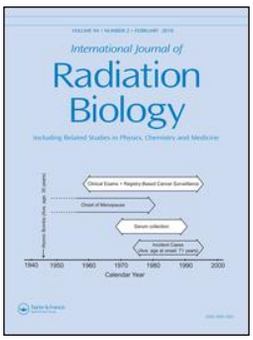

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ORIGINAL ARTICLE

Sex-specific lung cancer risk among radiation workers in the million-person study and patients TB-Fluoroscopy

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ABSTRACT

Background: The study of Japanese atomic bomb survivors, exposed briefly to radiation, finds the risk of radiation-induced lung cancer to be nearly three times greater for women than for men. Because protection standards for astronauts are based on individual lifetime risk projections, this sex-specific difference limits the time women can spend in space. Populations exposed to chronic or fractionated radiation were evaluated to learn whether similar differences exist when exposures occur gradually over years.

Methods and materials: Five occupational cohorts within the Million Person Study of Low-Dose Health Effects (MPS) and a Canadian Fluoroscopy Cohort Study (CFCS) of tuberculosis patients who underwent frequent chest fluoroscopic examinations are evaluated. Included are male and female workers at the Mound nuclear facility, nuclear power plants (NPP), and industrial radiographers (IR). Workers at the Mallinckrodt Chemical Works and military participants at aboveground nuclear weapons tests provide information on the risk among males. Cox proportional hazards and Poisson regression models were used to estimate sex-specific radiation risks for lung cancer and to compare any differences.

Results: Overall, 15,065 lung cancers occurred among the 443,684 subjects studied: 50,111 women and 395,573 men. The mean cumulative dose to the lung was 166.3 mGy (range 6 to 1,055 mGy) with the highest among the TB-fluoroscopy patients (mean 1,055 mGy). Mean lung dose for women in the worker cohorts was generally 4 times lower than for men. Of the 12 estimates of radiation-related risk, only one, for male IRs, showed a significant elevation (ERR 0.09; 95% CI 0.02–0.16, at 100 mGy). In contrast, the dose response for male NPP workers was negative (ERR −0.05; 95% CI −0.10, 0.01, at 100 mGy). Combined, these two cohorts provided little evidence for a radiation effect among males (ERR 0.01; 95% CI −0.04, 0.06, at 100 mGy). There was no significant dose-response among females within any cohort. There was no difference in the sex-specific estimates of lung cancer risk.

Conclusions: There was little evidence that chronic or fractionated exposures increased the risk of lung cancer. There were no differences in the risks of lung cancer between men and women. However, the sex-specific analyses are limited because of small numbers of women and relatively low doses. A more definitive study is ongoing of medical radiation workers which include 85,000 women and 85,000 men (overall mean dose 82 mGy, max 1,140 mGy). Additional understanding will come from the ongoing follow-up of the CFCS.

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Introduction

The evidence that low-LET radiation causes lung cancer comes mainly from acute high-dose-rate exposures and at moderate radiation doses (UNSCEAR 2008). The Japanese atomic bomb survivor study provides evidence for an increased radiation risk of lung cancer but also indicates that the risk of radiation-induced lung cancer is nearly three times greater for women than for men (Ozasa et al. 2012; NCRP 2014; Cahoon et al. 2017). In contrast, studies of tuberculosis patients undergoing frequent chest fluoroscopic examination to monitor lung collapse therapy in Canada and in Massachusetts have failed to find an increased risk of lung cancer despite lung doses that exceed those of the Japanese atomic bomb survivors (Davis et al. 1989; Howe 1995). It has not been clear why such differences exist. One possibility is that fractionation of dose over time results in lower risk than when the exposure is received in a short period of time (Fry 1996). This difference in sex-specific radiation lung cancer risk is of special interest to NASA which bases its protection standards on lifetime risk estimates for individuals based on the atomic bomb survivor study (NA/NRC 2012). Since women have a much higher risk of lung cancer on a relative

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scale than men, their lifetime risk estimates per unit dose are much higher and thus their time in space for long-term missions is limited.

Several radiation cohorts within the MPS have sufficient numbers of female workers to be able to contrast the risks among males with those among females. The studies evaluated here include the Mound facility workers in Ohio (Boice et al. 2014), nuclear power plant (NPP) workers (Boice, Cohen, Mumma, Hagemeyer, Chen et al. 2019), and industrial radiographers (IR) (Boice, Cohen, Mumma, Hagemeyer, Golden et al. 2019). These studies were analyzed in a similar fashion and radiation-related estimates of lung cancer mortality can be made for both males and females. Male workers at the Mallinckrodt Chemical Works (MCW) and participants at above-ground nuclear weapons tests (Boice, Till et al. 2019) were also included to provide additional estimates of lung cancer risk among males, and because a component of the lung dose among MCW workers comes from intakes of high-LET emitters (uranium and radium) (Ellis et al. 2018; Golden et al. 2019).

There are few studies that have focused on sex-specific differences in lung cancer radiation risks. The six studies selected for analysis in this paper were conducted by the authors; thus, the datasets could be analyzed for sex-specific lung cancer risks using the same methods. The studies preferentially included available cohorts within the MPS, the focus of this special issue. The total numbers, nearly 444,000 persons and broad dose distributions were recognized. Seven important studies could not be included, e.g. the study of Mayak workers, and are described in the discussion section. Several studies not explicitly discussed can be found in an informative summary of sex-specific differences by the German Commission on Radiological Protection (Strahlenschutzkommission 2009). Finally, since lung cancer has such a high case-fatality rate, the patterns for incidence would be expected to be similar to mortality investigations.

Materials and methods

Statistical methods

For the MPS cohorts, Cox proportional hazards models were used to compute hazards ratios (HR) and corresponding 95% confidence intervals (CI) for a continuous measure of radiation dose to the lung (Cox 1972). Age was used as the underlying timescale for the hazard function. To allow for a possible latent period between radiation exposure and any effect consequent to it, doses were lagged 10 years. All Cox models were conducted using SAS/STAT software (SAS/STAT software, Version 9.4 of the SAS System for Windows, SAS Institute Inc., Cary, NC, USA). Excess Relative Risks per Gy (ERR Gy^{-1}) along with corresponding CIs were estimated using the Peanuts program in Epicure (Preston et al. 2018). All models were adjusted for year of birth and a measure of socioeconomic status which varied by cohort and was either education level or pay type, such as hourly versus salary.

Further details of the analytic methods for the Canadian Fluoroscopy Cohort Study (CFCS) are available in Howe (Howe 1995). Briefly, standard Poisson regression models (Breslow and Day 1987) were used to compute relative risks and corresponding CIs for a continuous dose to the lung with a 10-year lag applied to account for a latent period. The Epicure program (Preston et al. 2018) was used to compute linear excess relative risks per Gy. All models included adjustment for age at risk, calendar year at risk, and sex by stratification.

For all cohorts, analyses were conducted within cohort except for the NPP and IR cohorts which were examined both individually as well as combined. This could be done with minimal bias because both populations were identified from the same databases, had the same covariates, and used the same procedures for obtaining and adjusting for socioeconomic status. Models were first stratified by sex and then combined over sex with further adjustment for male versus female. To test whether sex was an effect modifier, i.e. whether risk differed by sex, nested models with and without an interaction term between sex and radiation dose were compared using the likelihood ratio test (LRT).

Results and study descriptions

The occupational studies within the MPS and the CFCS studies are described below and in Tables 1–3.

Mound nuclear facility

The Mound Nuclear Facility near Dayton, OH, employed 7,270 workers during the years 1944–1971, including 4,954 workers monitored for radiation exposure (Boice et al. 2014; Tables 1–3). Among females, mean lung dose was 24.9 mGy and the maximum was nearly 1.5 Gy. There was no evidence for an increase in lung cancer deaths related to radiation (Tables 2 and 3). There was no increased risk in lung cancer mortality among the 971 female workers (ERR at 100 mGy$= -0.01$; 95% CI -0.07, 0.07) nor among the 3983 male workers (ERR at 100 mGy $= 0.01$; 95% CI -0.02, 0.04) (Table 2), and accordingly no difference in the sex-specific lung cancer risk estimates (LRT $p = .72$).

Nuclear power plant workers (NPP)

Over 135,000 workers first monitored at nuclear power plants in the United States from 1957–1984 were evaluated through 2011 (Boice, Till et al. 2019; Tables 1–3). There was no evidence for an increase in radiation-related lung cancer death, and the sex-adjusted dose response was negative and of borderline significance (ERR at 100 mGy$= -0.05$; 95% CI -0.10, 0.001). The mean dose to the lung was 40.5 mGy and ranged up to 1085 mGy. Overall, there were 4420 female workers and 130,773 male workers (Table 1). A radiation-related dose response was not seen for the female workers (ERR at 100 mGy $= 0.80$; 95% CI -0.96, 2.56) nor among the male workers (ERR at 100 mGy$= -0.05$; 95% CI -0.10, 0.01). The estimates of radiation risk for lung cancer mortality were not significantly different between females and males (LRT $p = .37$).

Table 1. Subject counts, lung cancer deaths and descriptive measures of dose, by cohort and sex.

Cohort	Females					Males				
	N subjects	N cases lung cancer deaths	Person-Years	Mean [Median] Dose, mGy	95th percentile [Maximum] Dose, mGy	*N* subjects	*N* cases lung cancer deaths	Person-Years	Mean [Median] Dose, mGy	95th percentile [Maximum] Dose, mGy
Mallinckrodt (Golden et al. 2019)	na	na	na	na	na	2514	157	107,920	67.3 [30.7]	273 [829]
Mound (Boice et al. 2014)	971	21	41,750	24.9 [1.6]	132 [1,460]	3983	182	159,771	112.9 [14.7]	555 [17,478]
Atomic Veterans (Boice, Till et al. 2019)	na	na	na	na	na	113,806	8027	5,350,400	6.21 [2.28]	25 [972]
Nuclear Power Plant (NPP) (Boice, Cohen, Mumma, Hagemeyer, Chen et al. 2019)	4420	48	131,642	17.9 [7.7]	75.7 [466]	130,773	3337	3,947,599	41.3 [21.4]	152 [1085]
Industrial Radiographers (IR) (Cohen, Mumma, Hagemeyer, Golden et al. 2019)	12,933	55	210,913	2.0 [0.02]	8.3 [302]	110,577	2060	2,427,345	12.0 [0.4]	67 [1,435]
Combined NPP and IR	17,353	103	342,555	6.1 [0.09]	35 [466]	241,350	5397	6,374,944	27.8 [9.8]	123 [1435]
TB Fluoroscopy – Canadian[a] (Howe 1995)	31,787	266	883,172	1072 [622]	4115 [9640]	31,920	912	725,318	1038 [617]	4210 [9280]

[a]Excludes person-years for age at risk <20 years and deaths and person-years at risk within 10 years of exposure.

Industrial radiographers (IR)

Over 123,000 industrial radiographers in the United States who were first monitored 1939–2011 were studied (Boice, Cohen, Mumma, Hagemeyer, Chen et al. 2019; Tables 1–3). The workers over the years were exposed only to external radiation and mainly iridium-192 and cobalt-60. The mean lung dose was 10.9 mGy and ranged up to 1435 mGy. The sex-averaged lung cancer risk estimate for mortality was significantly elevated (ERR at 100 mGy = 0.09; 95% CI 0.04, 0.19). There were 12,933 female industrial radiographers and 110,577 male radiographers (Table 1). The mean dose to the lung was 2.0 mGy for females and 12.0 mGy for males. The radiation risk estimates were non-significantly negative for females (ERR at 100 mGy= −0.33; 95% CI −0.45, 0.21) and significantly positive for males (ERR at 100 mGy = 0.09; 95% CI 0.02, 0.16). While a significant dose response was observed for radiation-induced lung cancer mortality among male radiographers, the difference in risk estimates between female and male workers was not significant (LRT $p = .43$).

The NPP and the IR worker studies were constructed using the same methodologies. The NRC REIRS database (NRC 2018) and the Landauer dosimetry records were used to select the study cohorts and the analytical and dosimetry approaches were exactly the same, including the adjustments for socioeconomic status based on areawide educational categories. A pooled analysis of these two cohorts was conducted to increase statistical power. The pooled analysis included 17,353 females and 241,350 males (Tables 1–3). There was no significant increase in the sex-adjusted radiation risk for lung cancer mortality (ERR at 100 mGy = 0.02; 95% CI −0.03, 0.07) overall, nor among females (ERR at 100 mGy = 0.16; 95% CI −0.49, 0.81) or males (ERR at 100 mGy = 0.01; 95% CI −0.04, 0.06). The pooled analysis did not support a radiation-related risk for lung cancer nor a statistically significant difference in sex-specific radiation lung cancer risk estimates (LRT $p = .86$).

Mallinckrodt chemical works

The Mallinckrodt Chemical Works (MCW) study evaluated 2514 white male workers employed 1942–1966 (Boice et al. 2018; Ellis et al. 2018; Golden et al. 2019; Tables 1–3). The workers over the years were exposed to external gamma radiation plus internal radiation from inhalation and ingestion of pitchblende dust (uranium, radium, and silica). Lung dose from occupational medical x-rays was included in the individual dose reconstructions as were ambient levels of radon and radon progeny. The mean dose to the lung was 67.3 mGy and ranged up to 829 mGy (Table 3). There was no evidence for a radiation dose response for lung cancer mortality (ERR at 100 mGy= −0.06; 95% CI −0.18, 0.06) and the negative trend was nearly significant. Because only males were included, the MCW study could not evaluate sex-specific radiation risks. It did suggest that chronic radiation exposures, including that from intakes of radionuclides that provide high-LET dose to lung tissue, is not associated with a detectable increase of lung cancer risk at the radiation

Table 2. Sex-specific excess relative risks (ERR) and hazard ratios (HR) at 100 mGy for lung cancer deaths, by cohort and sex.

	Females		Males	
Cohort	ERR at 100 mGy (95% CI)	HR at 100 mGy (95% CI)	ERR at 100 mGy (95% CI)	HR at 100 mGy (95% CI)
Mallinckrodt	na	na	−0.06 (−0.18, 0.06)	0.95 (0.81, 1.12)
Mound	−0.01 (−0.07, 0.07)	0.86 (0.48, 1.55)	0.01 (−0.02, 0.04)	1.01 (0.99, 1.03)
Atomic Veterans	na	Na	0.08 (−0.06, 0.22)	1.04 (0.90, 1.21)
Nuclear Power Plant (NPP)	0.80 (−0.96, 2.56)	1.80 (0.86, 3.78)	−0.05 (−0.10, 0.01)	0.96 (0.90, 1.02)
Industrial Radiographers (IR)	−0.33 (−0.45, 0.21)	0.69 (0.14, 3.49)	0.09 (0.02, 0.16)	1.09 (1.02, 1.17)
Combined NPP and IR	0.16 (−0.49,0.81)	1.17 (0.61, 2.24)	0.01 (−0.04, 0.06)	1.01 (0.97, 1.06)
TB Fluoroscopy – Canadian	−0.007 (−0.015, 0.002)	0.97 (0.81, 1.15)	0.002 (−0.003, 0.008)	0.96 (0.87, 1.057)

Table 3. Sex-adjusted ERR and HR at 100 mGy for lung cancer deaths by cohort, combined over sex.

Cohort	Total Subjects both sexes	Total Lung cancers deaths both sexes	Mean [Median] dose, mGy	95th percentile [Maximum] dose, mGy	Sex-adjusted ERR at 100 mGy (95%CI)	Sex-adjusted HR at 100 mGy (95%CI)	p^a
Mallinckrodt	2514	157	67.3 [30.7]	273 [829]	−0.06 (−0.18, 0.06)	0.95 (0.81, 1.12)	na
Mound	4954	203	95.6 [9.1]	442 [17,478]	0.01 (−0.03, 0.05)	1.01 (0.99, 1.03)	.72
Atomic Veterans	113,806	8027	6.21 [2.28]	25 [972]	0.08 (−0.06, 0.22)	1.04 (0.90–1.21)	na
Nuclear Power Plant (NPP)	135,193	3385	40.5 [20.9]	150 [1,085]	−0.05 (−0.10, 0.001)	0.96 (0.90, 1.02)	.37
Industrial Radiographers (IR)	123,510	2115	10.9 [0.3]	61 [1435]	0.09 (0.04, 0.19)	1.09 (1.02, 1.17)	.43
Combined NPP and IR	258,703	5500	26.4 [8.6]	119 [1435]	0.02 (−0.03, 0.07)	1.01 (0.97–1.06)	.86
TB Fluoroscopy - Canadian	63,707	1178	1055 [620]	4146 [9640]	0.00 (−0.005, 0.005)	0.96 (0.88, 1.05)	.097

[a]p-value from likelihood ratio test (LRT) for interaction between sex and dose in a Cox proportional hazards model with males and females.

doses received. A negative radiation dose response for non-malignant lung disease (Golden et al. 2019) provided some additional evidence that low-dose radiation exposures to the lung experienced over a period of years may be less carcinogenic than when the doses are received all at once and at a high level. The small numbers in this study, however, temper the strength of conclusions that might be drawn.

Nuclear weapons test participants (atomic veterans)

The United States conducted over 200 above-ground atmospheric weapons tests during the Cold War and many involved military personnel at the Nevada Test Site (NTS) and the Pacific Proving Grounds (e.g. Bikini Atolls) (Till et al. 2014; Caldwell et al. 2016; Beck et al. 2017; Tables 1–3).

The epidemiologic study of above-ground nuclear weapons test participants (atomic veterans) included 113,806 male military personnel who participated in weapons testing between 1945 and 1962. The atomic veterans are included as a component of the MPS that provides information on the radiation risk of death from lung cancer among males. Vital status was obtained for nearly 97% of the veterans and over 70% had died. There were 8027 deaths due to lung cancer. Overall, radiation doses to the lung were small, mean 6.21 mGy with a maximum of 972 mGy (Table 1). There was no statistical evidence for a radiation dose response over the very narrow range of lung doses (ERR 0.08; 95% CI −0.06, 0.22; at 100 mGy).

Canadian fluoroscopy cohort study (CFCS)

A lung cancer mortality study was conducted between 1950–1987 among 64,172 Canadian tuberculosis patients who received multiple chest fluoroscopic examinations during the monitoring of lung collapse therapy (Sherman et al. 1978; Howe and Yaffe 1992; Howe 1995; Tables 1–3). The current analyses are based on the previously published data (Howe 1995) using Poisson and Cox regression models. There were 31,917 female patients and 32,255 male patients (Table 1). The mean dose to the lung was 1055 mGy and the maximum was 9640 mGy (Table 3). Overall there was no evidence for a radiation-related increase in lung cancer among either females (ERR at 100 mGy= −0.007; 95% CI −0.015, 0.002) or males (ERR at 100 mGy = 0.002; 95% CI −0.003, 0.008) (Table 2). There was no difference between the sexes in their risk of radiation-induced lung cancer (LRT $p = .097$). These data are consistent with the Massachusetts TB-fluoroscopy study which also did not find a radiation-related risk for lung cancer (Davis et al. 1989; Brenner et al. 2007).

Socioeconomic status (SES)

SES was adjusted for in the analysis as a surrogate for demographic and lifestyle factors such as cigarette smoking (Wakeford 2005). SES was defined for each cohort as follows: for Mallinckrodt, it was pay code (Hourly vs. Salary); for Mound, it was self-reported educational achievement; for NPP and IR it was educational achievement based on census block group data; for Atomic Veterans, it was rank (Enlisted vs. Officer). The importance of this adjustment was clear in that significant SMRs for lung cancer were seen among workers categorized in the lowest SES levels and deficits were seen in the highest SES categories (e.g. Boice, Till et al. 2019; Golden et al. 2019).

Analyses were conducted (not shown) of the HRs at 100 mGy by SES status to learn whether there was a tendency for radiation risks to differ by SES status overall and by sex. There were no statistically meaningful differences by SES status or by sex, but the statistical variability was large.

More robust analyses will await the completion of the medical radiation worker study, and the Los Alamos National Laboratory and Rocky Flats cohort studies that have substantial numbers of workers, broad dose distributions and much larger numbers of female workers.

Discussion

There are few studies, that have focused on sex-specific differences in lung cancer radiation risks. Seven studies with estimates of sex-specific lung cancer risks are briefly summarized below: Massachusetts TB- fluoroscopy patients (Boice et al. 1978; Davis et al. 1989; Brenner et al. 2007); scoliosis patients (Ronckers et al. 2010); Hodgkin lymphoma patients (Gilbert et al. 2003); and workers within the Mayak (Gilbert et al. 2004, 2013; Gillies et al. 2017), INWORKS (Richardson et al. 2018) and Rocketdyne (Boice et al. 2011) studies.

Summaries of other published studies

TB- Fluoroscopy Massachusetts study

The Massachusetts TB-fluoroscopy mortality study included 13,385 patients treated between 1925–1954 (Boice et al. 1978; Davis et al. 1989; Brenner et al. 2007; Little 2018). The patients received an average of 77 x-ray fluoroscopic examinations, and the mean dose to lung tissue was 840 mGy. Risks were not reported for women and men separately. Lung cancer (SMR 0.8, $n = 69$) was not elevated despite a range of doses to the lung that reached over 8000 mGy; there was no evidence of a dose response. Adjustments for smoking and the amount of lung tissue at risk did not appreciably modify these observations. The authors concluded that frequent exposures to low doses of radiation over a period of several years did not increase the risk of lung cancer and that fractionated exposure appeared less effective in causing lung cancer than a single exposure of the same total dose.

U.S. Scoliosis study

The U.S. Scoliosis Study includes 5573 female patients monitored with frequent spinal x-rays for curvature changes during the adolescent growth spurt and before 20 years of age, 1912–1965 (Hoffman et al. 1989; Ronckers et al. 2010). The average number of x-rays was 22.9 and ranged up to 553. The average cumulative lung dose was 41 mGy and the maximum was 676 mGy. Breast cancer mortality was significantly elevated. Lung cancer mortality (SMR 0.8, $n = 57$), however, was not elevated; and the dose response was negative (ERR Gy^{-1} −1.4; 95% CI −7.1, 3.1). These results are identical to the Canadian and Massachusetts TB-fluoroscopy studies where significant positive dose-response relationships for breast cancer were observed (Boice et al. 1979) but evidence for increased lung cancer risk was absent (Davis et al. 1989; Howe 1995). These three studies of patients monitored with diagnostic radiation examinations for many years are not consistent with the Japanese study of atomic bomb survivors exposed acutely to radiation where strong relationships where found for both breast and lung cancer (Preston et al. 2002; Cahoon et al. 2017). Possible explanations raised by the authors of the scoliosis studies for these discrepancies in lung cancer findings included a low-dose threshold or non-linear radiation dose response when doses are fractionated, or failure to adequately control for the carcinogenic effects of smoking (Ronckers et al. 2010).

Rocketdyne workers

The Rocketdyne (Atomics International) study involved 46,970 workers employed 1948–1999 (Boice et al. 2011). Overall, 5801 workers were monitored for radiation activities (Boice et al. 2006). The mean dose to lung from external and internal radiation combined was 19 mSv (maximum 3600 mSv). Overall, there was no evidence for a radiation-associated risk for lung cancer mortality, i.e. the trend for lung cancer risk over categories of cumulative dose to the lung was negative but not significant. The RR at 100 mSv for lung cancer was estimated to be 1.01 (95% CI 0.89, 1.16). There was limited ability to evaluate sex-specific lung cancer radiation risk because only 8% of the population was female. The Rocketdyne study provides little evidence that fractionated exposures to the lung experienced over years is related to lung cancer risk. The study is limited by small numbers, but the dose range was broad and much of the high lung doses among workers came from intakes of radionuclides emitting high-LET alpha particles.

Hodgkin lymphoma patients

Cancer incidence studies of patients with Hodgkin lymphoma, treated with chest radiotherapy (Travis et al. 2002; Dores et al. 2002; Gilbert et al. 2003), provide evidence that high-dose radiotherapy causes lung cancer but not for risk differences by sex. The data for lung cancer were obtained within a population-based cohort of 19,046 Hodgkin lymphoma patients diagnosed from 1965–1994. Radiation dose was determined to the specific location in the lung where cancer developed, and tobacco use was adjusted for in the analyses. The mean dose to the lung was 36 Gy from the mantle radiotherapy received. Practically all radiotherapy doses to the lung were >5 Gy. Seventy-five percent of the patients with lung cancer within the nested case-control study were male and 25% were female. The radiation-related risk of lung cancer for the patients receiving >5 Gy was four times higher for males (RR 7.2; 95% CI 3.0, 18.6) than for females (RR 2.1; 95% CI 0.6, 11.5) but this difference was not statistically significant. This comprehensive study of lung cancer risk following radiotherapy at high doses provides no evidence for a difference in the sex-specific risk for radiation-induced lung cancer. The actuarial risk of lung cancer at 25 years after treatment was significantly higher in males (6.2%; 95% CI 5%, 7.4%) than females (3.2%; 95% CI 2.2%, 4.2%), although the radiation component was not separated from the entire cohort (Dores et al. 2002). The relevance of such very high doses to low-dose risk assessment is unclear.

UK national registry for radiation workers (NRRW)

The UK NRRW study includes 167,003 workers followed for 32 years and recently updated (Haylock et al. 2018). The overall mean lifetime external dose was 25.3 mSv, and higher among the 150,566 male workers (27.5 mSv) than among the 16,437 female workers (5.6 mSv). Nearly 25% of the workers were monitored for intakes of radionuclides such as plutonium, uranium, and tritium, but only the fact of monitoring was known, and internal doses were not included in the analyses. There were no statistically meaningful risks of lung cancer seen either for mortality (ERR $Sv^{-1} = 0.028$; 95% CI −0.44, 0.63; $n = 3058$) or for incidence (ERR $Sv^{-1} = 0.13$; 95%CI −0.35, 0.72; $n = 3263$). Cancers of the brain and mouth were significantly low whereas cancer of the rectum and bladder were significantly high. Cancer of the pleura (likely mesothelioma) was significantly based on incidence data. No sex-specific analyses were presented. There was no statistical evidence that cancer of the lung was associated with occupational external radiation, however the inability to take intakes of radionuclides into account tempers the strength of this observation.

Inworks

The INWORKS occupational mortality study consists of 308,297 nuclear workers in France, the United Kingdom, and the United States (Richardson et al. 2018). Overall there were 268,262 male workers and 40,035 female workers. The mean (and 95th percentile) cumulative lung doses were 22.8 mGy (106.3 mGy) for men and 4.8 mGy (18.8 mGy) for women. There were 5802 lung cancer deaths. The maximum likelihood estimate of excess relative risk per Gy for lung cancer mortality was 0.51 (90% CI 0.00, 1.09). A 10-year lag was applied; the risk was sex-adjusted but sex-specific estimates were not presented. A hierarchical Bayesian analytical method was also applied to estimate ERR Gy^{-1} with slightly higher risk estimates for lung cancer than provided by the maximum likelihood approach. The individual site-specific estimates in INWORKS are difficult to interpret because very high and statistically significant risks were seen for sites not found or rarely found to be increased following radiation exposures such as cancer of the rectum, peritoneum, pleura and mesothelioma, testis, larynx, and skin (e.g. melanoma), whereas sites that are frequently increased following radiation exposure were not, such as cancers of the colon, liver, bladder, and kidney (UNSCEAR 2008).

15-Country study

For completion, the 15-Country study reported an ERR $Sv^{-1} = 1.86$ (90% CI 0.49, 3.63) overall, and an ERR $Sv^{-1} = 1.87$ (90%CI 0.50, 3.66) for male workers and an ERR $Sv^{-1} = -1.04$ (90% CI <0, 11.1) for female workers (Cardis et al. 2007). Confounding by asbestos exposure is a concern as when cancer of the pleura was excluded from the analyses, the ERR Sv^{-1} was no longer significantly different from zero. Other uncertainties have tempered the conclusions that might be drawn (Wakeford 2005; NCRP 2012). Further, the large U.S. and U.K. components within the 15-Country study are also included in INWORKS, so results are not independent.

Mayak nuclear facility workers

A mortality study of lung cancer was conducted among 14,621 Mayak workers who were hired between 1948-1982 (Gilbert et al. 2004, 2013; Gillies et al. 2017). Significant differences between the female and male ERR Gy^{-1} for lung cancer for intakes from plutonium were reported with females being 4 times higher for mortality (Gillies et al. 2017). For internal dose, the excess absolute risk (EAR) for females was less than half that for males (Gilbert et al. 2004). The lung cancer risk estimates from gamma exposure were, on the other hand, 2–3 times lower than comparable risks in the Japanese atomic bomb survivor study (Preston et al. 2017). Interpretation, however, is challenging for several reasons including the differences in smoking prevalence: 74% of male workers smoked and only 5% of female worker smoked and ERR Gy^{-1} risks varied significantly by smoking status (Gillies et al. 2017); the overall lost-to-follow-up rate was high at 22% (Preston et al. 2017); it is challenging to separate out a gamma ray component to risk for workers who also had significant plutonium intakes; and the estimates of plutonium dose were based on incomplete coverage of only 42% of the workers employed at the plutonium facilities (Gillies et al. 2017). Further, 'A particularly important limitation of our lung cancer risk estimates relates to intrinsic difficulties in estimating doses from plutonium exposure. Despite extensive efforts by Russian and non-Russian dosimetrists, these doses are subject to many uncertainties including especially those resulting from imprecision in the urine measurements. Only 33% of the 6540 workers with estimates of positive plutonium doses had more than two measurements, although this percentage was higher (51%) for workers with estimated plutonium doses exceeding 0.2 Gy. For most workers, these measurements were taken many years after the exposure occurred, since routine plutonium monitoring did not begin until about 1970. Such measurement errors, often referred to as classical errors, are known to bias the dose-response coefficient toward zero and might also distort the shape of the dose-response' (Gilbert et al. 2013). In a comparable but much less powerful study of Sellafield workers, there was no difference in the male and female risk estimates (Gillies et al. 2017).

When the analysis of Mayak workers was restricted to workers who received <200 mGy, there was no difference in the male and female estimates of risk (Gillies et al. 2017). The mean dose to gamma-rays was 455 mGy (maximum 7595 mGy). The mean dose from plutonium-239 was 129-176 mGy (maximum 16,500-19,700 mGy). The differences related to the plutonium doses depends on whether the biokinetic models assumed either a slow clearance or a fast clearance from the lung, that is related to solubility. When the ERR Gy^{-1} analyses were allowed to depend on smoking status, the plutonium ERR Gy^{-1} for non-smokers was significantly greater than that for smokers which suggested a sub-multiplicative relationship. While the ERR Gy^{-1} for

non-smokers was estimated to be four times that for smokers, the female/male ratio was estimated to be 1.0 (95% CI 0.3, 3.4). That is, when the plutonium ERR Gy^{-1} was allowed to depend on smoking, the ratio of female and male risk estimates was reduced from 3.3 to 1.0. The study does raise the issue as to the most appropriate scale for comparisons: the excess relative risk which depends on the background rates or the absolute excess risk which depends less so. This is a remarkably comprehensive and important study regarding the risks of high-dose plutonium and high-dose gamma exposures, but there remains some uncertainty in the estimated radiation risks and in the risks of sex-specific radiation-induced lung cancer.

Japanese atomic bomb survivor study

The study of Japanese atomic bomb survivors provides strong evidence that acute exposures to ionizing radiation can lead to an increased risk of lung cancer. Females are reported to be at 2–3 times higher risk of radiation-induced lung cancer than males (Preston et al. 2007; Furukawa et al. 2010; Ozasa et al. 2012; Cahoon et al. 2017). The lung cancer incidence analyses showed that lung cancer risk strongly depended on smoking patterns, with radiation risk highest for those smoking 10 cigarettes per day and approaching no risk at 20 cigarettes per day. Most men smoked whereas most women did not. The female to male incidence ratio of excess risk decreased with increasing radiation dose. Application of these risk estimates to American workers, and to the NASA astronaut corps (NCRP 2014), is somewhat problematic because of the different population characteristics and circumstances: the Japanese population was exposed briefly in 1945 to the atomic bombings in Hiroshima and Nagasaki and lived in a war-torn country for many years after (NCRP 2014; Boice 2017).

The most recent analyses evaluated cancer incidence from 1958–2009 (Cahoon et al. 2017). There were 105,444 survivors evaluated of whom a little over 86,000 had estimates of radiation dose. For non-smokers, the ERR Gy^{-1} estimate for lung cancer was 0.81 (95% CI 0.15, 1.18) and the female to male ratio was 2.83. The estimate of risk was significantly high for low-to-moderate smokers and no radiation risk was apparent for heavy smokers. Smoking information was available for 64,465 subjects (81%). For those with information on smoking, 86% of men and 18% of women indicated that they had ever smoked. The authors mentioned that the results should be interpreted in the context of several limitations, e.g. smoking history was unknown for ≈40% of the lung cancer cases and ≈60% of the follow-up time. It was also peculiar that no or very low radiation risks were seen for those who smoked heavily whereas moderate smokers had the highest radiation risk for lung cancer, as previously reported (Furukawa et al. 2010, 2017).

The mortality data (Ozasa et al. 2012) are more comparable to our mortality studies of worker populations and TB-fluoroscopy patients, although not of the diagnostic quality of that for incidence data. The Japanese mortality data are more complete than the incidence data in the sense that the entire country of Japan after 1950 was covered for death determinations, whereas the two cancer registries in Hiroshima and Nagasaki began in 1958 and could not include the entire country for incidence determinations. The mortality analyses focused on the 86,611 lifespan study cohort members with dose estimates. The sex-averaged ERR Gy^{-1} was 0.75 (95% CI 0.51,1.03). The ERR Gy^{-1} was greater among females (1.1; 95% CI 0.68, 1.6) compared with males (0.40; 95% CI 0.17, 0.67). The male to female ratio was 2.7 (95% CI 1.3, 6.8). The excess absolute risk (EAR) ratio of females to males was 0.98 (95% CI 0.40, 1.8), indicating the importance of background rates of disease when making inferences on 'risk differences'.

Animal Experiments

An informative review of experimental studies on sex-specific difference can be found in Strahlenschutzkommission (2009). Only a brief overview is presented here. There is clear evidence in experimental studies that low dose-rate exposures are less effective in causing lung cancer than are high dose-rate exposures (Ullrich and Storer 1979a, 1979b; Ullrich et al. 1987; Fry 1996; NRC 2006, Figure 10b-1). The evidence for high-LET exposures, such as neutrons, is not as apparent (Ullrich et al. 1976, 1977; Storer et al. 1979; Storer and Ullrich 1983; Storer and Fry 1995; Heidenreich et al. 2006). Interestingly, the relative risk estimates for man and mouse for lung tumors were not significantly different (Storer et al. 1988). Apparently, for low-LET radiation, low-dose rates consistently result in dose-response relationships and risks significantly lower than that observed for acute or higher-dose rate exposures (Ullrich et al. 1976, 1987; Ullrich and Storer 1979a, 1979b; Ullrich et al. 1987, 1976). However, the evidence that male and female risk estimates differ is not clear and depended upon mouse strain, dose rate, and radiation quality. To evaluate more fully the information available from animal experiments as well as in humans, NCRP has assembled scientific committee (SC 1-27), entitled 'Sex-Specific Differences in Lung Cancer Risks and Guidance on Modification of Lifetime Risk Projections.'

The current study computed sex-specific lung cancer risks for occupational cohorts within the MPS and for TB patients who received frequent chest fluoroscopic examinations. Insights and preliminary conclusions can be drawn as to sex-specific radiation-related lung cancer risks when exposure is protracted or fractionated over time.

Six cohort analyses of occupational and patient exposures showed little evidence that prolonged or fractionated exposures increase the risk of lung cancer. Further, there were no significant differences in the radiation risk estimates between men and women, although the small numbers of females temper the strength of this conclusion. These data for low-LET radiation are consistent with studies of Hodgkin lymphoma patients and Rocketdyne workers. They are also consistent with animal studies showing a marked reduction in risk when low-LET radiation dose is delivered at a low rate, i.e. spread over time. The studies providing evidence for a sex-specific difference in lung cancer risk are those of the Japanese atomic bomb survivors and the study of Mayak

workers exposed to exceptionally high doses of plutonium and to relatively high doses from gamma-rays. Animal studies do not consistently find an ameliorating effect of protracted radiation on lung cancer risk when the exposures are to neutrons.

These data suggest that for low-LET radiation, chronic or fractionated exposures to radiation have little effect on increasing lung cancer risk among either men or women. Further, the new analyses of the occupational cohorts and the TB-fluoroscopy patients find no evidence for any differences in lung cancer risk between men and women. The reduction in lung cancer risk with protracted exposures is not seen in studies of radiation-induced breast cancer (Preston et al. 2002) and suggests that different tissues respond differently to the carcinogenic effects of chronic or fractionated exposures. Interestingly, the TB-fluoroscopy studies showing minimal radiation risk for lung cancer (Davis et al. 1989; Howe 1995) are the same studies showing, on an absolute scale, that breast cancer risk is not appreciably influenced by fractionation of dose (Miller et al. 1989; Boice et al. 1991). Similar observations of a significant breast cancer risk and the absence of a lung cancer risk are seen in the U.S. Scoliosis Study (Ronckers et al. 2010).

Of the six cohorts evaluated, the most informative on sex-specific lung cancer risk is the Canadian TB-fluoroscopy study because of the large numbers of females ($n = 31,917$) and the high mean cumulative dose to lung, 1072 mGy (Table 1). In contrast, the number of women in the other cohorts ($n = 18,324$) is 40% fewer and the mean lung doses much lower (from 2 to 24.9 mGy). The lower mean lung dose is related in part to the higher percentages of low dose subjects. The broad dose distributions are not reflected in the low mean dose as women received up to 300–1470 mGy; dose-response analyses could be conducted and risk estimates per 100 mGy could be made. Tables 2 and 3 indicate the consistency of the radiation risk estimates among the CFCS and the other five cohorts. The male-specific radiation risk estimates are spot on with few discernable differences. The female-specific differences are not as clear, in part because of the wide confidence intervals about the point estimates. Although the confidence intervals are narrower for the CFCS compared with the other studies, all female lung cancer radiation risks estimates are statistically compatible with each other. Nonetheless, while it seems justified to suggest that there may be a lowering of lung cancer radiation-related risk when the dose rate is chronic and not acute, the sex-specific differences are not so convincing, in part due to small numbers of women and the associated generally lower lung doses. Thus, strong conclusions cannot be made about whether there are or are not any sex-specific differences in lung cancer mortality based on these studies. These data, however, will be strengthened when several ongoing MPS cohorts are completed, specifically the medical radiation workers and the worker cohorts at the Los Alamos National Laboratory and the Rocky Flats plant for which large numbers of women ($n > 100,000$) and broad dose distributions are currently under study.

Strengths and weaknesses

The studies included in these analyses have been comprehensive, and the epidemiologic methods and approaches for dose reconstruction described (NCRP 2018a; NCRP 2018b). The follow-up rate was over 95% overall and the cause of death determination nearly complete. The causes of death were obtained in the same manner by the same investigators relying upon state and national death information in the United States for the occupational cohorts (Mumma et al. 2018). The numbers are large, with 443,684 individuals and 15,065 lung cancer deaths. The dose distribution was broad with mean lung doses ranging from 6 mGy to >1,000 mGy. The dose reconstruction procedures for each occupational cohort followed guidance found in NCRP Report 178 (NCRP 2018a) by essentially the same team of investigators. The TB-fluoroscopy studies have been ongoing for over 40 years with a focus on dose reconstruction, follow-up and death ascertainment. The findings of the TB-fluoroscopy studies with regard to breast cancer have been influential in understanding radiation risks and guiding protection guidance (Upton et al. 1977; NCRP 2018b).

Nonetheless, there are limitations that temper the strength of conclusions that can be drawn. First, despite the larger number of women (50,111) and their high mean cumulative dose to lung (677.1 mGy), the statistical power to discern sex-specific differences is low, in part because only one of the 12 sex-specific estimates of risks was significantly different from the null and tests to compare 'no effect' to 'no effect' are not very informative. Secondly, information on smoking histories was incomplete or not available. In the absence of individual data on tobacco use, it is important to have good measures of SES that can be used in the analyses as an adjustment for likely cigarette use. We used the best measures of SES available for each cohort. Nonetheless, such an adjustment cannot be expected to be completely successful (Wakeford 2005). For the occupational studies, education or job category were taken as measures of socioeconomic status and as an indirect way to account for lifestyle and behavior factors, but there remains some uncertainty as to the effectiveness of this adjustment to adequately control for smoking. A small interview study of Rocketdyne workers did confirm that hourly workers compared with salaried workers were significantly more likely to have smoked cigarettes, to start at a younger age, to quit at an older age, and to smoke for more years (Boice et al. 2006). Cigarette use was available for a fraction of subjects in the TB-fluoroscopy studies. In the CFCS, there was little variation in the prevalence of smoking by dose category, and thus smoking was not considered a confounder of the radiation risks of lung cancer (Howe 1995). Thirdly, because of the relatively small numbers exposed to intakes of radionuclides, the studies could not powerfully evaluate lung cancer risk following high-LET exposures except perhaps for the Mound study which involved intakes of polonium and relatively high doses to lung. Other studies initiated or planned within the MPS will be able to address high-LET exposures more powerfully, such as the plutonium workers at the Los Alamos National Laboratory (Wiggs et al. 1994), the Rocky Flats Nuclear Weapons Plant

and the Hanford site (Gilbert et al. 1993), and the uranium workers at the Fernald Feed Materials Production Center (Silver et al. 2013) and the Linde Air Products Company Ceramics Plant (Dupree et al. 1987).

The study of Japanese atomic bomb survivors continues to show a risk of radiation-induced lung cancer and a substantial difference between male and female risks. These observations could be causally related to acute exposures or perhaps related to uncontrolled confounding or incomplete smoking ascertainment, perhaps because few Japanese women smoked whereas most men smoked. Consistent with animal experiments a very brief exposure, or high dose-rate exposure, appears to carry more risk than a similar dose to the lung that is received gradually over time, or at a low dose rate. The Mayak study is exceptionally powerful and comprehensive but interpretations are with caution given the uncertainties in the dose reconstructions and to the possible influence of the very high lung doses that caused deterministic effects (tissue reactions), e.g., pulmonary fibrosis (termed plutonium pneumosclerosis) (Okladnikova et al. 1994). Conceivably the influence of such high doses might be different than that of lower doses as suggested in the companion study of the Sellafield workers who received very much lower doses and had little evidence of a lung cancer risk (Gillies et al. 2017).

More work could be done with regard to evaluating the excess absolute risks (EAR Gy^{-1}) in addition to the excessive relative risks (ERR Gy^{-1}) per unit radiation dose. When differences in radiation risks between men and women are reported, they usually are based on a relative risk scale which is related more strongly to the background disease rate than an absolute risk scale.

Conclusion

These analyses and evaluations provide little evidence that chronic or fractionated exposures to radiation increase the risk of radiation-induced lung cancer. Further, there was no evidence that radiation-related lung cancer risks differed between women and men. However, these conclusions are preliminary and limited by relatively small numbers of women who received relatively high doses. The findings, however, are supported by other epidemiologic studies that also fail to find a statistically meaningful increase in lung cancer risk: workers at Rocketdyne, in the UK NRRW, INWORKS, 15-Country Study, and patients receiving medical radiation for scoliosis, Hodgkin lymphoma, and to monitor lung collapse among Massachusetts TB patients. Lung cancer risk following high-LET exposures was evaluated in three MPS cohorts, i.e. Mound, Mallinckrodt and Rocketdyne, but numbers and doses were not sufficient to make strong conclusions. Ongoing studies will be more informative. The ongoing study of medical radiation workers within the MPS includes 85,000 women and 85,000 men and will provide substantial information as to the effectiveness of gradual exposures over time to cause lung cancer and to determine whether such exposure results in different radiation lung cancer risks between men and women (Boice 2017; Yoder et al. 2018). The CFCS of 64,000 patients includes equal numbers of men and women exposed at all ages. It is currently being updated for mortality and incidence and should provide essentially lifespan follow-up of the cohort.

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