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REVIEW ARTICLE

Ionizing radiation: a risk factor for mesothelioma

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Abstract In the majority of mesothelioma cases worldwide, asbestos is a likely causal factor, but several alternative factors, such as ionizing radiation, have been recognized. We reviewed ionizing-radiation evidence from epidemiology studies of (1) patients exposed to the diagnostic X-ray contrast medium "Thorotrast," (2) patients undergoing radiation therapy (i.e., to treat cancer), and (3) atomic energy workers chronically exposed to lower levels of radiation. The results from these populations are also supported by case reports of mesothelioma following therapeutic radiation. Statistically significant associations were found in many, but not all, epidemiology studies (particularly those of Thorotrast- and radiation-treated patients). Given the low mesothelioma rate in the general population, the consistently increased risk among these radiation-exposed individuals is noteworthy. Many studies were limited by the lack of a uniform manner in which mesothelioma was reported prior to introduction of a uniform classification system (ICD-10). Future studies that rely on ICD-10 should have greater power to detect an association. While the evidence falls short of a definitive causal link, considering studies in which statistical significance was achieved, the case reports, and the plausible mode of action, we conclude that the evidence is supportive of a causal link between ionizing radiation exposure and mesothelioma risk.

Keywords Pleural cancer · Thorotrast · Therapeutic radiation · Occupational · Nuclear · Risk · Epidemiology · Asbestos

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Introduction

Malignant mesothelioma is a relatively rare cancer, with about 2,000 new cases diagnosed in the US each year [1]. While asbestos is generally accepted as a risk factor for the majority of mesotheliomas (70–80%), several other potentially causal factors have been identified [2], including micro-environmental exposures to fibers from volcanic rocks [3, 4]; exposure to chemicals such as beryllium [5, 6] and liquid paraffin [7]; and chronic irritation, inflammation [8, 9], and infection [10]. Recent reports have suggested that the SV40 virus may also contribute to the development of mesothelioma [11–13], and that there may be a genetic susceptibility to mesothelioma [11].

Exposure to ionizing radiation has been identified as a risk factor for mesothelioma. The types of ionizing radiation specifically implicated in the induction of mesothelioma in humans include exposure to the diagnostic radiographic contrast medium "Thorotrast," which contains radioactive thorium dioxide ($^{232}ThO_2$) particles (α-emitters); undergoing radiation therapy (e.g., to treat cancer); and working in the atomic energy/nuclear engineering industries.

Methods

Literature search

We conducted a search of the National Library of Medicine's (NLM's) PubMed database for peer-reviewed epidemiological articles using search terms including "radiation and mesothelioma," "radiation and pleural cancer," "Thorotrast," and "Radiation or Nuclear Workers." To supplement these searches, the reference lists of

government reports and articles were reviewed and "related article" searches in PubMed were conducted.

Identification of disease status

Mesotheliomas were not classified in the International Classification of Diseases until the 10th Revision (ICD-10) (Table 1) [14]. Prior to the publication of the ICD-10 in 1992, studies often used pleural cancers as a surrogate for mesotheliomas because the majority of these cancers (70–90%) were likely to be mesotheliomas (Gardner et al. 1982, as cited in IARC) [15]. It is likely that some mesotheliomas were also classified as other respiratory cancers or diseases of the respiratory and circulatory systems [16]. We have reported what the original authors have described and have discussed the limitations in the "Discussion."

Statistical analyses

Several studies of radiation workers did not provide risk estimates. For these studies (when possible), we calculated Standardized Mortality Ratios (SMR) and 95% confidence intervals (CI) using the mid-*p* value method with Miettinen's modification [17], using open source epidemiological analysis software [18]. For studies that provided risk estimates and the observed number of cases, we back-calculated the expected number of cases, if it was not provided.

Results

Thorotrast

Thorotrast is a diagnostic radiographic contrast solution (colloidal $^{232}ThO_2$), which was used mostly between 1930

Table 1 International classification of diseases (ICD) codes historically used for mesothelioma

ICD code	ICD version	Publication date	Inclusive years[a]	Description	References
150–159	ICD-6	1948	–[b]	Malignant neoplasm of digestive organs and peritoneum	Wolfbane [75]
160–165	ICD-6	1948	–	Malignant neoplasm of respiratory system	Wolfbane [75]
158	ICD-7	1955	–	Malignant neoplasm of peritoneum	NIOSH [50]
162.2	ICD-7	1955	–	Malignant neoplasm of pleura	NIOSH [50]
158	ICD-8	1967	–	Malignant neoplasm of peritoneum and retroperitoneal tissue	ICDA [76]
163	ICD-8	1967	–	Malignant neoplasm of other and unspecified respiratory organs	ICDA [76]
158.8	ICD-9	1977	1979–1998	Malignant neoplasm of peritoneum, specified parts	Davis et al. [16]
158.9	ICD-9	1977	1979–1998	Peritoneum, unspecified parts includes parietal pleura, visceral pleura, other specified site of pleura, and pleura-unspecified	Davis et al. [16]
162.9	ICD-9	1977	1979–1998	Bronchus, lung unspecified	Davis et al. [16]
163	ICD-9	1977	1979–1998	Malignant neoplasm of pleura	NIOSH [50]
163.9	ICD-9	1977	1979–1998	Malignant neoplasm of pleura	Davis et al. [16]
195.1, 195.2	ICD-9	1977	1979–1998	Other and ill defined sites	Davis et al. [16]
199.0, 199.1	ICD-9	1977	1979–1998	Site unspecified, other site	Davis et al. [16]
390–459	ICD-9	1977	1979–1998	Diseases of the circulatory system (excludes mesothelioma)	Davis et al. [16]
460–519	ICD-9	1977	1979–1998	Diseases of the respiratory system (excludes other malignant neoplasms of pleura)	Davis et al. [16]
C-38.4	ICD-10	1992	1999–current	Malignant neoplasm of heart, mediastinum, and pleura (excludes other malignant neoplasms of peritoneum)	WHO [14]
C-45	*ICD-10*	*1992*	*1999–current*	*Malignant neoplasms of mesothelial and soft tissue—Mesothelioma (excludes other malignant neoplasms of pericardium)*	*WHO* [14]
C-45.1	ICD-10	1992	1999–current	Mesothelioma of peritoneum [mesentery, mesocolon, omentum, peritoneum (parietal, pelvic)]	WHO [14]
C-45.2	ICD-10	1992	1999–current	Mesothelioma of pericardium	WHO [14]
C-45.7	ICD-10	1992	1999–current	Mesothelioma of other sites	WHO [14]
C-45.9	ICD-10	1992	1999–current	Mesothelioma, unspecified	WHO [14]
9050–9055	ICD-O	2000	2000–current	Mesothelial neoplasms	WHO [14]

Italic row indicates the first standardized method of reporting malignant mesothelioma

[a] Inclusive years in the US NIOSH Occupation Respiratory Disease Surveillance Program (*Source* http://webappa.cdc.gov/ords/norms-icd.html#MESO)

[b] Not reported

and 1955 [19, 20]. ThO_2 is insoluble, and injected ThO_2 cannot be excreted; the majority of it is retained within the reticuloendothelial system—e.g., liver, spleen, and red bone marrow—with small retention in almost all tissues, including the lung and pleura. Once in the body, Thorotrast continues to decay, emitting mostly α-particles. The bronchial epithelium is also exposed to α-particles from a ^{232}Th decay-product gaseous radionuclide (^{220}Rn) [21]. Thorotrast exposure has been noted to increase the risk of malignant mesothelioma (mostly of the pleura and peritoneum) in cohorts of Thorotrast-exposed patients in Denmark, Sweden, Japan, Germany, and the US (Table 2) [21–25].

Andersson et al. [20] compared lung cancer and mesothelioma incidences among 999 Danish neurological patients treated with Thorotrast for cerebral angiography between 1935 and 1947 to the general population (based on the Danish cancer registry) and to 1,480 similar patients examined with cerebral angiography without Thorotrast between 1946 and 1963. The investigators estimated that Thorotrast-exposed patients received a dose between 1 and 21 ml of the ThO_2 colloid, with the majority receiving a dose of ≥11 ml over 30 years. Andersson et al. [20] reported a statistically significant increased risk of peritoneal cancer (four observed, SMR = 11.54, 95% CI: 3.10–29.54) and a non-significant increase in pleural cancer (one observed, SMR = 4.05, 95% CI: 0.05–22.51). The control population had no cases of peritoneal cancer (SMR = 0) and one case of pleural cancer (SMR = 1.95, 95% CI: 0.03–10.86). Andersson et al. [22] reported that rates of malignant tumors of the pleura and peritoneum combined in these Thorotrast-treated patients were significantly increased when compared to the Danish cancer registry (SMR = 8.33, 95% CI: 2.69–19.45) and when compared to a control group of similar patients not exposed to Thorotrast (RR = 9.41, 95% CI: 1.05–444.75).

Andersson et al. [22] reviewed the pathology records used in the Andersson et al. [20] study and identified three additional mesothelioma cases that were previously misdiagnosed as two liver carcinomas and one carcinoid of the lung (Table 2). When compared to the Danish population, they found that Thorotrast patients had a higher incidence of mesothelioma [seven observed, 0.6 expected (based on tumors of the pleura and peritoneum)]. The risk of mesothelioma for patients treated with >20 ml Thorotrast was 7.8%, compared to 1.4% for patients administered smaller quantities of Thorotrast. Andersson et al. [22] also reported that Thorotrast patients with mesothelioma were younger than Thorotrast patients at the time of injection (mean = 22 vs. 37 years) and had received a higher dose of Thorotrast (mean 27 vs. 19 ml). The exposure time from injection to diagnosis of cancer or death was relatively long (mean = 30 vs. 20 years).

Travis et al. [24] evaluated site-specific cancer rates among 1,650 patients from the US, Denmark, and Sweden who were exposed to Thorotrast during cerebral angiography between 1935 and 1963, and a group of similar patients who were exposed to a non-radioactive agent ($n = 1{,}392$) and survived 2 or more years. There was likely overlap between the Danish subjects in this study and those described in the Andersson et al. [20, 22] studies discussed earlier. Five cases of peritoneal or "other digestive" malignancies were observed in the Danish and Swedish subjects (SIR = 14.6, $p < 0.05$), while no cases were observed in the Danish control group (RR = ∞, 95% CI: 1.7–∞). The risk significantly increased with increasing cumulative radiation dose ($p_{trend} = 0.01$). An increased cancer risk for all digestive organs and the peritoneum was also observed in the US cohort (external comparison: SMR = 3.4, $p < 0.05$; internal comparison: RR = 8.9, 95% CI: 3.0–38.1).

van Kaick et al. [25] examined cancer rates in a German cohort of 2,326 Thorotrast-exposed patients (26% females) and 1,890 similar patient controls (25.5% females) whom they followed since 1968. The majority of patients received Thorotrast for cerebral angiography (70%) or arteriography of the lower limbs (30%), and the mean injection volume was 20.8 ml. These investigators reported four peritoneal and five pleural mesotheliomas among the Thorotrast-exposed patients versus none among the controls (risk ratio not calculated).

Two studies of Thorotrast-exposed patients noted a lack of association with mesothelioma. Ishikawa et al. [21] examined rates based on the autopsies of 370 Japanese patients (male:female ratio of 9.6:1) who received a mean Thorotrast injection of 17 ml at a mean age 26 years. These investigators reported one case of peritoneal mesothelioma in a 44-year-old man who received a Thorotrast injection for an angiography 25 years prior, but they did not calculate a risk estimate. Instead, they calculated rates based on all malignancies of the peritoneal cavity (including the mesothelioma noted earlier, two retroperitoneal sarcomas, and one mesentery sarcoma). Ishikawa et al. [21], however, did report an increased risk of all peritoneal malignancies in those exposed to Thorotrast (4/370 or 1.1%) compared to patients who were not exposed (based on general autopsy records, 344/162,000 or 0.2%) (O/E = 5.1; $p < 0.005$).

The Portuguese cohort is the largest Thorotrast cohort (2,427 exposed and 2,258 unexposed) and was followed for over 50 years [26]. Mesothelioma was not noted as a cause of death for any Thorotrast-treated patients, but the investigators stated that in certain cases, pneumonia may have been listed incorrectly as the cause of death. dos Santos Silva et al. [26] suggested that some of these deaths were likely a consequence of Thorotrast exposure, so some may actually have been attributable to mesothelioma.

Table 2 Mesothelioma risks in patients treated with Thorotrast

Country (reference)	Thorotrast-treated population (*n*)	Comparison population (*n*)	Volume (ml) average (range)	Follow-up period (years)	Average follow-up in years (range)	Radiation dose	Cancer	Treated	Comparison	Risk estimate (95% CI)
Japan (Ishikawa et al. [21])	Patients injected iv with Thorotrast (370)	Pleuroperitoneal and retroperitoneal patients (162,000)	17	1945–1992	27 (20–33)	5.3 mGy/year (to lung)[i]	Mesothelioma	1/370	–[a]	–
							Peritoneal malignancies	4/370	344/162,000	SMR = 5.1 ($p < 0.005$)
Denmark (Andersson et al. [20, 22])	Neurological patients treated with Thorotrast (1,003)[g]	Neurological patients treated with non-Thorotrast contrast medium (1,480)	27 (10–50)[f]	1935–1992	30 (22–36)[f]	0.177 Gy[e]	Pleural and peritoneal mesotheliomas	7/1,003[g]	1/1,480	SMR = 8.33 (2.69–19.45) RR = 9.41 (1.05–444.75)
Germany (van Kaick et al. [25])	Patients treated with Thorotrast for angiography or arteriography of the limbs (2,326)	Hospital-based controls (1,890)	20.8[h]	1968–1990s	–	0.21 Gy/year	Pleural and peritoneal mesotheliomas	9/2,326	0/1,890	–
Denmark, Sweden, US (Travis et al. [23, 24])	Patients treated with Thorotrast for cerebral angiography from Denmark and Sweden (1,204) and the US (446)	Cerebral angiography patients treated with non-radioactive contrast medium in Denmark (1,180) and the US (212)	20.1 (3–92)	1932–1992	26.6	–	Peritoneal and other digestive cancers	Denmark 5/1,204	Sweden 0/1,180	RR = ∞ (1.7–∞)
								US 32/439	4/207	RR = 8.9 (3.0–38.1)
										SMR = 3.4 ($p < 0.05$)
										SIR = 14.6 ($p < 0.05$)
Portugal (dos Santos Silva et al. [26])	Patients treated with Thorotrast (2,427)	Patients treated with a nonradioactive contrast agent (2,258)	Median: 20 (2–148)	1946–1996	15.3[b] 38.2[c]	–	–[d]	–[d]	–[d]	–[d]

[a] –, Not stated

[b] Systematically exposed

[c] Locally exposed

[d] Mesothelioma not discussed, but some deaths coded as pneumonia may have been attributable to mesothelioma

[e] 0.177 Gy assumes the dose rate is 48.3 $\times$ 10^{-5} Gy per ml Thorotrast injected per year and allows for a latency period of 5 years (Hoffmann et al. 1990 as reported by Andersson et al. [20])

[f] Data only for patients with malignant mesothelioma (not entire exposed group)

[g] We have reported here the whole study population of 1,003 where the time for diagnosis is substituted with the time of death, emigration, or end of follow-up [20]

[h] Based on the mean injected volume in the 1,019 patients with liver tumors

[i] Reported in Ishikawa et al. [77]

Results among these studies are remarkably consistent: the risks of pleural or peritoneal mesotheliomas are generally higher among Thorotrast-treated patients than among untreated controls. The incidence of peritoneal cancer in these studies is notable because, of the mesotheliomas directly attributable to asbestos exposure, pleural mesothelioma is the most common form [27]. Also, because there is no reason to expect that asbestos exposure differed among treatment groups, it is not likely to be a confounder in these studies.

Radiotherapy

Numerous reports demonstrate development of malignant mesothelioma in organs close to areas in the body treated with therapeutic ionizing radiation (Tables 3, 4). The association between malignant mesothelioma and radiation therapy was initially established based mostly on case reports, several of which are described in Table 3 [28]. Evidence also comes from several large-scale retrospective cohort studies that evaluated the occurrence of mesothelioma following exposure to therapeutic radiation for treatment of several types of primary cancer in population-based registries around the world. Several of these studies use data abstracted from the US National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) Program. In addition, some studies examined second primary cancers in individuals with the same type of primary cancer. Cavazza et al. [29] included patients with 17 different initial cancer types in SEER. Patients in the SEER registry with Hodgkin's lymphoma (HL) were included in studies by Neugut et al. [30], Teta et al. [31], and Hodgson et al. [32]. Those with breast cancer were included in studies by Neugut et al. [30] and Tward et al. [33] and those with non-Hodgkin's lymphoma (NHL) were included in the studies by Tward et al. [34] and Teta et al. [31]. Although there is an overlap in subjects among these studies because several of these studies included patients with more than one primary cancer or included individuals from several registries, we have discussed them all below.

The first analysis of SEER data for second primary cancers after an initial diagnosis was that conducted by Cavazza et al. [29]. These investigators analyzed the incidence of pleural mesothelioma as a second primary cancer in patients registered in the SEER database or the Connecticut Tumor Registry and diagnosed between 1935 and 1972. The initial primary cancer types included those of the oral cavity, colon, rectum, pancreas, larynx, lung, bone or connective tissue, melanoma, breast, uterine corpus/cervix, prostate, bladder, kidney, and unspecified digestive and other sites, as well as NHL and leukemia. Of 1,489,643 patients, 142 had mesothelioma as a second primary cancer (O/E = 0.88, 95% CI: 0.74–1.04). Patient median age was 68.5 years (range 35–86 years), the median latency between first cancer and mesothelioma was 4.3 years (range 2 months–29.9 years), and the majority (89%) of patients were men. Only 33 of the 142 patients were initially treated with radiation alone and four were treated with both radiotherapy and chemotherapy.

Neugut et al. [30] analyzed mesothelioma risk in a cohort of 251,750 women diagnosed with breast carcinoma and 13,743 individuals with HL registered in the SEER Program between 1973 and 1993. These investigators reported two cases of malignant pleural mesothelioma in breast carcinoma patients treated with radiotherapy, and four in women not treated with radiotherapy. No cases occurred in the patients with HL. Rates were increased, but not significantly, in breast cancer patients treated with radiotherapy (O/E = 1.78, 95% CI: 0.20–6.42) or all patients combined treated with radiotherapy (O/E = 1.56, 95% CI: 0.18–5.63). Rates were also null in patients not receiving radiotherapy (overall O/E = 0.91, 95% CI: 0.24–2.24). Tward et al. [33] followed-up the breast cancer cohort through 2002 ($n = 328{,}878$). They reported no increased risk for mesothelioma overall (32 observed, O/E = 0.82, 95% CI: 0.56–1.15) or in patients who survived $\geq$10 years from diagnosis and received radiotherapy (O/E = 1.29, 95% CI: 0.26–3.76).

Hodgson et al. [32] followed the HL cohort from SEER from 1970 to 2001, while Teta et al. [31] followed them (and those with NHL) from 1973 to 2003. Hodgson et al. [32] examined rates of second cancers in 18,862 5-year HL survivors from population-based registries in Denmark, Finland, Norway, and Sweden, as well as the US (using data from the SEER program). Although dose estimates were not available, the investigators reported an estimated mean dose of 14.4 Gy to the lungs (range 4.2–35) following administration of 35 Gy in the Mantle Field, or a mean of 1.5 Gy following administration in the Inverted Y-field for HL treatment.[1] Hodgson et al. [32] reported that the largest risk associated with radiation treatment was for pleural cancer (12 observed, RR = 19.5, 95% CI: 7.3–40.3).

Teta et al. [31] recently examined the incidence of mesothelioma in patients in the SEER database who received therapeutic radiation for HL or NHL. Of 10,578 patients with HL and 26,266 with NHL who received radiation therapy between 1973 and 2003, 14 developed mesothelioma as a second primary cancer. Teta et al. [31] reported a statistically significant increase in mesothelioma risk among men with HL who received radiation (four

[1] Radiation therapy to the region of the neck, chest, and/or lymph nodes under the arms is called "mantle field" radiation, whereas the radiation field from the heart to the groin is called the "inverted Y-field."

Table 3 Case reports of mesothelioma following radiation therapy

Sex	Reason for radiotherapy	Age at exposure (years)	Age at diagnosis (years)	Latency period	Outcome after diagnosis	References
F	Cervical cancer	55	62	7	Death at 7 months	Babcock et al. (1976)[c]
M	Hodgkin's disease	29	34	5	–[a]	Brody et al. (1977)[c]
M	Seminoma	50	66	16	Death at 24 months	Stock et al. (1979)[c]
M	Hodgkin's disease	27	34	7	Death at 9 months	Brenner et al. (1982)[c]
M	Unknown	–	–		–	Hirsch et al. (1982)[c]
F	Breast cancer	30	40	10	Alive at 48 months	Antman et al. (1983)[c]
F	Teratocarcinoma	6	24	18	Death at 10 months	Cavazza et al. (1996)[c]
F	Thyroidectomy scar	29	55	26	–	Antman et al. (1983)[c]
M	Seminoma	33	57	24	Death (time –)	Hoffman et al. (1983)[c]
M	Seminoma/cecal lymphoma	24/38	55	17	Death at 22 months	Antman et al. (1983)[c]
F	Cervical cancer	50	59	9	Death at 9 months	Beier et al. (1984)[c]
M	Hodgkin's disease	23	28	5	Death (time –)	Tester et al. (1984)[c]
M	Wilms' tumor	3	44	41	–	Antman et al. (1984)[c]
M	Wilms' tumor	6	22	16	Death at 42 months	Antman et al. (1984)[c]
M	Non-Hodgkin's lymphoma	47	61	14	Death at 15 months	Efremedis et al. (1985)[c]
M	Wilms' tumor	2	16	14	–	Andersson et al. (1985)[c]
F	Wilms' tumor	4	24	20	Death at 2 weeks	Austin et al. (1986)[c]
M	Seminoma	35	61	26	Death at 2 months	Gilks et al. (1988)[c]
F	Breast cancer	34	64	30	Death at 13 months	Kawashima et al. (1990)[c]
F	Hodgkin's disease	4	24	20	Alive at 24 months	Lerman et al. (1991)[c]
F	Hodgkin's disease	13	22	9	Death at 5 months	Hofmann et al. [78]
F	Breast cancer	39	73	34	–	Shannon et al. (1995)[d]
F	Breast cancer	63	75	12	–	Shannon et al. (1995)[d]
F	Breast cancer	49	78	29	Alive at 1 week	Cavazza et al. (1996)[d]
F	Breast cancer	55	76	21	–	Cavazza et al. (1996)[d]
F	Hodgkin's disease	1	25	24	Death at 4 years	Cavazza et al. (1996)[d]
M	Hodgkin's disease	5	22	17	Death at 3 years	Cavazza et al. (1996)[d]
M	Hodgkin's disease	7	32	25	–	Weissmann et al. (1996)[d]
M	Hodgkin's disease	20	31	11	Death at 4 months	Cavazza et al. (1996)[d]
M	Hodgkin's disease	21	43	22	Death	Cavazza et al. (1996)[d]
M	Hodgkin's disease	28	49	21	Death	Cavazza et al. (1996)[d]
M	Hodgkin's disease	32	44	12	–	Weissmann et al. (1996)[d]
F	Ovarian cancer	11	20	9	Alive at 8 years	Pappo et al. (1997)[d]
M	Hodgkin's disease	7	18	11	Alive at 7 months	Pappo et al. (1997)[d]
M	Seminoma	24	53	29	Death at 12 months	Tassile et al. [79]
NS	Wilms' tumor	5	23	18	–	Li et al. (1997)[d]
M	Hodgkin's disease	40	64	24	Alive at 6 years	Kramer et al. (2000)[d]
M	Seminoma	35	52	17	Alive at 6 months	Sato et al. [80]
M	Teratoma	30	65	35	Death at 7 months	Amin et al. [81]
M	Seminoma	37	54	17	Death at 6 months	Amin et al. [81]
F	Hodgkin's disease	25	49	24	Death at 2 years	Velissaris et al. [82]
F	Hodgkin's disease	18	30	12	–	Henley et al. [83]
M	Seminoma	40	56	16	Death at 18 months[b]	Bani-Hani and Gharaibeh [84]
F	Lung cancer	49	66	17	Death at 5 months	Witherby et al. [28]

[a] –, not stated

[b] Death due to myocardial infarction

[c] *Source*: Hofmann et al. [78]

[d] *Source*: Witherby et al. [28]

Table 4 Mesothelioma risks in patients treated with radiation therapy

Reference	Tumor registry	Initial primary cancer	Diagnoses (year)	Subjects (*n*)	Follow-up (person-year)	Observed cancer (*n*)	Risk estimate (95% CI)
Cavazza et al. [29]	SEER	17 cancer sites	US: 1973–1992	1,489,643[a]	6,304,466[a]	Pleural mesothelioma (142)[b]	O/E = 0.88 (0.74–1.04)
	CT Tumor Registry		CT: 1935–1972				
Neugut et al. [30]	SEER	Breast carcinoma (F) or Hodgkin's disease (all)	1973–1993	69,414[a]	273,123.4[a]	Pleural mesothelioma (2)	O/E = 1.56 (0.18–5.63)
Travis et al. [35]	Canada, SEER, Denmark, Finland, Norway, Sweden	Testis	1943–2001	40,576[a]	458,383[a]	Pleural mesothelioma (15)	**RR = 4.0 (2.0–8.1)**
Brown et al. [36]	Denmark, Finland, Norway, Sweden	Breast cancer (women)	1943–2002	376,825	2,990,587	Pleural cancer (40)	**SIR = 1.42 ($p < 0.05$)**
Tward et al. [33]	SEER	Non-Hodgkin's lymphoma	1973–2001	21,111	112,281	Mesothelioma (9)	**O/E = 0.82 (0.56–1.15)**
Tward et al. [34]	SEER	Breast cancer	1973–2002	28,595	–[c]	Mesothelioma (<32)	O/E = 1.29 (0.26–3.76)
Teta et al. [31]	SEER	Hodgkin's lymphoma (M)	1973–2003	5,610	60,200	Mesothelioma (4)	**SIR = 6.59 (1.79–16.87)**
		Hodgkin's lymphoma (F)		5,148	57,100	Mesothelioma (0)	SIR = 0.0 (0–25.65)
		Non-Hodgkin's lymphoma (all)		26,266	144,800	Mesothelioma (10)	**SIR = 2.24 (1.07–4.12)**
Deutsch et al. [37]	NSABP	Breast	1971–1994	22,140[a]	–[c]	Pleural mesothelioma	**RR = 3.74 ($p = 0.039$)**[d]
Hodgson et al. [32]	Denmark, Finland, Norway, Sweden, SEER	Hodgkin's lymphoma	1970–2001	18,862[a]	160,753[a]	Pleural cancer (12)	**RR = 19.5 (7.3–40.3)**
De Bruin et al. [39]	The Netherlands	Hodgkin's lymphoma	1965–1995	2,567	–[c]	Mesothelioma (13)	**SIR = 25.7 (13.7–44.0)**[e]

Bold font indicates a statistically significant result

[a] Includes all patients in the study, not just those treated with radiotherapy

[b] Thirty-three were initially treated with radiation alone; four were treated with both radiotherapy and chemotherapy

[c] –, not stated

[d] Based on SEER rates for US woman of the same age

[e] 5-year survivors of HL compared to the general population based on Eindhoven Cancer Registry (The Netherlands) and the Netherlands Cancer Registry rates

observed, SIR = 6.59; 95% CI: 1.79–16.87), but not among women (0 observed). In patients who received radiation treatment for NHL, there was an increased risk of mesothelioma among men and women combined (10 observed, SIR = 2.24, 95% CI: 1.07–4.12). Among patients not receiving radiation treatment, no increased rates of mesothelioma were observed.

Tward et al. [33] also analyzed rates of second cancers in NHL patients in SEER, but followed them from 1973 to 2001 (vs. 2003 in the Teta et al. [31] study). These investigators focused on 21,111 NHL patients who were treated with radiotherapy, followed for 30 years, and reported to the SEER program. On average, the second primary cancers were diagnosed 10 years after the initial diagnosis and treatment. Patients treated with radiation had a significantly increased risk of mesothelioma (O/E = 2.26, 95% CI: 1.03–4.28), while patients not receiving radiation treatment did not (O/E = 0.86, 95% CI: 0.39–1.63).

Only one study examined mesotheliomas in individuals with primary testicular cancer. Travis et al. [35] examined second primary cancers occurring after radiation treatment and/or chemotherapy in men with a primary cancer of the testis in 14 population-based tumor registries in Europe and North America, including SEER (1943–2001). They found a significant increase in malignant mesotheliomas of the pleura in the study cohort of 40,576 patients (15 observed, O/E = 2.80, 95% CI: 1.57–4.62). The risk was increased among patients who received radiation alone (RR = 4.0, 95% CI: 2.0–8.1).

In a retrospective cohort study, Brown et al. [36] analyzed treatment-related second cancers in a cohort of 376,825 1-year breast cancer survivors who were diagnosed between 1943 and 2002 and were reported to cancer registries in Denmark, Finland, Norway, and Sweden. Although patients receiving radiotherapy were not reported, the authors stated, "Standard management of breast cancer during the time period of the study included large doses of radiation to the chest field and lymph nodes (typically 40–60 Gy total)." It should be noted that because follow-up occurred over such a long period of time, it is likely that treatment for breast cancer differed significantly at the beginning of this time period versus at the end. The investigators found that these breast cancer survivors had an increased risk of pleural cancers (40 observed, SIR = 1.42, $p < 0.05$). This risk was highest in those with the longest follow-up (for those followed for ≥30 years, SIR = 5.6, $p < 0.05$) or with the youngest age at diagnosis (for those who were <40 years of age at their breast cancer diagnosis, SIR = 8.56, $p < 0.05$).

Deutsch et al. [37] investigated the risk of mesothelioma following radiotherapy for primary breast cancer. They examined follow-up records from 22,140 patients in 11 National Surgical Adjuvant Breast and Bowel Project (NSABP) clinical trials for treatment of primary breast cancer between 1971 and 1994. While the specific geographic locations of the individuals included in the study are not listed, the NSABP database includes information from nearly 1,000 medical centers and health maintenance organizations in the US, Canada, Puerto Rico, Australia, and Ireland [38]. In the Deutsch et al. [37] study, postoperative radiotherapy was administered to 9,342 (42.1%) of the patients. The investigators identified three cases of pleural mesothelioma in the ipsilateral thorax of radiation-treated patients versus none in those not treated with radiation ($p = 0.009$). All three cases had received post-lumpectomy irradiation for ductal carcinoma in situ and had no known exposure to asbestos.

Finally, DeBruin et al. [39] showed induction of malignant mesothelioma in patients following radiotherapy for treatment of HL in the Netherlands. These investigators reported that after a median follow-up time of 18.1 years, 13 of 2,567 5-year survivors of HL developed mesothelioma. This is an almost 26-fold increased risk for mesothelioma compared to mesothelioma rates in the general population (SIR 25.7; 95% CI 13.7–44.0) and an almost 30-fold increased risk among patients treated with radiotherapy (SIR 29.4; 95% CI 15.7–50.4). Similar to HL patients in other studies (Table 3), the median age of first radiation treatment for HL was 27.4 years (range of 3–50 years) and the median time from radiotherapy for HL to mesothelioma diagnosis was 27.7 years, which occurred at a median age of 56.4 years. The excess number of mesotheliomas was 3.5 cases per 10,000 patients per year. Medical records were screened and general practitioners were contacted to identify possible exposure to asbestos, and of the cases of mesothelioma, 54% ($n = 7$) had some asbestos exposure, which was less than the expected 85% ($n = 11$). The pathologically confirmed cases of mesothelioma were similar in histological characteristics to those attributed to asbestos exposure.

In addition to diffuse malignant pleural mesotheliomas, radiation may also induce localized benign mesotheliomas (also called "localized fibrous tumor" of the pleura) [40]. These tumors are rare, representing less than 5% of all pleural mesotheliomas (Theros et al. 1977, as reported by Hill et al. [41]), but are notable because, unlike malignant diffuse pleural mesotheliomas, there is no evidence of a causal link to asbestos exposure [41]. Two case reports support the association between exposure to therapeutic radiation and the development of mesothelioma [41, 42].

It is notable that associations between radiotherapy and mesothelioma have been observed as a second primary cancer in individuals with several types of initial primary cancers (e.g., testis cancer, breast cancer, HL, NHL) but have not generally been observed among patients who did

not receive radiotherapy [43]. In contrast to the association between secondary leukemias and lymphomas and prior treatment with alkylating agents (chemotherapeutic drugs), the risk of developing secondary malignant mesotheliomas appears to be specifically due to radiation [44]. Studies that support this association report factors such as: malignant mesothelioma developing in a prior radiation field, pathology results indicating radiation damage, a relatively short latency period (compared to asbestos-mediated disease), and a lack of other explanatory factors [28].

As was the case for Thorotrast-treated patients, there is nothing to suggest that asbestos exposure differed between patients treated with radiotherapy and untreated patients, suggesting that it is not a significant confounder [31]. Asbestos can be confidently ruled out based on several considerations: (1) the association has been observed with several different types of cancer (see Tables 2, 3); (2) the association is generally limited to those who were irradiated and is not observed among those who were not; and (3) for younger patients treated with radiotherapy, there is little opportunity for asbestos exposure (or the associated long latency period) [31]. Taken together, the results from the Thorotrast and radiotherapy studies indicate that ionizing radiation can play a causal role in mesothelioma [43, 45].

Radiation workers

Occupational exposure to ionizing radiation is an established risk factor for cancer [46]. There are two main sources of occupational radiological exposure: (1) external γ-ray exposure that results in a relatively uniform whole-body dose; (2) internal depositions of radionuclides that deliver radiation doses primarily to the lung and lymphatic system (e.g., uranium dust) [47]. Epidemiological investigations of workers exposed to these types of radiation have been conducted around the world (US, Australia, Belgium, Canada, Finland, Hungary, Japan, South Korea, Lithuania, inter alia). These workers were exposed to X- and γ-radiation, and elevated rates of pleural and peritoneal mesotheliomas have been reported in all studies of these workers.

Atkinson et al. [48] examined mortality rates in 51,367 employees, of whom 10,249 were deceased, who worked for the British Atomic Energy Authority between 1946 and 1996 and were followed-up through 1997 (Tables 5, 6). Mortality was compared externally to national rates and internally between radiation and non-radiation workers. Radiation workers included those with industrial, scientific, and/or laboratory jobs, and others with potential exposure, such as cleaners. Although mortality risk from all malignant neoplasms was lower among radiation workers than the general population (SMR = 80, 95% CI: 77.3–83.1), this was not the case for mesothelioma (SMR = 104, 95% CI: 49.6–190.7). In addition, the risk of mortality from pleural cancer was higher among radiation workers than non-radiation workers (RR = 5.35, 95% CI: 1.36–∞), although a dose-response was not found.

Matanoski et al. [49] examined cancer rates in US shipyard workers involved in nuclear-powered ship overhauls between 1957 and 1982 (Tables 5, 6). Radiation workers were certified to work in areas with potential exposure to radioactivity and had both an employment and dosimetry record. Radiation exposures were generally incidental following exposure to neutron-activated corrosion products of the coolant system. Based on a stratified random sample of the entire study population, 28,000 workers exposed to $\geq$5.0 mSv (from a ^{60}Co source), 10,462 to <5.0 mSv, and 33,353 non-nuclear workers were analyzed. Cancer rates were compared internally to workers exposed to 5.0–9 mSv and externally to US Caucasian males. Mesothelioma rates were higher in both nuclear and non-nuclear workers when compared to US males; however, they were twice as high in the nuclear workers: those with $\geq$5.0 mSv of exposure had an SMR of 5.11 (95% CI: 3.03–8.08), and those with <5.0 mSv exposure had an SMR of 5.75 (95% CI: 2.48–11.33), while the non-nuclear workers had an SMR of 2.41 (95% CI: 1.16–4.43). No analyses were conducted to determine whether these were significantly different. In addition, internal comparisons were conducted using those exposed to 5–9 mSv as the comparison group. In these internal comparisons the associations were not statistically significant, but it is unclear whether significance would have been found if non-nuclear workers had been used as the comparison group rather than the 5–9 mSv group.

The Idaho National Engineering and Environmental Laboratory (INEEL) is a US Department of Energy facility where nuclear reactor design and testing, nuclear material chemical processing, and the construction, servicing, and demolition of large-scale nuclear facilities occurs [50]. Rates for pleural and peritoneal cancer were compared to rates in Idaho, Montana, Utah, and Wyoming combined. Fourteen cases of pleural and peritoneal cancers were identified (SMR = 2.05, 95% CI: 1.12–3.49), but the authors noted that additional mesothelioma cases may have been missed due to classification as "other and unspecified cancers" in ICD-9. Of the 14 cases, three were asbestos workers (SMR = 6.00, 95% CI: 1.21–19.7) and 11 were non-asbestos workers (SMR = 1.74, 95% CI: 0.87–3.18). Although the risk ratio estimate was not statistically significant, the fact that 11 cases occurred in non-asbestos workers suggests radiation as a risk factor.

The Savannah River Site (SRS) in Aiken, SC has operated five large reactors, two chemical separation areas,

Table 5 Cohorts of workers occupationally exposed to radiation

Study	Cohort	Subjects (*n*)	Deaths	Exposure period	Follow-up period	Follow-up (person-year)	Exposure	Average dose (range) [mSv]	Cancer
Cardis et al. [57]	15-country study	407,391	18,993		1943–2000	5,192,710	X- and γ-rays	19.4 (3.5–62.3)	Pleural cancer
Boice et al. [52]	Rocketdyne (Atomics International)	5,801	1,468	1948–1999	Through 1999	1,264,582	Ionizing radiation	2.6	Pleural or peritoneal cancer or mesothelioma
NIOSH [50]	Idaho National Engineering and Environmental Laboratory	63,561	10,906	1949–1991	Through 1999	–[a]	^{60}Co, γ, β, and neutron radiation, fission products, transuranic radionuclides	12.89	Pleural or peritoneal cancer
Atkinson et al. [48]	UK Atomic Energy Authority	51,367	10,249	1946–1995	1946–1997	–	Plutonium and other radiation	3.95	Pleural cancer
Omar et al. [55, 56]	British Nuclear Fuels	14,319	3,854	1947–1975	1971–1992	415,431.6	Plutonium and other radiation	–	Pleural cancer
Richardson et al. [51]	Savannah River	18,883	5,098	1950–2002	Through 2002	–	Ionizing radiation	–	Pleural cancer
Telle-Lamberton et al. [53]	French Atomic Energy Commission	58,320	5,106	1946–1993	1946–1994	1,327,479.50	X- and γ-rays	–	Pleural cancer
Matanoski et al. [49]	US Nuclear Shipyard	71,815	6,933	1957–1982	1957	920,907	^{60}Co, γ-rays	–	Mesothelioma

[a] –, not stated

Table 6 Mesothelioma risks in workers occupationally exposed to radiation

Study and cohort	Dose (mSv) or exposure group	Observed	Expected	Risk estimate (95% CI)
Cardis et al. [47]	*Dose*			
15-country study	0	20	23.4	*SMR = 0.85 (0.54–1.30)*
	5	4	3.2	*SMR = 1.25 (0.40–3.02)*
	10	4	3.6	*SMR = 1.11 (0.35–2.68)*
	20	5	4.4	*SMR = 1.14 (0.42–2.52)*
	50	3	2.3	*SMR = 1.30 (0.33–3.55)*
	100	1	0.8	*SMR = 1.25 (0.06–6.17)*
	150	2	0.4	*SMR = 5.00 (0.84–16.52)*
	200	0	0.5	
	300	0	0.2	
	400	0	0.1	
	500	0	0	
	Total	39	38.9	*SMR = 1.00 (0.72–1.36)*
Boice et al. [52]	*Dose*			
Rocketdyne (Atomics International)	Not monitored	7	5.4	*SMR = 1.30 (0.57–2.56)*
	<5	0	0.6	
	5-	1	0.1	*SMR = 10.00 (0.50–49.32)*
	10-	0	0.2	
	50-	0	0	
	100-	0	0	
	≥200	0	0	
	Total monitored	1	1	
NIOSH [50]	*Worker*			
Idaho National Engineering and Environmental Laboratory	Asbestos	3	*0.5*	**SMR = 6 (1.21–19.7)**
	Others	11	*6.3*	SMR = 1.74 (0.87–3.18)
	Total	14	*6.8*	**SMR = 2.05 (0.12–3.49)**
Atkinson et al. [48]	*Worker*			
UK Atomic Energy	All	11	14.6	SMR = 0.76 (0.37–1.35)[a]
	Non-radiation	1	4.9	SMR = 0.2 (0.003–1.14)[a]
	Radiation	10	9.7	SMR = 1.04 (0.5–1.91)[a]
	Monitored for internal contamination	5	3.8	SMR = 1.32 (0.43–3.08)[a]
	Dose			
	Total radiation			**RR = 5.35 (1.36–∞)**
	<10	2	3.4	*RR = 0.59 (0.10–1.94)*
	10–20	2	1.8	*RR = 1.11(0.19–3.67)*
	20–50	3	2.2	*RR = 1.36 (0.35–3.71)*
	50–100	3	1.5	*RR = 2.00 (0.51–5.44)*
	100+	0	1.2	*RR = 00*
	Monitored for internal contamination			
	All monitored for internal contamination			RR = 1.80 (0.43–∞)
	Internal contamination < 10	0	0.4	
	Internal contamination 10 to <20	0	0.7	
	Internal contamination 20 to <50	2	1.1	
	Internal contamination 50 to <100	3	1.5	
	Internal contamination 100+	0	1.3	

Table 6 continued

Study and cohort	Dose (mSv) or exposure group	Observed	Expected	Risk estimate (95% CI)
Omar et al. [55, 56]	*Worker*			
British Nuclear Fuels	Plutonium	8	1.7	**SMR = 4.71[a] (*2.19–8.94*)**
	Other radiation	6	1.54	**SMR = 3.90[a] (*1.58–8.10*)**
	Non-radiation	0	0.76	SMR = 0
	All	14	3.99	**SMR = 3.51[a] (*2.00–5.75*)**
	Radiation workers (dose)			
	<10	2	1.8	*SMR = 1.11 (0.19–3.67)*
	10–19	1	1.3	*SMR = 0.77 (0.04–3.79)*
	20–49	1	2.4	*SMR = 0.42 (0.02–2.06)*
	50–99	1	2	*SMR = 0.50 (0.03–2.47)*
	100–199	3	2.1	*SMR = 1.43 (0.36–3.89)*
	200–399	5	2.3	*SMR = 2.17 (0.80–4.82)*
	400+	1	2.1	*SMR = 0.48 (0.02–2.35)*
	Plutonium dose ± external radiation (dose)			
	<10	0	0.1	*SMR = 0.00*
	10–19	0	0.2	*SMR = 0.00*
	20–49	0	0.8	*SMR = 0.00*
	50–99	1	0.9	*SMR = 1.11 (0.06–5.48)*
	100–199	2	1.3	*SMR = 1.54 (0.26–5.08)*
	200–399	3	1.8	*SMR = 1.67 (0.42–4.54)*
	400+	1	1.9	*SMR = 0.53 (0.03–2.60)*
Richardson et al. [51]	*Sex*			
Savannah River	Male	7	*1.6*	SMR = 4.25 (1.99–7.97)[b]
	Female	0		
	Salary			
	Monthly paid	1	*0.4*	SMR = 2.28 (0.12–10.82)[b]
	Weekly paid	2	*0.4*	SMR = 5.34 (0.95–16.83)[b]
	Hourly paid	4	*0.8*	**SMR = 4.79 (1.64–10.96)[b]**
	Employment (years)			
	<10	2	*0.6*	SMR = 3.26 (0.58–10.2)[b]
	10 to <20	1	*0.3*	SMR = 3.56 (0.18–16.76)[b]
	20 to <30	1	*0.4*	SMR = 2.33 (0.12–10.19)[b]
	30+	3	*0.3*	**SMR = 9.23 (2.58–24.5)[b]**
	Years employed			
	Employed 1985–1989	4	*0.3*	**SMR = 12.55 (4.29–28.72)[b]**
	Employed 1990–1994	1	*0.4*	SMR = 2.37 (0.12–11.25)[b]
	Employed 1995–1999	1	*0.4*	SMR = 2.64 (0.14–12.55)[b]
	Employed 2000–2002	1	*0.03*	**SMR = 30.29 (1.55–143.76)[b]**
Telle-Lamberton et al. [53]	*Sex*			
French Atomic Energy Commission	Males	28	15.7	**SMR = 1.79 (1.27–2.45)[b]**
	Males, 55+ years old	23	11.03	**SMR = 2.09 (1.43–2.95)[b]**
	Females	1	1.12	SMR = 0.89 (0.04–4.21)[b]

Table 6 continued

Study and cohort	Dose (mSv) or exposure group	Observed	Expected	Risk estimate (95% CI)
Matanowski et al. [49]	*Dose*			
US Nuclear Shipyard	0 (Non-nuclear workers)	10	*4.15*	**SMR = 2.41 (1.16–4.43)**
	<5.0	8	*1.39*	**SMR = 5.75 (2.48–11.33)**
	≥5.0	18	*3.52*	**SMR = 5.11 (3.03–8.08)**
	Dose (vs. 5–9 mSv dose group)			
	0 (non-nuclear workers)			RR = 0.61 (0.2–3.4)
	<5.0			RR = 1.45 (0.4–8.5)
	5–9			RR = 1.00
	10–49			RR = 1.21 (0.3–9.1)
	50+			RR = 1.61 (0.4–9.7)

Italic font indicates calculation was not presented in original study (95% CI estimates were calculated using the "mid-p test"; see "Methods")

Bold font indicates a statistically significant result

[a] In original study, SMR was multiplied by 100 and expressed as a %. We have divided by 100 for consistency

[b] 90% confidence interval

a heavy water extraction plant, nuclear fuel handling, target fabrication plants, test reactors, power plants, and laboratories. In the most recent study of this cohort, Richardson et al. [51] examined mortality in 18,883 workers hired between and 1950 and 1986 and followed through 2002. Risk was significantly increased for pleural cancer in men (SMR = 4.25, 90% CI: 1.99–7.97), and was highest in hourly paid workers or those working 30 years or more. They were also highest in those employed between 1985 and 1989 or between 2000 and 2002. Mesothelioma risk was based only on those who died between 1999 and 2002 because this cancer type was not separately coded prior to ICD-10. There were only two deaths during this 3-year period (both in men), and the risk in men was not elevated (SMR = 0.92, 90% CI: 0.16–2.89).

Boice et al. [52] examined cancer rates in nuclear technology development workers employed at seven Rocketdyne facilities in California between 1948 and 1999. At these facilities, activities included the research and development of nuclear energy, the fabrication of nuclear fuel (including plutonium and uranium), the disassembly and decontamination of reactor facilities, the decladding of spent nuclear fuel, and the storage of nuclear material. Of 5,801 workers in the study, 5,743 were monitored externally and 2,232 were also monitored internally for radiation. Rates of pleural and peritoneal cancer and mesothelioma were compared to the general population in California. Only one case was identified, leading to a non-elevated SMR of 1.01 (95% CI: 0.03–5.61).

The most recent study of Commissariat a l'Energie Atomique (CEA) workers in France (who were exposed to X- and γ-rays) was conducted by Telle-Lamberton et al. [53]. These investigators examined all-cause mortality in 58,320 workers employed and followed from 1946 to 1994. Cancer rates were ascertained between 1968 and 1994. While the all-cancer mortality rate was lower than that among the general population (SMR_{men} = 0.66, 95% CI: 0.63–0.69), the rates of pleural cancer were increased (SMR_{men} = 1.79, 90% CI: 1.27–2.45)—particularly in those 55 years of age and older (SMR_{men} = 2.09, 90% CI: 1.43–2.95).

Shilnikova et al. [54] examined cancer risk in ~18,800 workers at the Mayak Nuclear complex in Russia, who were hired between 1948 and 1972. There were 53 deaths in male workers from other respiratory (non-lung) cancer and three in female workers. Unfortunately, it is unknown how many, if any, of these were mesothelioma.

Omar et al. [55, 56] analyzed mortality in 14,319 workers employed at the Sellafield plant of British Nuclear Fuels (plutonium production and nuclear fuel reprocessing) between 1947 and 1976 and followed through 1992. Rates for pleural cancer were increased in plutonium workers (SMR = 471, $p < 0.001$) and for workers exposed to other forms of radiation (SMR = 390, $p < 0.05$), but not for non-radiation workers (no pleural cancers observed).

In the largest and most recent cohort study of radiation workers, Cardis et al. [57] examined cancer rates in 407,391 nuclear industry workers in 15 countries who were employed between 1943 and 2000 (employment and follow-up varied by country). Workers were individually monitored for external photon (X- and γ-) radiation exposure (range 100–300 keV). Cardis et al. [57] compared observed numbers of cancer in each dose category with expected numbers, calculated by "assuming that within stratum defined by levels of the stratification variables, the mortality rate in each dose category was the same as that of the entire stratum." Although 39 cases of pleural cancer were reported, this did not reach statistical significance

[excess relative risk (ERR) per Sv = 5.28, 90% CI: <0.0–39.9] and RR at 100 mSv was 1.53, and the dose-response relationship also did not reach significance. The ERR for pleural cancer, however, was one of the highest among all the cancers examined in this study.

In contrast to studies of patients receiving Thorotrast or radiotherapy, some of the workers described earlier could have also been exposed to asbestos. Although it cannot completely be ruled out as a confounder, it is unlikely that asbestos can completely explain the results for these workers because it is not expected that workers exposed to increasing levels of radiation should have increasing exposures to asbestos.

Discussion

Asbestos is generally accepted as a causal factor in the majority of mesotheliomas, but for the remaining cases, alternative factors appear to play a role. For example, there is no history of asbestos exposure in ~20% of male cases and the majority of female cases [29]. In many of these instances, ionizing radiation may play a causal role. Evidence for this comes from studies of individuals treated with Thorotrast or therapeutic radiation, as well as from studies of nuclear industry workers exposed to ionizing radiation. Not all of these studies reported statistically significant associations, but, as discussed below, when biological plausibility, information bias, statistical power, dose-response, and confounders are considered, the weight of evidence supports radiation being a causal factor for mesothelioma.

Ionizing radiation is a known human carcinogen and has been linked to many different tumor types [19]. Human and animal data support a role for ionizing radiation in mesothelioma [58]. The human evidence, reviewed earlier, suggests that ionizing radiation from α- and β-emitters (in Thorotrast treatment), γ-radiation (^{60}Co and X-ray radiotherapy), and γ-radiation from occupational exposures are all associated with increased mesothelioma risk (at equivalent doses, α-particles are more cytotoxic than γ-radiation and have been shown to induce more oncogenic transformations) [58]. The fact that mesothelioma risks were observed for different types of ionizing radiation exposures strengthens the evidence for a potential causal role of radiation.

Although the occupational studies reviewed here included up to millions of person-years, the number of individuals with mesothelioma in most studies is quite small [59]. Also, the majority of mesotheliomas result from asbestos exposure, so the number of cases attributable to other causes is even smaller. As discussed further below, many cases may have been misclassified, leading to even lower numbers. Finally, mesothelioma can have a long latency period—up to 41 years among cases reviewed here (Table 3). This could have led to mesothelioma cases being missed in studies that did not follow individuals long enough.

Studies of patients treated with Thorotrast generally had sufficient statistical power to detect an association between ionizing radiation and mesothelioma, but in groups of patients receiving radiation treatment, the number of individuals who develop mesothelioma may be small. This may be due to some patients not surviving the original cancer long enough for mesothelioma to be diagnosed [60]. In addition, primary tumor types (Table 3) generally occur in young patients [28] who have five times the risk of developing a second primary cancer [29]. Thus, the magnitude of the association between radiation and mesothelioma may be more significant than what was reported in the Thorotrast and radiotherapy studies reviewed here (Tables 2, 3).

It is noteworthy that mesothelioma, a rare disease, was consistently noted among studies of ionizing radiation, even though statistical significance was not always achieved. While not definitive evidence of causality, considering both case reports and mode of action, it is certainly suggestive.

A major source of misclassification of disease status stems from the lack of uniformity in the manner in which malignant mesothelioma is reported (Table 1). Pleural mesothelioma was not recognized as a specific cancer type until 1960, and peritoneal mesothelioma was not recognized until 1964 (arguably when the Surgeon General's 1964 report [61] on smoking raised awareness about the relationship between smoking and lung cancer) [62]. Mesotheliomas could have been recorded as fibrosarcoma, abdominal carcinomatosis, or adenocarcinoma metastatic to pleura [63]. This led to considerable misclassification of disease status, which in many cases was not resolved until death records or autopsy files were investigated manually [22].

Recent publications indicate that misclassification of disease status is not isolated to the US, or even historical reports in the literature. In a study of mesothelioma cases (all sites) listed in the Scottish cancer registry from 1981 to 1999, the ICD-9 code of 163 (malignant neoplasm of the pleura) was listed for only 40% of the confirmed mesothelioma cases [64]. This was slightly lower than the 55% detection rate reported in the UK mesothelioma registry from 1986 to 1991 [65]. This is also similar to an autopsy series study in Trieste, Italy, in which 45% of male cases of mesotheliomas may have remained undiagnosed on the death certificates [66]. It has also been noted that respiratory diseases (such as pneumonia) may have been entered in death certificates as the underlying cause of death when the true cause of death was a result of Thorotrast exposure [26]. These respiratory diseases may in fact have been mesothelioma [67].

Bias can also result from the misclassification of exposure. The majority of studies of patients treated with Thorotrast or radiotherapy compared risks in subjects who were treated versus those who were not. In studies where exposure status was dichotomous (exposed vs. not), it is unlikely that patients were misclassified. Determining the patients' actual exposures to ionizing radiation, however, is not necessarily clear cut, and could have biased results in dose-response analyses.

Accurate dosimetry and exposure assessment in workers occupationally exposed to radiation is less problematic because individuals who are employed in fields working with radiation are often externally monitored for photon, β, and neutron radiation using devices such as Kodak NTA film badges or TLD-based albedo dosimeters [50, 57]. While there may be some errors [68], these are generally minor, and do not substantially affect risk estimates (Inskip et al. 1987; Little et al. 1993; Shin et al. 2005, all as cited in Cardis et al. [57]).

The misclassification of disease is likely to be non-differential, and could bias results either toward or away from the null. In studies of patients treated with Thorotrast or radiotherapy, exposures to the target tissue are likely to be overestimated and likely biased results toward the null. Both of these types of misclassification bias could have led to inaccuracies in dose-response assessments.

Some of the epidemiology studies presented here attempted to determine a dose-response function, or a trend relating ionizing radiation exposure to the incidence of, or mortality from, mesothelioma. This type of analysis is historically problematic for ionizing radiation [58]. This partially stems from there being small numbers of exposed and/or diseased individuals in each study, leading to low statistical power.

Differentiating the carcinogenic versus the tumoricidal component of ionizing radiation dose to the target tissue from radiotherapy is challenging. The cumulative dose of external beam radiation therapy administered during therapeutic radiation (either focused beam or standard radiation therapy) is greater than the cumulative radiation dose that initiates malignant cell transformation. This would bias an observed association between radiation and mesothelioma toward the null [43]. Xu et al. [69] argued that larger epidemiology studies are needed to accurately quantify the risk in the low-dose region.

This is also true for Thorotrast. ThO_2 exposure from Thorotrast can vary among and within the organs by a factor of $\sim$100 [70]. In addition, the particles in the colloidal suspension can aggregate, facilitating significant self-absorption [71]. These chemical properties combined with varying levels of administered volumes, as well as incomplete records of the clinically administered dose, make historical dose-reconstruction efforts difficult.

As noted earlier, examining dose-response in radiation worker studies is potentially useful because exposure levels are generally known. Most studies that attempted to examine this, however, are underpowered in that there are too few subjects in each exposure group to assess whether an association exists. For example, in the 15-country study, Cardis et al. [57] reported an ERR of pleural cancer of 5.28 per Sv. Although not statistically significant (90% CI: <0.0–39.9), pleural cancers showed one of the highest absolute risks of all cancer types. Overall, however, these data are not sufficiently robust to determine dose-response relationships between ionizing radiation and mesothelioma risk.

Several other exposures/confounders may have influenced associations reported between ionizing radiation and mesothelioma, the most significant of which is asbestos. Asbestos has been linked to mesothelioma since as early as 1960, when 33 cases of pleural mesothelioma were discovered among residents of the northwestern Northern Cape Province in South Africa, 32 of whom had been occupationally exposed to amosite asbestos [71]. In the studies of Thorotrast and radiotherapy patients, it is unlikely that asbestos exposure differed by treatment regimen [43]. Asbestos is potentially a more problematic confounder in occupational studies, if it was present in the workplace.

In addition to asbestos-mediated carcinogenicity, other factors have been implicated in mesothelioma carcinogenicity. Fibers from volcanic rocks have been implicated in studies in Turkey [3] and the US [4]. Organic chemicals such as liquid paraffin have been shown to induce pleural malignant mesothelioma [7]. Beryllium (Be) [5, 6] and over a dozen other chemical and physiochemical agents have also been implicated [2]. Chronic irritation, inflammation, and infection may be potential confounding factors in some studies [8–10]. The DNA tumor virus, Simian Virus 40 (SV40), has also been implicated as a possible factor in the carcinogenicity of malignant mesothelioma (reviewed in Carbone et al. [72]). There is also evidence of genetic susceptibility [11].

Another potential confounder stems from cancer patients routinely receiving a tandem of chemotherapy, radiation therapy, and surgery to treat primary tumors. This combined modality therapy has the potential to alter patients' immune status and place them at additional risk of malignant mesothelioma [73]. At sufficient levels, ionizing radiation exposure is certainly a cancer risk. Due to lack of medical record information, it is often times not possible to determine whether confounders like immune status (HIV status or immunocompromised) and chemotherapy (type or dose) may have played a role in the progression of the disease. Given that malignant mesothelioma, as well as many of the tumor types listed in Table 3 (e.g., HL, Wilms' tumor, seminoma), are relatively uncommon, it is also

possible that that host factors may be playing a role in carcinogenesis [29].

The degree to which these confounders likely affected the interpretation of results varied among the epidemiology studies and the individuals being studied. Because there were many types of studies (e.g., case reports, case–control studies, cohort studies) and associations were noted among different types of exposures (Thorotrast, radiotherapy, occupational exposure), it is unlikely that these confounders completely explain all the reported associations between radiation and mesothelioma.

Conclusion

Statistically significant increases in mesothelioma risk have been observed in studies of individuals exposed to Thorotrast and radiation therapy. Studies of workers in the nuclear industry show fewer statistically significant associations, but were often limited by statistical power and information bias. The observation of mesothelioma risk in these studies, given the rarity of the disease in the general population, was notable. Although asbestos exposure is the primary cause of mesothelioma worldwide, it does not explain all cases [74, 75] and was accounted for in many of the studies reviewed here. Improved diagnostic methods to identify mesothelioma, coupled with proper coding, may result in the identification of additional radiation-associated cases and increased power to analyze this association. The weight of evidence from currently available data strongly suggests that ionizing radiation increases mesothelioma risk.

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