*		*.24*	
	Hazard ratio (95% CI) at 100 mGy		*1.10 (0.96–1.27)*		*1.09 (0.95–1.26)*	

[a]Adjusted for sex, year of first monitoring, year of birth, SES, and ever monitored at a shipyard.
[b]*p*-Value for test for linear trend in the HRs computed using a measure of continuous dose.

other monitored workers, the referent category was taken as 1 – <10 mGy for internal analyses. None of the HRs for dose categories above the 1–9 mGy reference category were significantly elevated. From a model treating dose as a continuous (linear) variable, the estimated HR at 100 mGy was 1.10 (95% CI 0.96–1.27) and there was no significant increase in the HR with increasing dose ($p = .18$). When adjusted for duration of monitoring, the HRs were essentially the same, again with no evidence of a linear trend.

Because of apparent confounding from asbestos exposure, that is, jobs with high potential for asbestos exposure also having high potential for radiation exposure, we carried out an internal analysis for radiation dose effects among the 83,441 IR workers who were not known to have been employed in shipyards. These workers also had lower radiation exposure (mean and 95th percentile lung doses of 10.2 and 53.7 mGy, respectively, compared with 23.3 and 116.5 mGy for IR workers who had been employed in shipyards). Due to small numbers of mesothelioma deaths (only nine) among non-shipyard working IR, hazard ratios by dose categories are not shown. A test for linear trend over increasing cumulative lung dose using a continuous measure of dose was not significant ($p = .56$).

Discussion

Several epidemiologic studies have reported on risks of mesothelioma among radiation-exposed workers. We briefly review the existing literature before discussing results and implications from this study.

Radiotherapy and Thorotrast patients

Several follow-up studies of cancer patients treated with high-dose ionizing radiation have reported increased rates of mesothelioma, suggesting that radiotherapy is a probable, though rare, cause of mesothelioma (Crew et al. 2005; Goodman et al. 2009; Carbone et al. 2012; Farioli et al. 2016). In addition, Thorotrast (colloidal $^{232}ThO_2$), a diagnostic radiographic contrast medium injected into the body for cerebral angiography, has been linked to small excesses of cancers of the peritoneum and pleura in epidemiologic studies in Denmark, Sweden, Portugal, Germany, and the US (Andersson et al. 1995; Travis et al. 2003; Becker et al. 2008). The colloidal Thorotrast would aggregate into 'hot spots', remain in the body for life irradiating mesothelial cells to high doses of alpha particles and cause chronic inflammation (NRC 1988). The non-radiation properties of Thorotrast, a heavy metal, could not be completely ruled out as contributing to the mesothelioma increase (Andersson et al. 1995).

Atomic bomb survivors

Among the nearly 100,000 atomic bomb survivor cohort, no significant increases in cancer of the pleura (one case in men) or peritoneum (three cases in women) were reported (Grant et al. 2017), nor have there been reports of increased mesothelioma. A case report of mesothelioma among a Nagasaki survivor concluded that work at a shipyard and inhalation of asbestos fibers was the likely cause (Mizuki et al. 1997).

Occupational groups with chronic low-dose radiation exposure

Metz-Flammant et al. (2011) reviewed 17 studies of nuclear workers and noted that, while 15 showed elevations of malignant pleural mesothelioma, of the 12 studies conducting radiation dose response analyses, only 1 found a significant association with mesothelioma. The reviewers concluded that asbestos was an important confounder in most studies, and that ionizing radiation was not associated with mesothelioma mortality. More recent large-scale occupational studies of workers exposed to chronic low dose radiation also tend not to find significant associations between radiation and mesothelioma mortality (Habib et al. 2006; Gillies and Haylock 2014; Schubauer-Berigan et al. 2015; Haylock et al. 2018; Richardson et al. 2018). Asbestos exposures were present in all cohorts, with mesothelioma elevations interpreted to be most likely due to asbestos rather than radiation exposure (Muirhead et al. 2009).

There were four notable studies of radiation-exposed workers with significant elevations in mesothelioma deaths that were able to evaluate the potential for asbestos exposures based on job categories or work in areas with known asbestos exposure. These were studies of workers at the Savannah River Site (SRS) (Makie et al. 2005; Richardson et al. 2007), the Idaho National Laboratory (INL) (Schubauer-Berigan et al. 2005), the Portsmouth Naval Shipyard (PNS) (Rinsky et al. 1988; Silver et al. 2004; Zaebst et al. 2009; Schubauer-Berigan et al. 2015), and military

participants at above-ground nuclear weapons tests (Till et al. 2018).

Savannah River Site (SRS)

Among 15,264 male workers at the SRS, a significant SMR of 4.7 was found for cancer of the pleura which was notable among hourly-paid workers (Richardson et al. 2007). Industrial hygiene reports from the 1970s found increased asbestos exposure for some activities based on area-wide sampling, and medical evaluations, including chest radiographs among 1368 SRS workers as part of the SRS Former Production Worker Health Project (Makie et al. 2005). Pleural abnormalities were higher in former SRS workers than in the general population, and were associated with jobs with likely occupational exposure to asbestos, for example, 'Electrical construction work (including asbestos workers engaged in insulation)'.

Idaho National Laboratory (INL)

Among 63,561 workers at INL, significantly increased SMRs were found for asbestosis (SMR 3.67, $n = 10$) and respiratory cancers likely to be mesothelioma (SMR 1.74, $n = 22$) (Schubauer-Berigan et al. 2005). The association with asbestosis indicates that high levels of asbestos were present, since asbestos is the only cause of asbestosis (Silver et al. 2004). Significant excess asbestos-related deaths occurred among 36,534 workers monitored for radiation exposure: asbestosis (SMR 3.21, $n = 6$) and likely mesothelioma (SMR 2.59, $n = 15$), but there was no association with radiation dose. Industrial hygiene data were collected at INL and 2741 workers with high likelihood of asbestos exposure were identified based on job titles such as asbestos mechanic, asbestos foreman, engineer asbestos, asbestos worker, insulation worker, boiler maker, and pipefitter. Standardized rate ratios for asbestos workers were notable and significantly high for asbestosis (SRR 25.6; 95% CI 6.25, 105) and likely mesothelioma (SRR 4.28; 95% CI 1.19, 15.5). The cases were restricted to workers with jobs related to maintenance and construction activities, and were highest in the group of jobs with likely asbestos exposure.

Portsmouth Naval Shipyard (PNS)

Among 37,853 workers at PNS, significantly high SMRs for asbestosis (SMR 5.71, $n = 12$) again indicated that high levels of asbestos were present. An expert panel also was able to estimate the potential for asbestos exposure for all workers on the basis of shop, job title, and time-period available from each worker's employment history (Zaebst et al. 2009). The significant elevations in asbestosis mortality occurred among the 13,468 workers monitored for radiation, whereas asbestosis occurred below expectation among the 24,385 non-monitored workers (SMR 0.79). Mesothelioma and pleural cancers combined were significantly elevated in a pooled analysis of five U.S. nuclear facilities (SMR 2.80; 95% CI 2.27, 3.42, $n = 96$) with most of the excess coming from the PNS cohort (Schubauer-Berigan et al. 2015). A radiation dose-response analysis for mesothelioma and pleural cancer deaths combined, revealed a positive but not statistically significant trend. The significantly high SMR for asbestosis among monitored workers and the deficit of asbestosis deaths among non-monitored workers indicated a strong correlation between radiation work and asbestos work. That is, radiation workers were more heavily exposed to asbestos than were other workers, and that asbestos was the most likely cause of mesothelioma and pleural cancers.

For completion, increased rates of mesothelioma also were observed in combined cohorts of uranium enrichment works, including Oak Ridge Gaseous Diffusion Plant (also known as K-25) in Oak Ridge, Tennessee; the Portsmouth Gaseous Diffusion Plant in Piketon, Ohio; and the Paducah Gaseous Diffusion Plant Paducah, Kentucky (Yiin et al. 2017). A non-significant association between radiation and mesothelioma was reported. Unfortunately, asbestos had not been identified *a priori* as an important workplace exposure and was not assessed.

Atomic veterans

A study of 114,270 military participants at above-ground nuclear weapons tests was able to explain a notably high increase in deaths due to mesothelioma by exposure to asbestos and not to low-dose radiation (Till et al. 2018). Mesothelioma mortality was significantly increased in the entire study population (SMR 1.56; 95% CI 1.32–1.82; $n = 153$). The increase was seen, however, only among 70,309 navy personnel (SMR 2.15; 95% CI 1.80–2.56; $n = 130$), and not among the other services: army (SMR 0.45), air force (SMR 0.85), or marine corps (SMR 0.75). Asbestos was used in naval vessels for insulation in the boiler room, engine room, and other areas. The 12,880 sailors with job categories having the highest potential for asbestos exposure, that is, machinist's mates, boiler technicians, water tenders, pipe fitters, and firemen, had the highest mortality increase (SMR 6.47; 95% CI 5.03–8.19; $n = 69$). The 27,176 sailors with no potential for asbestos exposure did not have a significant increase in mesothelioma mortality (SMR 1.28; 95% CI 0.87–1.83; $n = 30$). Similarly, 65 deaths from asbestosis occurred (SMR 2.13; 95% CI 1.64–2.71), and the increased mortality was concentrated entirely among navy personnel (SMR 3.22; 95% CI 2.45–4.14; $n = 60$). Furthermore, Navy enlisted sailors with job categories with the highest potential for asbestos exposure had very high rates of asbestosis (SMR 10.0; 95% CI 6.90–14.2; $n = 32$). Asbestos exposure among naval personnel serving on ships during nuclear weapon testing explained the large excess of mesothelioma and asbestosis deaths seen among atomic veterans in this low-dose radiation cohort.

Current study

This study confirmed and quantified high mortality rates of mesothelioma and asbestosis among workers at NPP and in

shipyards. The excess rate among IR workers appeared only for those who had worked in shipyards, a setting with known asbestos exposure in ship building and repair (Tagnon et al. 1980; IARC 2012). No increase in mesothelioma or asbestosis was seen among radiation-exposed IR who had not been employed in shipyards or NPP, thus providing evidence that mesothelioma is not caused by low-level radiation when confounding by asbestos can be ruled out or at least minimized. Similarly, the sixfold increase in mesothelioma among NPP workers can be attributable to an increased probability of on-site exposure to asbestos used as insulation materials in the plants. A notable observation is that mesothelioma mortality remained high after 30 years of follow-up and was increased sixfold during 2000–2011, indicating both the very long latency of mesothelioma and suggesting the need for continued monitoring for these occupational groups. The very high SMRs for asbestosis among the NPP workers and the shipyard workers and the absence of a risk among IR workers who did not work at a shipyard confirms these observations as well as the presence of asbestos in NPP and shipyards.

The ability to evaluate the risk of mesothelioma in relation to ionizing radiation in these occupational settings was aided by the availability of annual and individual radiation monitoring data for the IR and NPP cohorts. Radiation doses to the lung were broad and cumulative doses were over 100 mGy for nearly 3000 workers. Radiation dose to the lung was not associated with a statistically significant dose-response trend for mesothelioma (HR at 100 mGy = 1.10; 95% CI 0.96–1.27; $p = .18$).

The difficulty in estimating an independent effect of ionizing radiation on malignant mesothelioma in any occupational setting with known asbestos exposure cannot be overstated. While some have questioned the potential for confounding by asbestos (Matanoski et al. 2008; Goodman et al. 2009), it has been demonstrated in several cohorts that job titles with a higher likelihood of ionizing radiation exposure also had a higher likelihood of asbestos exposure (Matanoski et al. 2008; Schubauer-Berigan et al. 2005, 2015). The pooled study of U.S. nuclear workers (Schubauer-Berigan et al. 2015), which included the PNS study (Rinsky et al. 1988; Silver et al. 2004; Yiin et al. 2007), suggested that exposure to asbestos was positively correlated with radiation dose within the pooled cohort and that asbestos was a confounder at PNS for lung cancer. Furthermore, the strong correlation between radiation and deaths due to asbestosis (which is only caused by asbestos) seen at INL signifies a strong link between radiation work and asbestos work (Schubauer-Berigan et al. 2015). Our results are consistent with and strengthen these prior findings indicating the key role of asbestos in inducing mesothelioma in NPP and IR workers. Other large occupational cohorts within the MPS such as the 170,000 medical radiation workers (where exposure to asbestos in the workplace is unlikely) should help further elucidate the association between long-term radiation exposure and mesothelioma (Yoder et al. 2018).

Strengths and limitations

The strengths of this study include the large size of the radiation cohorts, the comprehensive follow-up covering 70 years, the comprehensive estimation of cumulative radiation dose to lung, and the large number of mesothelioma and asbestos deaths observed. The ability to identify over 83,000 workers who had only minimal likelihood of asbestos exposure provided an opportunity to evaluate a low-dose radiation association with mesothelioma with minimal confounding by asbestos. Radiation doses were recorded for each worker according to reporting regulations and reasonably accurate radiation doses to the lung were reconstructed. Internal cohort analyses compared workers to workers over radiation dose categories and thus minimized a 'healthy worker effect' which can occur when comparisons are made with the general population.

Limitations included the inability to estimate the potential for asbestos exposure for individual workers, the assumption that cancers of the pleura and peritoneum are mainly mesotheliomas, the limited number of female workers, the absence of data on smoking, the absence of specific job categories which involved asbestos exposure and asbestos exposure measurements. Prior to the use of ICD-10 codes in mortality data, an ICD code specific to malignant mesothelioma did not exist. ICD codes for malignant cancers of the pleura and peritoneum likely underestimate the true number of deaths from mesothelioma (Davis et al. 1992).

Confounding by asbestos for radiation associations was demonstrable by the correlation between radiation and asbestosis, which is only caused by asbestos. IR workers at shipyards who had a high potential for asbestos exposure could be identified and separated, allowing analyses of IR workers with likely and unlikely exposures to asbestos. However, we did not have access to job titles or any other data to quantify asbestos exposure among individual workers. Residual confounding by asbestos for radiation dose-response analyses could not be discounted.

Conclusion

Asbestos. Our study of 253,632 workers monitored for occupational radiation exposure as IRs or NPP workers confirms and quantifies the high rates of mesothelioma mortality (SMR = 6.1; $n = 421$) and asbestosis mortality (SMR = 11.4; $n = 189$) in these professions. The high mortality rates have persisted for over 30 years and increases remained near sixfold through 2011, reflecting the long latencies for these asbestos-related conditions. While the absolute number of asbestos-related deaths were small in comparison with the large number of workers, an awareness and need for monitoring is clearly indicated.

Radiation. Therapeutic doses of radiation and injection with Thorotrast, an alpha-particle emitting colloidal solution of thorium dioxide used as a diagnostic radiographic contrast medium, are likely causes of mesothelioma, including cancers of the pleura and peritoneum. However, cancer of the pleura is not increased among atomic bomb survivors, and large-scale studies of occupational groups exposed to

low radiation levels are either negative or the increases are attributed to asbestos exposure. Associations between radiation and asbestosis (which is only caused by asbestos) indicate that jobs with relatively high radiation exposures are highly correlated with jobs with relatively high asbestos exposure. Over 83,000 IRs not employed at shipyards did not have an excess of mesothelioma or asbestosis, and there was no clear evidence of a radiation dose-response relationship in the overall cohort. Low-dose radiation received in these occupational setting was not found to be associated with mesothelioma.

Disclosure statement

M. T. Mumma and W. J. Blot have previously consulted with a former manufacturer of products containing asbestos on matters related to litigation. Other authors report no conflict of interest. The authors alone are responsible for the content and writing of the paper.

Funding

This work was supported in part by a grant from the U.S. Nuclear Regulatory Commission [NRC-HQ-60-14-G-0011], a grant from the Centers for Disease Control and Prevention [5UE1EH000989], a grant from the National Aeronautics and Space Administration [Grant No. NNX15AU88G], and grants from the U.S. Department of Energy [Grant No. DE-SC0008944 and Grant No. DE-AU0000042 awarded to the National Council on Radiation Protection and Measurements, which included interagency support from the U.S. Nuclear Regulatory Commission, the U.S. Environmental Protection Agency, and the National Aeronautics and Space Administration]. Furthermore, contract support was received by Oak Ridge National Laboratory from the Office of Radiation and Indoor Air, U.S. Environmental Protection Agency, under Interagency Agreement DOE No. 1824 S581-A1, under contract No. DE-AC05-00OR22725 with UT-Battelle; and contract support was received by Oak Ridge Associated Universities from the U.S. Department of Energy under contract No. DE-SC0014664.

Notes on contributors

Michael T. Mumma is the Director of Information Technology at the International Epidemiology Institute and the International Epidemiology Field Station for Vanderbilt University Medical Center. He has over 20 years of experience in data analysis and conducting epidemiologic investigations.

Jennifer L. Sirko is an epidemiologist with over 10 years of experience in occupational and public health research. In addition to her work with the International Epidemiology Institute, she is currently a research officer with the Pew Charitable Trusts.

John D. Boice is a radioepidemiologist with over 40 years of experience. He is the President of the National Council on Radiation Protection and Measurements and a professor of medicine at Vanderbilt University. He is the recipient of the E.O. Lawrence award from the Department of Energy. Dr. Boice is the creator and leader of the Million Person Study in the United States.

William J. Blot is professor of medicine at Vanderbilt University School of Medicine and chief executive officer of the International Epidemiology Institute. Prior to co-founding IEI in 1994, he directed research into the causes of cancer for 20 years at the National Cancer Institute. He currently directs the NIH-funded Southern Community Cohort Study, one of the largest epidemiologic studies yet undertaken to assess reasons for racial disparities in cancer incidence and mortality.

ORCID

Michael T. Mumma http://orcid.org/0000-0001-7506-8710
John D. Boice http://orcid.org/0000-0002-8755-1299

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