The epidemiology of lung cancer following radiation exposure

Lydia B. Zablotska, David B. Richardson, Ashley Golden, Elisa Pasqual, Brian Smith, Estelle. Rage, Paul A. Demers, Minh Do, Nora Fenske, Veronika Deffner, Michaela Kreuzer, Jonathan Samet, Stephen Bertke, Kaitlin Kelly-Reif, Mary K. Schubauer-Berigan, Ladislav Tomasek, Charles Wiggins, Dominque Laurier, Iulian Apostoaei, Brian A. Thomas, Steven L. Simon, F. Owen Hoffman, John D. Boice Jr., Lawrence T. Dauer, Sara C. Howard, Sarah S. Cohen, Michael T. Mumma, Elizabeth D. Ellis, Keith F. Eckerman, Rich W. Leggett & David J. Pawel

Published online: 22 Aug 2022.

Submit your article to this journal ⤤

View related articles ⤤

View Crossmark data ⤤

Taylor & Francis
Taylor & Francis Group

Check for updates

MEETING REPORT

The epidemiology of lung cancer following radiation exposure

Lydia B. Zablotska[a], David B. Richardson[b], Ashley Golden[c] (iD), Elisa Pasqual[d], Brian Smith[e], Estelle. Rage[f],
Paul A. Demers[g], Minh Do[g], Nora Fenske[h], Veronika Deffner[h], Michaela Kreuzer[h], Jonathan Samet[i],
Stephen Bertke[j], Kaitlin Kelly-Reif[j], Mary K. Schubauer-Berigan[k] (iD), Ladislav Tomasek[l], Charles Wiggins[m,n],
Dominque Laurier[f] (iD), Iulian Apostoaei[o], Brian A. Thomas[o], Steven L. Simon[d], F. Owen Hoffman[o],
John D. Boice, Jr.[p,q], Lawrence T. Dauer[r] (iD), Sara C. Howard[c], Sarah S. Cohen[s], Michael T. Mumma[t] (iD),
Elizabeth D. Ellis[c] (iD), Keith F. Eckerman[u], Rich W. Leggett[v], and David J. Pawel[w]

aDepartment of Epidemiology & Biostatistics School of Medicine, University of California, San Francisco, CA, USA; bEnvironmental and
Occupational Health, Program in Public Health, Susan and Henry Samueli, College of Health Sciences, University of California, Irvine, CA,
USA; cOak Ridge, Oak Ridge Associated Universities, Tennessee, USA; dDivision of Cancer Epidemiology and Genetics, National Cancer
Institute, Rockville, MD, USA; eDepartment of Biostatistics, College of Public Health, University of Iowa, Iowa City, Iowa, USA; fFontenay-Aux-
Roses, Institute for Radiological Protection and Nuclear Safety (IRSN), France; gOccupational Cancer Research Centre, Toronto, Canada;
hFederal Office for Radiation Protection (BfS), Munich (Neuherberg), Germany; iColorado School of Public Health, Aurora, Colorado, USA;
jNational Institute for Occupational Safety and Health, Cincinnati, OH, USA; kInternational Agency for Research on Cancer (IARC), Lyon,
France; lNational Radiation Protection Institute, Prague, Czech Republic; mDepartment of Internal Medicine, Division of Epidemiology,
University of New Mexico, Albuquerque, NM, USA; nNew Mexico Tumor Registry, Albuquerque, NM, USA; oOak Ridge Center for Risk
Analysis, Inc, Oak Ridge, TN, USA; pDivision of Epidemiology, Department of Medicine, Vanderbilt Epidemiology Center and Vanderbilt-
Ingram Cancer Center, Nashville, TN, USA; qNational Council on Radiation Protection and Measurements (NCRP), Bethesda, MD, USA;
rMemorial Sloan Kettering Cancer Center, New York, NY, USA; sEpidStrategies, Cary, NC, USA; tInternational Epidemiology Institute, Rockville,
Maryland, USA; uEasterly Scientific, Knoxville, Tennessee, USA; vOak Ridge National Laboratory, Oak Ridge, Tennessee, USA; wEnvironmental
Protection Agency, Washington DC, USA

Introduction

Epidemiological studies of occupational, medical, and environmental exposures have provided important information on lung cancer risk and how those risks might depend on the type of exposure, dose rate, and other potential modifying factors such as sex and age of the exposed. Analyses of data from underground miner cohorts and residential case-control studies provide convincing evidence that radon is a leading cause of lung cancer. For low-LET radiation, risk models derived from results from the Lifespan Study of Japanese atomic bomb survivors suggest that for acute exposures, lifetime attributable risks for lung cancer are greater than for other specific cancer sites and are substantially larger for females than males. However, for protracted and fractionated exposures other than from radon, results from epidemiological studies are seemingly often contradictory.

This report includes summaries of oral presentations during a symposium on radiogenic lung cancer risk given by a panel of experts on October 5 during the Radiation Research Society's 67th annual meeting. This session included presentations on: 1) the largest pooled study of male uranium miners (PUMA) exposed to radon; 2) the most recent analysis of the Canadian Fluoroscopy cohort featuring state-of-the-art dosimetry for radiation exposures associated with frequent medical diagnostic procedures; 3) an update from the Million Person Study on risks from fractionated occupational exposures, and 4) studies of second primary malignancies – including lung cancer – in patients who had been treated for thyroid cancer.

Low-level radon exposure and lung cancer in the pooled uranium miners analysis (PUMA)

D. B. Richardson, E. Rage, P. A. Demers, M. Do, N. Fenske, V. Deffner, M. Kreuzer, J. Samet, S. Bertke, K. Kelly-Reif, M. K. Schubauer-Berigan, L. Tomasek, L. B. Zablotska, C. Wiggins, and D. Laurier

Introduction

Two years after Marie Curie succeeded in isolating radium, radon was discovered while studying radium's decay chain. In the decades that followed, awareness of the risk of radon as a cause of lung cancer in miners of uranium and other ores increased. The International Agency for Research on Cancer classified radon and its decay products as "carcinogenic to humans" (Group 1) in 1987 (IARC, 1988). The US EPA asked the National Academies of Sciences (NAS) to undertake a study on radon and its decay products, and, in 1988, a US NAS report concluded that epidemiological and experimental data established the carcinogenicity of radon (National Research Council 1988). That report also provides estimates of risk based on modeling of data from studies of underground miners. In 1999, a subsequent NAS report (BEIR VI) further elaborated quantitative estimates of the radon-lung cancer association based on an expanded epidemiological data set (National Research Council 1999). Building on the work of these NAS committees, the PUMA study represents an international collaboration among partners investigating radon exposures and mortality among uranium miners. PUMA includes major cohorts of Canadian, Czech, French, German and US miners with quantitative exposure assessments and reasonable follow-up to address the study questions (Rage et al. 2020; Richardson et al. 2020). Here, the recent findings of the PUMA study are described.

Results

This analysis of PUMA data is the largest pooled study of cohorts of male underground uranium miners ($n = 118,329$). The cohorts were followed from the 1940s and include 52,000 deaths and 4.1 million person-years of observation.

Reference rates for each PUMA cohort were based on national rates of cause-specific mortality for males by categories of age and calendar period. Overall, all-cause mortality is 5% in excess compared to reference mortality rates, cancer mortality is 23% in excess, due primarily to excess lung cancer (nearly 8,000 lung cancers, almost twice what was expected based on general population rates); there are also excesses of cancer of the stomach (8%), liver (15%), and larynx (10%). There were no excesses of chronic obstructive pulmonary disease, circulatory disease, or other smoking-related diseases, nor of leukemia or kidney cancer.

Focusing on miners employed during the more contemporary period of the uranium mining industry when radon exposures tended to be comparatively low, and individual exposure data are available, here we report on exposure-lung cancer trends in an analysis that includes 57,873 male uranium miners first employed in 1960 or later, encompassing 1,217 lung cancer deaths, and 1.9 million person-years. Estimates of ERR per WLM of cumulative radon progeny exposure for mortality from lung cancer were derived by internal Poisson regression. A 5-year lag assumption was made to allow for a time interval between exposure and death from cancer, and to facilitate comparison with other studies of lung cancer among underground miners. The relative rate of lung cancer increased in a linear fashion with cumulative exposure to radon progeny (ERR/100 WLM $=1.33$; 95% CI: 0.89, 1.88). A test of heterogeneity by study cohort was rejected. Attained age was a modifier of this association, showing a decrease in ERR/WLM with increasing attained age. Further modifiers were age at exposure or time since exposure and exposure rate.

Discussion

International collaborative studies can strengthen our understanding of risks associated with occupational and environmental radon exposures. Based on a collaborative initiative including European and North American cohorts of uranium miners, PUMA provides the most precise and informative estimates to date of the association between low-level exposure to radon progeny and lung cancer mortality. PUMA provides direct evidence at lower exposure rates of a positive association between radon exposure and lung cancer risk, compared with prior NAS reports; this is of major importance for consolidating the system of radiological protection (Laurier et al. 2020). The associations estimated from the PUMA dataset are consistent with those from the earlier NAS reports in terms of projection at lower exposure rates but are more precise. Previous results demonstrated that the

carcinogenic impact of radon exposure on lung cancer risk clearly diminishes with time since exposure. Our results show that this can be equivalently described as an association that decreases with attained age, and with younger ages at exposure. PUMA plans to address several additional topics. These include risk of cancers other than lung; risk of nonmalignant disease; combined effects of radon and smoking; and effects of other exposures in uranium mines.

Summary

Radon and its progeny are a leading environmental and occupational cause of lung cancer. To better inform risk-based radiation protection standards, we assembled an international cohort study of workers employed in uranium mining in Canada, the Czech Republic, France, Germany, and the United States. We report standardized mortality ratios and analysis of exposure-lung cancer associations among miners employed during the more contemporary period of the uranium mining industry when radon exposures tended to be comparatively low and individual exposure data are available. Estimates of excess relative rate (ERR) per working level month (WLM) of cumulative radon progeny exposure for mortality from lung cancer were derived by internal Poisson regression. The relative rate of lung cancer increased linearly with cumulative exposure to radon progeny and lagged 5 years (ERR/100 WLM $=1.33$; 95% CI: 0.89, 1.88). Attained age was a clear modifier of this association, showing a decrease in ERR/WLM with increasing attained age. Further modifiers were age at exposure or time since exposure and exposure rate. PUMA provides the most precise and informative estimates to date of the association between low-level exposure to radon progeny and lung cancer mortality.

Radiation risks of lung cancer mortality after frequent X-ray diagnostic imaging procedures in the Canadian fluoroscopy cohort study

L. Zablotska, I. Apostoaei, B. Thomas, S. Simon, F. O. Hoffman, and J. D. Boice Jr

Disclaimer- This content is the personal opinion of the pre-senter. This does not represent opinion or policy of NCI, NIH, DHHS or the RRS

Introduction

Lung cancer is the second most common cancer and by far the leading cause of cancer death, accounting for 25% of all cancer deaths in Canada (Tables 84F0209X Mortality 2022; Canadian Cancer Statistics Advisory Committee (CCSAC) 2020, https://ccarcc.ca/canadian-cancer-statistics-a-2020-spe-cial-report-on-lung-cancer/). Epidemiological studies of radi-ation-related risks of lung cancer showed that high-dose exposures have been consistently associated with signifi-cantly increased risks (United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR): Sources and Effects of Ionizing Radiation 2008; United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR): Sources and Effects of Ionizing Radiation 2010). However, these studies do not address radiation exposures that are spread over time, as is the case with mul-tiple computerized tomography (CT) examinations (Linet et al. 2012). Studies of the association between multiple CT scans in children and subsequent risk of many cancers have been published (Mathews et al. 2013; Pearce et al. 2012) but concerns have been raised as to their validity and absence of individual dosimetry (Walsh et al. 2014; Boice 2015). Due to short follow-ups, these studies could not adequately investi-gate the effects on lung cancer. Data from populations exposed to low-to-moderate doses from repeated X-ray examinations, who were followed up for a long time, could help verify current risk projections for diagnostic imaging procedures based on the studies of high-dose exposures. Tuberculosis patients from Canada and the U.S. (Massachusetts) were treated in tuberculosis sanatoria for several years and received repeated fluoroscopies to monitor lung collapse therapy [pneumothorax (PT), pneumoperito-neum (PP), aspirations (AS)] or non-pulmonary tuberculosis [(gastrointestinal series (GI)] and chest radiographies. Previous analyses indicated significantly increased risks of breast cancer (Howe and McLaughlin 1996; Boice et al. 1991), but not lung cancer (Howe 1995; Davis et al. 1989), suggesting that risks from fluoroscopic examinations could be lower than would be predicted by current radiation risk models based on the study of atomic bomb survivors. The excess relative risk per gray (ERR/Gy) for lung cancer in Canada was estimated as: −0.00 (95% CI: −0.06, 0.07) (Howe 1995). However, this analysis assumed total dose esti-mates from PT only were delivered instantaneously at a fixed point in time during treatment and did not allow examination of the effects of time-dependent annual radi-ation exposures on the risk of lung cancer. Lung collapse therapy and associated fluoroscopy would occur every two weeks or so and could last between 3 to 5 years on average. Here we present the results of analyses of mortality from lung cancer in the Canadian Fluoroscopy Cohort Study (CFCS) using state-of-the-art dosimetry for estimating annual organ doses from all diagnostic procedures and applying time-dependent regression models for risk estima-tion. Results are then compared with those from the previ-ous analyses of this cohort.

Methods

The methods used to assemble the cohort have been described (Zablotska et al. 2014) and are summarized briefly below. The medical records of tuberculosis patients in all Canadian institutions treated during the period 1930–1969 were abstracted for information on personal identifiers and on treatments for tuberculosis, including detailed histories of diagnostic imaging procedures. Deaths of patients known to be alive at the start of follow-up in 1950 were ascertained via computerized record linkage with the Canadian Mortality Database for 1950–1987.

We recently developed a new dosimetry system (FLUXOR) to estimate 1,000 alternative realizations of aver-age individual organ doses from fluoroscopic examinations to cohort members using up-to-date hybrid anthropo-morphic phantoms (Apostoaei et al. 2021). In order to prop-erly account for shared exposure attributes in FLUXOR, radiation dose estimates were reconstructed using the Two-Dimensional Monte Carlo method (Simon et al. 2015). In the original analysis, only radiation doses associated with fluoroscopy with pneumothorax (PT) procedures were esti-mated (Howe 1995). In the current analysis, we used newly estimated doses from PT, pneumoperitoneum (PP), aspira-tions (AS) and gastrointestinal series (GI). We used a single value of mean dose to lungs (either from PT, PP, AS, GI or combined) per patient (averaged over the 1,000 realizations) to estimate the effect of cumulative 10-year lagged X-ray doses on lung cancer mortality. ERR/Gy was estimated using the grouped Poisson regression model of the EPICURE package (Preston et al. 2015).

Results

Table 1 presents descriptive characteristics of the CFCS cohort. A total of 63,715 patients were included, 50% of whom were female. About 45% of patients were exposed to

Table 1. Characteristics of the Canadian Fluoroscopy Cohort Study.

Descriptive characteristics	Value
Number of subjects	63,715
Year of birth, median (range)	1917 (1853–1949)
Females (%)	49.9
Pulmonary TB (%)	86.8
Most advanced TB stage recorded, N (%)	
Minimal	15,264 (24.0)
Moderate	22,696 (35.6)
Advanced	16,253 (25.5)
Smoking, N (%)	
Non-smoker	3,456 (5.4)
Ever smoker	10,172 (16.0)
Not specified	50,079 (78.6)
Number of fluoroscopies,a mean (95% CI)b	92 (1–360)
Duration of fluoroscopies,a years, mean (range)	2.7 (0.05–35)
Cumulative dose to the lungs,c Gy, mean (95% CI)d	
From PT	0.300 (0.140, 0.530)
From PP	0.020 (0.008, 0.037)
From AS	0.007 (0.003, 0.012)
From GI series	0.00007 (0.00001, 0.00023)
From all fluoroscopy-guided procedures	0.320 (0.160, 0.560)

AS: aspirations; CI: confidence interval; GI series: gastrointestinal series; Gy: gray; PP: pneumoperitoneum; PT: pneumothorax; SD: standard deviation; TB: tuberculosis.
[a]Averaged across all patients in the cohort who received any of the fluoroscopy-guided procedures.
[b]2.5th and 97.5th percentiles among patients in the cohort who received the listed procedure.
[c]Averaged across all members of the cohort.
[d]Mean and 95% CI of estimated cohort average doses from 1,000 alternative realizations using Monte Carlo sampling techniques.

repeated fluoroscopic examinations over an average period of 2.7 years (range: 0.05–35). The mean cumulative dose to the lungs from PT averaged across all members of the cohort was 0.3 Gy (0.69 Gy among exposed) and 0.32 Gy from all fluoroscopy-guided procedures. The mean age at first fluoroscopy was 28 years (range: 1–84 years), with about 1 in 5 patients first exposed during childhood or adolescence. During follow-up, 1,161 patients (25% females) died from lung cancer.

We repeated Howe analyses (Howe 1995) using new FLUXOR doses and observed no increase in radiation risks of lung cancer mortality with either PT doses (ERR/Gy: −0.03, 95% CI: −0.09, 0.06) or with doses from all procedures (PT + PP + AS + GI) (ERR/Gy = −0.03 (95%CI: < −0.07, 0.06). We did not observe differences in risks for males and females using doses from all procedures, ERR/Gy =0.02 (−0.07, 0.14) and ERR/Gy = −0.07 (95% CI: < −0.07, 0.02), respectively. We did not observe any significant heterogeneity in radiation risks by age or time since first exposure or type of tuberculosis (pulmonary vs. non-pulmonary). We observed significant heterogeneity in radiation risks ($P < .001$) by stage of tuberculosis (non-significant increased risks were estimated for moderate tuberculosis but not for minimal or advanced stages) and by smoking category (highest radiation risks in heavy smokers; 25+ cigarettes/day, ERR/Gy =0.16, 95%CI could not be estimated).

Discussion

The Canadian Fluoroscopy Cohort Study is one of the few studies uniquely positioned to address critical gaps in knowledge of the effects of repeated radiation exposures from diagnostic imaging procedures. The exposure regimen of CFCS patients is similar to that of patients today receiving repeated CT scans. Additional strengths of this study include its unique opportunity to have essentially a lifetime mortality follow-up in a nationwide population sample, to implement doses based on the most advanced and detailed representation of the human body (Borrego et al. 2019), and to estimate radiation risks across various cofactors such as sex, age at exposure, time since exposure and smoking history. The CFCS covers a wide range of ages at exposure distributions (1–81 years). More than half of the cohort did not receive fluoroscopy examinations but were treated by other means such as bed rest or surgery in the same Canadian hospitals, and thus provide a valuable comparison group. One of the main limitations is the issue of the relevance of lung cancer risks in this cohort to a general population of people without severe lung damage. However, radiation risks were also not increased among ∼15% of the cohort who had non-pulmonary tuberculosis.

The study team plans to capitalize on the existing CFCS study by: a) **extending** follow-up through the Canadian Mortality Database by 32 years (1988–2019); b) **broadening** our perspective by including incidence follow-up through the Canadian Incidence Database (1969–2019); c) **expanding** the knowledge on radiation risks of fractionated radiation exposures from X-ray fluoroscopies by using newly estimated organ doses from the FLUXOR radiation dosimetry system; and d) **improving precision** of radiation-related risks by using newly retrieved data from original medical records on lifestyle factors and new statistical methods to

assess effects of uncertainties in doses, of missing or incomplete data and exposure misclassification on risk estimates. Further analyses will shed more light on the effects of repeated radiation exposures on the risks of lung cancer (and other cancer and non-cancer outcomes) and on any differences in radiation risks by sex or other co-factors.

Summary

We assessed the association between repeated exposure to X-ray radiation and the risk of lung cancer mortality in a cohort of 63,715 patients (~50% female) within the Canadian Fluoroscopy Cohort Study (CFCS). Patients were examined with fluoroscopic procedures between 1930–1969 and followed through 1987. Cumulative 10-year lagged radiation lung doses were estimated for each patient by applying the FLUoroscopy X-ray ORgan-specific (FLUXOR) dosimetry system. Excess relative risks per gray (ERR/Gy) for lung cancer mortality were estimated using a grouped Poisson regression model. We did not observe associations between repeated exposures to X-ray radiation and lung cancer mortality, neither from fluoroscopy exams related only to a pneumothorax (PT) treatment (ERR/Gy -0.03, 95% CI -0.09–0.06) or from all procedures involving fluoroscopy exams [PT, pneumoperitoneum, aspirations or gastrointestinal series] (ERR/Gy $= -0.03$ (95%CI: < -0.07, 0.06). We did not observe any differences in risk between males and females. There was significant heterogeneity in radiation risks ($P < .001$) by stage of tuberculosis and by smoking history. Further analyses using extended mortality and incidence follow-up (1950–2019) will address critical gaps in knowledge of the effects of protracted radiation exposures from diagnostic imaging procedures on the risks of lung cancer and on any differences in radiation risks by sex.

Sex-specific lung cancer risk following fractionated low-dose radiation in occupational cohorts: an update from the million person study

A. Golden, J. D. Boice, Jr., L.T. Dauer, S. C. Howard, S. S. Cohen, M. T. Mumma, E. D. Ellis, K. F. Eckerman, and R. W. Leggett

Disclaimer- This content is the personal opinion of the presenter. This does not represent opinion or policy of ORAU, NCRP, or the RRS

Introduction

Previous studies of sex-specific differences in radiation-induced lung cancer risks have produced varying results. Studies of the Japanese atomic bomb survivors indicate an almost three times risk of lung cancer for females compared to males (Ozasa et al. 2012; NCRP 2014; Cahoon et al. 2017). Recently published results from five occupational cohorts within the Million Person Study (MPS) and the Canadian TB-Fluoroscopy Cohort Study found limited evidence that chronic or fractionated exposures increased the risk of lung cancer ($n = 403,067$ men and 50,679 women), with no significant differences observed between men and women (Boice et al. 2022). This presentation at the Special Session on Lung Cancer at the Radiation Research Society Virtual meeting discussed the preliminary sex-specific lung cancer results from an additional four Million Person Study cohorts. These four cohorts comprise approximately 95,570 males and 75,824 females with external exposures and/or internal intakes of plutonium or uranium.

Methods

The four cohorts within the Million Person Study assessed in this review included: Los Alamos National Laboratory (LANL) (Boice et al. 2022a); Tennessee Eastman Corporation (TEC) (Boice et al. 2022c), Rocky Flats (RF) (Wilkinson et al. 1987), and Medical Radiation Workers (MRW) (Boice et al. 2022b). While these cohorts are described in detail elsewhere, a brief description is provided here. The LANL cohort includes 26,328 workers (25% females) who were first employed in 1943–1980 and who worked at least 30 days. The RF cohort includes 9,397 workers (16% females) 7 of who were first employed in 1952–1970 for at least 30 days. The TEC cohort includes 26,650 workers (52% females) who were employed from 1943 to 1947 for at least 90 days. The MRW cohort includes 109,019 workers (49% females) who were employed from 1965 to 1994 and who worked at least 2 years.

For each of the workers in these cohorts, organ dose estimates were based on all sources of exposure. These sources varied across cohorts but included exposures to gamma radiation (all), neutrons (LANL, RF) and intakes of uranium (RF, TEC), or plutonium (LANL, RF).

Lung cancer was of primary concern because of the relatively high intakes of radionuclides in these cohorts. For each of the four cohorts in this presentation, Cox Proportional Hazard Models and Excess Relative Risk (ERR) models analyzed the relationship between sex-specific lung cancer mortality and cumulative radiation exposure with adjustments for attained age (as underlying time-scale), birth cohort, and a measure of socioeconomic status (education, pay type, or job category) as a surrogate for tobacco use. For a subset of the TEC population, self-reported tobacco use was available and used in nested sensitivity analyses to evaluate the impact of smoking on the lung cancer dose-response relationship.

Results

In total, the presentation reviewed the preliminary results for 95,570 males and 75,824 females with over 2,462 and 1,231 lung cancer deaths, respectively. These results pertain to the four cohorts described in this review and do not include aggregate results from other cohorts. The mean lung dose from all sources of exposure varied across cohorts, ranging from <10 to over 400 mGy, with larger lung doses observed in cohorts with substantial intakes of plutonium and/or uranium. Higher mean doses were observed for male workers compared to female workers except for the TEC cohort.

The sex-adjusted ERRs (95% CI; number of lung cancer deaths) for lung cancer at 100 mGy for LANL, RF, TEC, and MRW were 0.01 (−0.02, 0.03; $n = 839$), 0.01 (−0.01, 0.02; $n = 361$), −0.005 (−0.01. 0.001; $n = 1,654$), and 0.15 (0.02, 0.27; $n = 850$), respectively. No sex-specific difference in lung cancer mortality was observed for LANL, RF, or TEC. While the ERR for males in the MRW cohort was elevated and higher than that for females, confidence intervals for the estimates were still overlapping, indicating no significant sex difference was discernible in the data.

For TEC, tobacco use information was available for a subset of the cohort. Over 50% of the cohort did not have reported tobacco use information, but sensitivity analyses for both male and female models were still completed. Among tobacco users, a higher proportion of women were hourly compared with salaried workers, although the difference was not at the level of statistical significance in part because just 20% of the women were salaried workers and the ability to discern a statistical difference was limited. Overall, these results suggested, similar to the previous study primarily of men (Dupree et al. 1995), that hourly workers were more likely to use tobacco when compared with

salaried workers, and that pay code (hourly/salaried) could be considered a reasonable surrogate for smoking. A sensitivity analysis, adjusting for tobacco use instead of pay category, did not modify the dose-response relationship between lung cancer and internal radiation dose to the lung for females. While the ERR estimate was higher for males when adjusting for tobacco use instead of the pay category, the estimates from the two models were not statistically different from one another.

Discussion

Although many of these results are still preliminary, they provide evidence against large sex-specific differences in lung cancer mortality in occupationally exposed, low-dose radiation cohorts. The ability to assess female mortality in more contemporary cohorts that experienced chronic, generally low dose exposure to various radiation sources over the course of their careers is a major strength of these analyses. Individually, the results from some of these cohorts are limited by the low frequency of females and lower doses compared to males. However, within the TEC cohort, which did include more females with a substantial number of lung cancer deaths and larger doses than males, the mortality risk was not statistically different. A significant limitation of the analyses of these cohorts was the lack of direct tobacco use information. Although each model included a measure of socioeconomic status, such as education or pay category, as a surrogate for tobacco use, only the TEC cohort had direct tobacco use information available for a small subset of the cohort. While the analyses of the TEC cohort with the direct tobacco use information did not show meaningful differences with models adjusted for socioeconomic status, the possibility still remains that tobacco use and its effect on lung cancer mortality may not be fully captured by the socioeconomic status adjustment. Additionally, it can be very difficult to ascertain co-exposures such as dust or beryllium for workers, which may affect the mortality risk estimates. Despite these limitations, these cohorts provide further evidence that lung cancer mortality risk may not be different between males and females exposed to fractionated, low doses. More studies on sex-specific differences, particularly those that can pool multiple cohorts such as these to increase statistical power, are needed to fully assess the possible differences.

Risk of second primary malignancies after radioactive iodine treatment for thyroid cancer in patients younger than 45 years: a SEER (1975–2017) database analysis

E. Pasqual

Disclaimer- This content is the personal opinion of the presenter. This does not represent opinion or policy of NCI or NIH.

Introduction

The incidence of differentiated thyroid cancer (DTC) increased in the U.S. beginning in the 1970s, including among adolescents and young adults (Bernier et al. 2019; Ferlay et al. 2020). Small (<1 cm) DTCs at low risk of recurrence which have an excellent (>98%) survival rate are the main contributor to this increase. Radioactive iodine (RAI) is used to ablate thyroid tissue remaining after surgical removal of the thyroid; however, emerging evidence has shown small-to-no survival benefit of RAI in patients with low-risk DTC. Following additional concerns over RAI late effects, the adult American Thyroid Association (ATA) clinical guidelines (2009; 2015) have progressively recommended against the use of RAI for low-risk DTCs (Cooper et al. 2009; Haugen et al. 2016). The ATA pediatric guidelines have been slower in shifting toward a more restricting use of RAI (Francis et al. 2015). RAI exposes many radiosensitive organs to doses >100 mGy and current evidence, based mostly on the study with relatively short follow-up (<10 years), indicates that RAI is associated with increased leukemia risk about 2–3 years after exposure (Yu et al. 2018). It remains unclear if RAI is associated with an increased risk of solid cancer. Additionally, despite it being well known that children are at higher risk of radiation-induced malignancies (UNSCEAR 2013), only a few studies were conducted on young populations (Iyer et al. 2011; Marti et al. 2015). Here, the results of a recently published study aimed to estimate the risk of second primary malignancies in patients diagnosed with DTC before age 45 and treated with radioactive iodine (RAI) (Pasqual et al. 2022) are described.

Methods

Using 9 U.S. Surveillance, Epidemiology, and End Results cancer registries (1975–2017), relative risks (RRs) were estimated for solid and hematopoietic malignancies associated with RAI (yes versus no/unknown) with Poisson regression among 27,050 5- and 32,171 2-year non-metastatic DTC survivors (<45 years at diagnosis), respectively. For comparison with similar previous studies (Iyer et al. 2011; Marti et al. 2015), the Standardized Incidence Ratio (SIR) was also estimated, comparing the cancer rate between each DTC survivor's treatment cohort (RAI versus non-RAI) and the general U.S. population.

Results

Over a maximum follow-up of 43 years, RAI was associated with a statistically significant increased RR for hematological malignancies (RR = 1.92; 95% CI 1.04–3.56) and solid cancer (RR = 1.23; 95% CI 1.11–1.37), the latter particularly >20 years after DTC diagnosis ($RR_{solid-cancer}$ = 1.47; 95% CI 1.24–1.74). Among solid cancer, RR was elevated for uterine cancer (RR = 1.55; 95% CI 1.03–2.32), breast (RR = 1.18; 95% CI 0.99–1.40), lung (1.42; 95% CI 0.97–2.08), and salivary gland cancer (2.15; 95% CI 0.91–5.08). There were indications that confounding by smoking behavior might have biased the SIR estimation (comparison with the general population) toward values below one for smoking-related cancer (including lung cancer), as it is well reported that thyroid cancer patients smoke less than the general population (Cho and Kim 2014). Indeed, the SIR for lung cancer was 0.62 (95% CI 0.49; 0.78) for the non-RAI cohort and 0.94 (95% CI 0.68; 1.27) for the RAI cohort, and the Standardized Mortality Ratio (SMR) for Chronic Obstructive Pulmonary Disease (COPD), a disease strongly associated with smoking but not with radiation, was decreased for both RAI (0.46; 95% CI 0.21–0.88) and no-RAI cohorts (0.50; 95% CI 0.34–0.72). As a patient's smoking behavior is not a factor influencing clinical decision over RAI use for DTC, it is very unlikely that smoking behavior might have confounded the RR estimation (comparison between RAI versus no-RAI cohorts).

Conclusions

This study confirmed previous studies reporting an association between RAI use for DTC and an increased risk of leukemia. Additionally, it is shown that RAI use for DTC in young patients is associated with increased risks of several solid malignancies, including breast and lung cancer, with the highest risks observed more than 20 years following the DTC diagnosis. Reliance on SIR estimation only to describe second cancer risk in thyroid cancer survivors may challenge the interpretation of smoking-related cancer risk, since thyroid cancer patients are less likely to smoke. Overall, these results may stimulate continued discussion between patients and physicians over the risks versus benefits of RAI in young DTC patients.

Acknowledgements

Disclosure statement

Funding

ORCID

Ashley Golden http://orcid.org/0000-0002-9430-7702
Mary K. Schubauer-Berigan http://orcid.org/0000-0002-5175-924X
Dominque Laurier http://orcid.org/0000-0003-1432-4738
Lawrence T. Dauer http://orcid.org/0000-0002-5629-8462
Michael T. Mumma http://orcid.org/0000-0001-7506-8710
Elizabeth D. Ellis http://orcid.org/0000-0003-2871-1587

Notes on contributors

Lydia B. Zablotska, M.D., Ph.D., is a *Salvatore Pablo Lucia* Professor of Epidemiology and Public Health in the Department of Epidemiology and Biostatistics in the School of Medicine at the University of California, San Francisco (UCSF), where she serves as the Leader of the Occupational and Environmental Epidemiology Area of Concentration. Dr. Zablotska is a physician and epidemiologist with extensive training and publications in radiation epidemiology, biostatistics, and risk modeling. Her research activities have focused primarily on the examination of risks of radiation exposures in various occupational and environmental settings. Dr. Zablotska's work has clarified the understanding of the effects of occupational radiation exposures on health risks of nuclear power industry workers and workers of the uranium fuel production cycle in various occupational cohorts from the United States and Canada. She has also led/been involved in studies of those affected by the Chernobyl accident in Ukraine and of patients exposed to repeated radiation diagnostic imaging procedures. Dr. Zablotska is a member of NCRP and was responsible for a highly acclaimed workshop for young radiation epidemiology investigators for the Conference of Radiation and Health and RRS.

David B. Richardson, Ph.D., MSPH, is Associate Dean for Research in Public Health and Professor in Environmental and Occupational Health at UC Irvine. Prior to this position he was Professor in the Department of Epidemiology, School of Public Health at the University of North Carolina at Chapel Hill and Deputy Director of the North Carolina Occupational Safety and Health Education and Research Center and director of the center's Program in Occupational Epidemiology. His research focuses on the health effects of occupational and environmental exposures, particularly with regards to carcinogens. He has conducted studies of cancer among workers in the United States and abroad. Dr. Richardson's current research includes studies of mortality among nuclear industry workers and uranium miners, and development of new methods for occupational cohort studies. He is a member of Committee 1 (Radiation Effects) of the International Commission on Radiological Protection, serves as a Lead Coordinating Writer for the United Nations Committee on Epidemiological Studies of Radiation and Cancer, Scientific Committee on the Effects of Atomic Radiation (UNSCEAR), and serves as Associate Editor of the journals Occupational and Environmental Medicine and American Journal of Epidemiology.

Ashley Golden, Ph.D, is a senior biostatistician and Director of ORISE Health Studies at Oak Ridge Associated Universities in Oak Ridge, Tennessee, where she conducts multidisciplinary research projects in occupational epidemiology, radiation exposure and dosimetry, medical surveillance, and environmental assessments. She has been a collaborator on the Million Person Study of Low-Dose Health Effects for 8 years.

Elisa Pasqual, MD and PhD, is a postdoctoral Fellow at the Radiation Epidemiology Branch at the National Cancer Institute. Dr. Pasqual's research interests include medical radiation epidemiology, cancer etiology, and patient safety. Dr. Pasqual is working under the mentorship of Cari Kitahara, Ph.D., senior investigator, on long term effects of radioactive iodine treatment. She also works on thyroid cancer etiology.

Brian J Smith, Ph.D., is Professor of Biostatistics in the College of Public Health and Director of Biostatistics for the Holden Comprehensive Cancer Center at the University of Iowa. His research is cancer-focused and includes past study of residential radon, as a member of the Iowa Radon Lung Cancer Study, and ongoing studies in the areas of medical imaging, radiation oncology, and lymphoma. In addition, he recently served as an expert panel member of the United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR), where he helped develop a report on lung cancer risk from exposure to radon.

References

Apostoaei AI, Thomas BA, Hoffman FO, Kocher DC, Thiessen KM, Borrego D, Lee C, Simon SL, Zablotska LB. 2021. Fluoroscopy X-ray organ-specific dosimetry system (FLUXOR) for estimation of organ doses and their uncertainties in the Canadian Fluoroscopy Cohort Study. Radiat Res. 195(4):385–396.

Bernier M, Withrow DR, Berrington de Gonzalez A, Lam CJK, Linet MS, Kitahara CM, Shiels MS. 2019. Trends in pediatric thyroid cancer incidence in the United States, 1998-2013. Cancer. 125(14): 2497–2505.

Boice JD, Ellis ED, Golden AP, Zablotska LB, Mumma MT, Cohen SS. 2022. Sex-specific lung cancer risk among radiation workers in the million-person study and patients TB-Fluoroscopy. Int J Radiat Biol. 98(4):769–780.

Boice JD Jr, Cohen SS, Mumma MT, Golden AP, Howard SC, Girardi DJ, Ellis ED, Bellamy MB, Dauer LT, Samuels C, et al. 2022a. Mortality among workers at the Los Alamos National Laboratory, 1943–2017. Int J Radiat Biol. 98(4):722–749.

Boice JD, Cohen SS, Mumma MT, Howard SC, Yoder RC, Dauer LT. 2022b. Mortality among medical radiation workers in the United States, 1965–2016. Int J Radiat Biol. 1–25.

Boice JD Jr, Cohen SS, Mumma MT, Golden AP, Howard S, Girardi DD, Ellis ED, Bellamy M, Dauer LT, Samuels C. 2022c. Mortality study of women and men working at a uranium processing facility during World War II., 1943–1947. The Tennessee Eastman Corporation (Y-12) Worker Study. Int J Radiat Biol.

Boice JD Jr. 2015. Radiation epidemiology and recent paediatric computed tomography studies. Ann ICRP. 44(1 Suppl):236–248.

Boice JD Jr, Preston D, Davis FG, Monson RR. 1991. Frequent chest X-ray fluoroscopy and breast cancer incidence among tuberculosis patients in Massachusetts. Radiat Res. 125(2):214–222.

Borrego D, Apostoaei AI, Thomas BA, Hoffman FO, Simon SL, Zablotska LB, Lee C. 2019. Organ-specific dose coefficients derived from Monte Carlo simulations for historical (1930s to 1960s) fluoroscopic and radiographic examinations of tuberculosis patients. J Radiol Prot. 39(3):950–965.

Cahoon EK, Preston DL, Pierce DA, Grant E, Brenner AV, Mabuchi K, Utada M, Ozasa K. 2017. Lung, laryngeal and other respiratory cancer incidence among Japanese atomic bomb survivors: an updated analysis from 1958 through 2009. Radiat Res. 187(5): 538–548.

Canadian Cancer Statistics Advisory Committee (CCSAC) 2020. Canadian Cancer Statistics: A 2020 special report on lung cancer. Toronto, ON: Canadian Cancer Society.

Cho YA, Kim J. 2014. Thyroid cancer risk and smoking status: a meta-analysis. Cancer Causes Control. 25(9):1187–1195.

Cooper DS, Doherty GM, Haugen BR, Hauger BR, Kloos RT, Lee SL, Mandel SJ, Mazzaferri EL, McIver B, Pacini F, et al. 2009. Revised American Thyroid Association management guidelines for patients with thyroid nodules and differentiated thyroid cancer. Thyroid. 19(11):1167–1214.

Davis FG, Boice JD Jr, Hrubec Z, Monson RR. 1989. Cancer mortality in a radiation-exposed cohort of Massachusetts tuberculosis patients. Cancer Res. 49(21):6130–6136.

Dupree EA, Watkins JP, Ingle JN, Wallace PW, West CM, Tankersley WG. 1995. Uranium dust exposure and lung cancer risk in four uranium processing operations. Epidemiology. 6(4):370–375.

Ferlay J, Ervik M, Colombet M, et al. 2020. Global cancer observatory: cancer today. Lyon, France: International Agency for Research on Cancer, IARC.

Francis GL, Waguespack SG, Bauer AJ, Angelos P, Benvenga S, Cerutti JM, Dinauer CA, Hamilton J, Hay ID, Luster M, et al. 2015. Management guidelines for children with thyroid nodules and differentiated thyroid cancer. Thyroid. 25(7):716–759.

Haugen BR, Alexander EK, Bible KC, Doherty GM, Mandel SJ, Nikiforov YE, Pacini F, Randolph GW, Sawka AM, Schlumberger M, et al. 2016. 2015 American thyroid association management guidelines for adult patients with thyroid nodules and differentiated thyroid cancer: the American thyroid association guidelines task force on thyroid nodules and differentiated thyroid cancer. Thyroid. 26(1):1–133.

Howe GR, McLaughlin J. 1996. Breast cancer mortality between 1950 and 1987 after exposure to fractionated moderate-dose-rate ionizing radiation in the Canadian fluoroscopy cohort study and a comparison with breast cancer mortality in the atomic bomb survivors study. Radiat Res. 145(6):694–707.

International Agency for Research on Cancer (IARC). 1988. Man-made mineral fibers and radon. Lyon, France: IARC;

Iyer NG, Morris LGT, Tuttle RM, Shaha AR, Ganly I. 2011. Rising incidence of second cancers in patients with low-risk (T1N0)

thyroid cancer who receive radioactive iodine therapy. Cancer. 117(19):4439–4446.

Howe GR. 1995. Lung cancer mortality between 1950 and 1987 after exposure to fractionated moderate-dose-rate ionizing radiation in the Canadian fluoroscopy cohort study and a comparison with lung cancer mortality in the Atomic Bomb survivors study. Radiat Res. 142(3):295–304.

Laurier D, Marsh JW, Rage E, Tomasek L. 2020. Miner studies and radiological protection against radon. Ann ICRP. 49(1_suppl):57–67.

Linet MS, Slovis TL, Miller DL, Kleinerman R, Lee C, Rajaraman P, Berrington de Gonzalez A. 2012. Cancer risks associated with external radiation from diagnostic imaging procedures. CA Cancer J Clin. 62(2):75–100.

Mathews JD, Forsythe AV, Brady Z, Butler MW, Goergen SK, Byrnes GB, Giles GG, Wallace AB, Anderson PR, Guiver TA, et al. 2013. Cancer risk in 680 000 people exposed to computed tomography scans in childhood or adolescence: data linkage study of 11 million Australians. BMJ. 346:f2360.

Marti JL, Jain KS, Morris LGT. 2015. Increased risk of second primary malignancy in pediatric and young adult patients treated with radioactive iodine for differentiated thyroid cancer. Thyroid. 25(6): 681–687.

National Research Council 1988. Committee on the Biological Effects of Ionizing Radiation (BEIR IV). In: Health Risks of Radon and other Internally Deposited Alpha-emitters. Washington, DC: National Academy Press.

National Research Council 1999. Committee on Health Risks of Exposure to Radon (BEIR VI). In: Health effects of exposure to radon. Washington, DC: National Academy Press.

Ozasa K, Shimizu Y, Suyama A, Kasagi F, Soda M, Grant EJ, Sakata R, Sugiyama H, Kodama K. 2012. Studies of the mortality of atomic bomb survivors, report 14, 1950-2003: an overview of cancer and noncancer diseases. Radiat Res. 177(3):229–243.

Pasqual E, Schonfeld S, Morton LM, Villoing D, Lee C, Berrington de Gonzalez A, Kitahara CM. 2022. Association between radioactive iodine treatment for pediatric and young adulthood differentiated thyroid cancer and risk of second primary malignancies. JCO. 40(13):1439–1449.

Pearce MS, Salotti JA, Little MP, McHugh K, Lee C, Kim KP, Howe NL, Ronckers CM, Rajaraman P, Craft S, et al. 2012. Radiation exposure from CT scans in childhood and subsequent risk of leukaemia and brain tumours: a retrospective cohort study. Lancet. 380(9840):499–505.

Preston DL, Lubin JH Pierce DA, McConney ME Shilnikova NS. 2015. Epicure risk regression and person-year computation software: command summary and user guide. Ottawa, Canada: Risk Sciences International.

Rage E, Richardson DB, Demers PA, Do M, Fenske N, Kreuzer M, Samet J, Wiggins C, Schubauer-Berigan MK, Kelly-Reif K, et al. 2020. PUMA - pooled uranium miners analysis: cohort profile. Occup Environ Med. 77(3):194–200.

Richardson DB, Rage E, Demers PA, et al. 2020. Mortality among uranium miners in North America and Europe: the Pooled Uranium Miners Analysis (PUMA). Int J Epidemiol. 50(2):633–643.

Simon SL, Hoffman FO, Hofer E. 2015. The two-dimensional Monte Carlo: a new methodologic paradigm for dose reconstruction for epidemiological studies. Radiat Res. 183(1):27–41.

Tables 84F0209X Mortality. 2022. Summary List of Causes.

United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR): Sources and Effects of Ionizing Radiation 2008. UNSCEAR 2006 Report to the General Assembly with Scientific Annexes. Volume I. Annex A: Epidemiological studies of radiation and cancer. (United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR) ed. New York: UNSCEAR.

United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR): Sources and Effects of Ionizing Radiation 2010. UNSCEAR 2008 Report to the General Assembly with Scientific Annexes. Volume I. Annex A: Medical Radiation Exposures. ((United Nations Scientific Committee on the Effects of Atomic Radiation) ed. New York: United Nations.

UNSCEAR 2013. Sources, Effects and Risks of Ionizing Radiation, Volume II: Scientific Annex B - Effects of Radiation Exposure of Children. United Nations, New York.

Walsh L, Shore R, Auvinen A, Jung T, Wakeford R. 2014. Risks from CT scans–what do recent studies tell us? J Radiol Prot. 34(1):E1–E5.

Wilkinson GS, Tietjen GL, Wiggs LD, Galke WA, Acquavella JF, Reyes M, Voelz GL, Waxweiler RJ. 1987. Mortality among plutonium and other radiation workers at a plutonium weapons facility. Am J Epidemiol. 125(2):231–250.

Yu CY, Saeed O, Goldberg AS, Farooq S, Fazelzad R, Goldstein DP, Tsang RW, Brierley JD, Ezzat S, Thabane L, et al. 2018. A systematic review and meta-analysis of subsequent malignant neoplasm risk after radioactive iodine treatment of thyroid cancer. Thyroid. 28(12): 1662–1673.

Zablotska LB, Little MP, Cornett RJ. 2014. Potential increased risk of ischemic heart disease mortality with significant dose fractionation in the Canadian Fluoroscopy Cohort Study. Am J Epidemiol. 179(1): 120–131.