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Fluoroscopy X-Ray Organ-Specific Dosimetry System (FLUXOR) for Estimation of Organ Doses and Their Uncertainties in the Canadian Fluoroscopy Cohort Study

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As part of ongoing efforts to assess lifespan disease mortality and incidence in 63,715 patients from the Canadian Fluoroscopy Cohort Study (CFCS) who were treated for tuberculosis between 1930 and 1969, we developed a new FLUoroscopy X-ray ORgan-specific dosimetry system (FLUXOR) to estimate radiation doses to various organs and tissues. Approximately 45% of patients received medical procedures accompanied by fluoroscopy, including artificial pneumothorax (air in pleural cavity to collapse of lungs), pneumoperitoneum (air in peritoneal cavity), aspiration of fluid from pleural cavity and gastrointestinal series. In addition, patients received chest radiographs for purposes of diagnosis and monitoring of disease status. FLUXOR utilizes age-, sex- and body size-dependent dose coefficients for fluoroscopy and radiography exams, estimated using radiation transport simulations in up-to-date computational hybrid anthropomorphic phantoms. The phantoms include an updated heart model, and were adjusted to match the estimated mean height and body mass of tuberculosis patients in Canada during the relevant time period. Patient-specific data (machine settings, exposure duration, patient orientation) used during individual fluoroscopy or radiography exams were not recorded. Doses to patients were based on parameter values inferred from interviews with 91 physicians practicing at the time, historical literature, and estimated number of procedures from patient records. FLUXOR uses probability distributions to represent the uncertainty in the unknown true, average value of each dosimetry parameter. Uncertainties were shared across all patients within specific subgroups of the cohort, defined by age at treatment, sex, type of procedure, time period of exams and region (Nova Scotia or other provinces). Monte Carlo techniques were used to propagate uncertainties, by sampling alternative average values for each parameter. Alternative average doses per exam were estimated for patients in each subgroup, with the total average dose per individual determined by the number of exams received. This process was repeated to produce alternative cohort vectors of average organ doses per patient. This article presents estimates of doses to lungs, female breast, active bone marrow and heart wall. Means and 95% confidence intervals (CI) of average organ doses across all 63,715 patients were 320 (160, 560) mGy to lungs, 250 (120, 450) mGy to female breast, 190 (100, 340) mGy to heart wall and 92 (47, 160) mGy to active bone marrow. Approximately 60% of all patients had average doses to the four studied organs of less than 10 mGy, 10% received between 10 and 100 mGy, 25% between 100 and 1,000 mGy, and 5% above 1,000 mGy. Pneumothorax was the medical procedure that accounted for the largest contribution to cohort average doses. The major contributors to uncertainty in estimated doses per procedure for the four organs of interest are the uncertainties in exposure duration, tube voltage, tube output, and patient orientation relative to the X-ray tube, with the uncertainty in exposure duration being most often the dominant source. Uncertainty in patient orientation was important for doses to female breast, and, to a lesser degree, for doses to heart wall. The uncertainty in number of exams was an important contributor to uncertainty for ~30% of patients. The estimated organ doses and their uncertainties will be used for analyses of incidence and mortality of cancer and non-cancer diseases. The CFCS cohort is an important addition to existing radio-epidemiological cohorts, given the moderate-to-high doses received fractionated over several years, the type of irradiation (external irradiation only), radiation type (X rays only), a balanced combination of both genders and inclusion of people of all ages.

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INTRODUCTION

In the late 19th and early 20th centuries, tuberculosis was a leading cause of death in Canada (*1–3*). Early diagnosis of disease, accompanied by rest and supportive therapies in sanatoria and in hospitals with specialized tuberculosis units, was the most important factor in the decline of mortality from tuberculosis before the introduction of antimicrobial therapy in the 1950s. By the 1930s, such tuberculosis units operated in all provinces in Canada (*4, 5*).

In addition to standard bedrest and nutrition, a common therapy for suitable cases of pulmonary tuberculosis was a surgical intervention to produce a collapse, or compression, of the diseased lung, accomplished by inserting air into the pleural cavity (pneumothorax) or the abdomen (pneumoperitoneum) to exert pressure in the pleural space from above or below the diaphragm. The patient would return every one to two weeks to determine the degree of lung collapse and receive a refill with air if necessary to ensure long-term maintenance of the collapse. Fluoroscopic examinations were performed before and sometimes after air was inserted, to determine the degree of lung collapse and the need for refill with air (*6–8*). Accumulation of fluid in the pleural space was a common complication and aspiration (removal) of fluid was sometimes required. Chest radiographs were used to record the disease status, and gastrointestinal (GI) series fluoroscopic examinations were performed on some patients to diagnose tuberculosis of the GI tract.

In the early 1970s, archived medical records of admissions and lung collapse treatments were used to assemble a cohort of patients from almost all medical institutions treating tuberculosis patients in Canada (*9*). Measurements from contemporary fluoroscopes, from dosimeter sites in organs of interest in Alderson-Rando phantoms, and radiation transport calculations were previously used to estimate organ doses to lungs, bone marrow, and female breast to patients in this cohort. As part of the Canadian Fluoroscopy Cohort Study (CFCS), estimated doses to lungs and breasts were used to conduct dose-response analyses of lung and female breast cancer and cardiovascular diseases (*9–13*).

Currently, efforts are ongoing to produce updated evaluations of incidence and mortality risks from cancer and non-cancer diseases, based on a follow-up of this cohort until the end of 2017. In support of these efforts, we developed a new FLUoroscopy X-ray ORgan-specific dosimetry system (FLUXOR) for estimation of doses and their uncertainties from historical fluoroscopic and radiographic examinations of tuberculosis patients, to organs both in the direct path of the radiation beam and outside it, based on age-, sex- and body size-dependent dose coefficients obtained using up-to-date computational hybrid anthropomorphic phantoms. This article describes the approach to calculating organ doses, and presents estimates of doses, with uncertainties, to lungs, female breast, active bone marrow and heart wall.

TABLE 1
Number of Procedures per Patient[a]

Procedure	Average[b] (95% CI)[c]		
	Males	Females	All patients
Pneumothorax	88 (1, 354)	95 (1, 364)	92 (1, 360)
Pneumoperitoneum	71 (3, 230)	73 (3, 235)	72 (3, 234)
Chest aspirations	10.7 (1, 69)	8.4 (1, 52)	9.6 (1, 61)
GI series	1.5 (1, 4)	1.5 (1, 4)	1.5 (1, 4)
Chest radiographs	20.8 (1, 78)	22.0 (1, 80)	21.4 (1, 79)

[a] Patients could have had only one type of procedure or multiple types of procedures. For example, a patient could have been treated with pneumothorax procedures only, another patient could have pneumoperitoneum only, while yet another patient could have received both pneumothorax and pneumoperitoneum procedures.

[b] Average across all patients in the cohort who received the listed procedure.

[c] 2.5th and 97.5th percentiles among patients in the cohort who received the listed procedure.

METHODS

Sources of Data for Assessment of Doses

Estimation of organ doses relies on data specific to fluoroscopic and radiographic procedures in Canadian tuberculosis sanatoria, and other information in the literature on practices in the treatment of tuberculosis during the period 1930–1969. Sources of information include: 1. abstracted medical records of tuberculosis patients; 2. interviews with a sample of physicians who treated tuberculosis patients in Canada during the period of interest; 3. previous studies of CFCS patients (*9, 10, 12*); 4. previous dose assessments for patients who received similar treatments for tuberculosis in sanatoria in Massachusetts (*11*); and 5. general scientific literature on historical fluoroscopic and radiographic practices.

Patient Information

Medical charts for tuberculosis patients in the cohort were abstracted and summarized in electronic records for 92,707 patients first admitted for treatment in sanatoria in Canada between 1930 and 1952, and treated until the end of 1969 (*8, 9, 13*). After application of multiple exclusion criteria (invalid information on birth year, year or age at first admission, year or age at end of follow-up, year of death or last contact), the study cohort now includes 63,715 patients (31,928 males, 31,787 females), with 30,130 patients (14,695 males, 15,435 females) having had medical procedures involving fluoroscopic examinations. The number of procedures peaked in the late 1940s and early 1950s. Average numbers of procedures per patient, shown in Table 1, indicate males and females received similar treatment regimens. The majority of patients in the study cohort were adults during treatment, but children (ages $<$18 years) also were exposed to radiation during treatment for tuberculosis in sanatoria (Fig. 1).

Treatment records include the type of procedure (e.g., pneumothorax), dates (day, month and year) when a series of treatments started and ended, and the total number of procedures during that period; records do not include the actual dates of any procedure. In some records, a treatment rate prescribed by a medical doctor was available (e.g., one refill with air per week for a patient with an artificially-induced pneumothorax). For some patients these data were incomplete. Missing data possibly included portions or the entire start or end dates, and/or treatment information (number of procedures, prescribed treatment rate or both). Any part of a treatment record that was missing was imputed based on average treatment rates and treatment durations estimated for each medical procedure from patients in the cohort for whom the treatment records were complete.

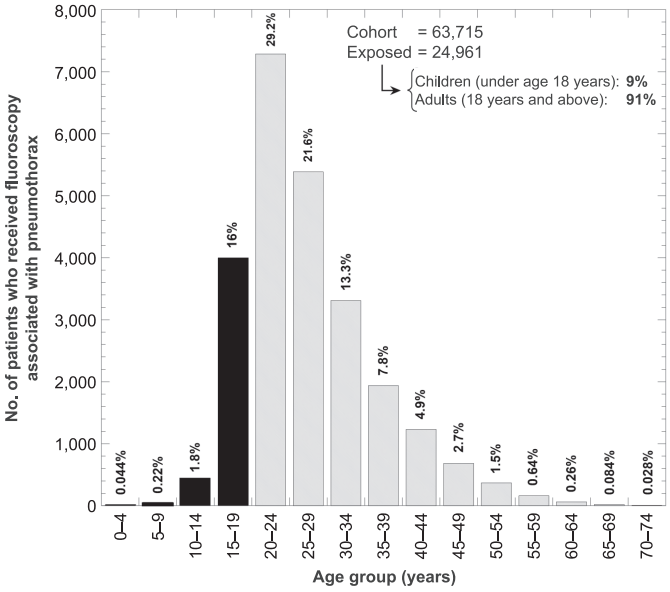

FIG. 1. Distribution of number of patients who received fluoroscopies associated with pneumothorax, by age at first treatment.

Physician Interviews

Information about fluoroscopic exams related to lung collapse procedures was obtained primarily from interviews with 91 physicians who treated tuberculosis patients in Canada during the period of interest, supplemented by information from previous studies of tuberculosis patients in Canada and elsewhere, and information from the general scientific literature. Physician interviews provided information on parameters relevant to fluoroscopy exams administered during pneumothorax procedures: tube voltage, tube current, exposure duration, patient orientation, shuttering of the beam, the use of a second fluoroscopic viewing after refill with air. Information on tube output [i.e., Gy in air per mA per second at a given tube voltage and total filtration] and the use of beam filtration was obtained from measurements on historical fluoroscopes typical of those used in tuberculosis sanatoria and from the general literature (*10, 11*). Table 2 shows the number of physicians who provided answers regarding these parameters. Details about data available for each parameter are provided in Appendix A (Supplementary Information; https://doi.org/10.1667/RADE-20-00212.1.S1). Data reported by physicians in Nova Scotia (23 physicians) and in other provinces (68 physicians) were analyzed separately, because information on medical practice in Canadian sanatoria (*6, 7*) indicated that patients in Nova Scotia were preferentially examined facing the X-ray tube and away from the examiner [anterior-posterior (AP) orientation; Fig. 2], to reduce the chance of infective droplets being sprayed toward the examiner if a patient coughed. On the other hand, fluoroscopic viewings in other provinces were more commonly carried out in posterior-anterior (PA) orientation. Data reported by physicians confirmed these reports. Most other parameter values reported by physicians in the two areas were otherwise similar (Supplementary Information, Appendix A; https://doi.org/10.1667/RADE-20-00212.1.S1).

Modern Computational Phantoms

A major feature of FLUXOR is the use of age-, sex- and body size-dependent dose conversion coefficients for fluoroscopy and radiography exams (*14*). The dose conversion coefficients were estimated using Monte Carlo radiation transport simulations in up-to-date computational hybrid anthropomorphic phantoms developed by the University of Florida (Gainesville, FL) and the U.S. National Cancer Institute (Bethesda, MD) (*15*). The phantoms include lymphatic nodes and an updated heart model, and were adjusted to match the mean height and body mass of tuberculosis patients in Canada during the period of interest (*16*). New dose conversion coefficients were developed for CFCS with values estimated for 58 and 57 organs and tissues in males and females respectively, including tissues outside the X-ray irradiation field during fluoroscopy or radiography. Dose conversion coefficients were provided for radiography and for fluoroscopic procedures not previously considered in the dosimetry of this cohort (i.e., pneumoperitoneum, chest aspirations and GI series). The collection of dose conversion coefficients derived for this study includes values for a large combination of exposure parameters, which allowed us to account for the variation and also uncertainties related to tube voltages and total filtration in operation of fluoroscopes, orientation of patient, shuttering, position of the incident beam, and average heights and body masses of patients. Supplementary Information, Appendix A (https://doi.org/10.1667/RADE-20-00212.1.S1) provides further details about the dose conversion coefficients.

TABLE 2
Parameters for which Information from Physician Interviews is Available

Parameter	Number of physicians	
	Nova Scotia	Other provinces
Tube voltage (kV)	3	21
Tube current (mA)	11	32
Exposure duration (s)	23	65
Patient orientation	22	60
Shuttering of beam	7	26
Fluoroscopies after refill	22	53

Approach to Estimating Organ Doses

Radiation exposure conditions in fluoroscopy or radiography are characterized by the X-ray machine settings (tube voltage, tube current, total filtration, shuttering, tube output at given machine settings), and by parameters imposed by medical needs such as duration of fluoroscopy exposure, orientation of a patient relative to the X-ray tube [e.g., anterior-posterior (AP) or posterior-anterior (PA), as shown in Fig. 2], and position of the incident beam (e.g., chest). Radiation doses to CFCS patients were estimated based on: 1. estimated average organ doses per procedure of each type; and 2. the number of procedures of each type (e.g., pneumothorax) from medical records. All reported radiation doses are absorbed doses in Gy. An organ dose per procedure was calculated as the product of tube output (Gy in air at skin entrance per mA per second at a given tube voltage and total filtration); tube current (milliampere; mA); exposure duration (second; s); organ-, sex- and age-specific dose conversion coefficient (Gy in tissue per Gy in air at skin entrance); and an average number of fluoroscopy viewings per procedure, in cases of medical procedures that involved a refill with air (one fluoroscopic exam before refill and, sometimes, one after refill). Estimated average organ doses per procedure account for the fraction of procedures in which shuttering of the beam occurred and the fraction of procedures in each orientation of the patient. Organ doses were calculated for each medical procedure separately based on estimates of exposure durations and procedure-specific position of the incident beam (chest versus upper abdominal areas). Doses depended on patient's sex and age at the time of a procedure and the location where treatment was received (Nova Scotia or other provinces), with approximately 90% of all patients being treated at least once in provinces other than Nova Scotia. Organ doses were estimated for each year of treatment (annual doses) and then summed across all years of treatment to estimate a total dose to each patient. Details of the mathematical approach for calculation of doses are provided in Supplementary Information, Appendix B (https://doi.

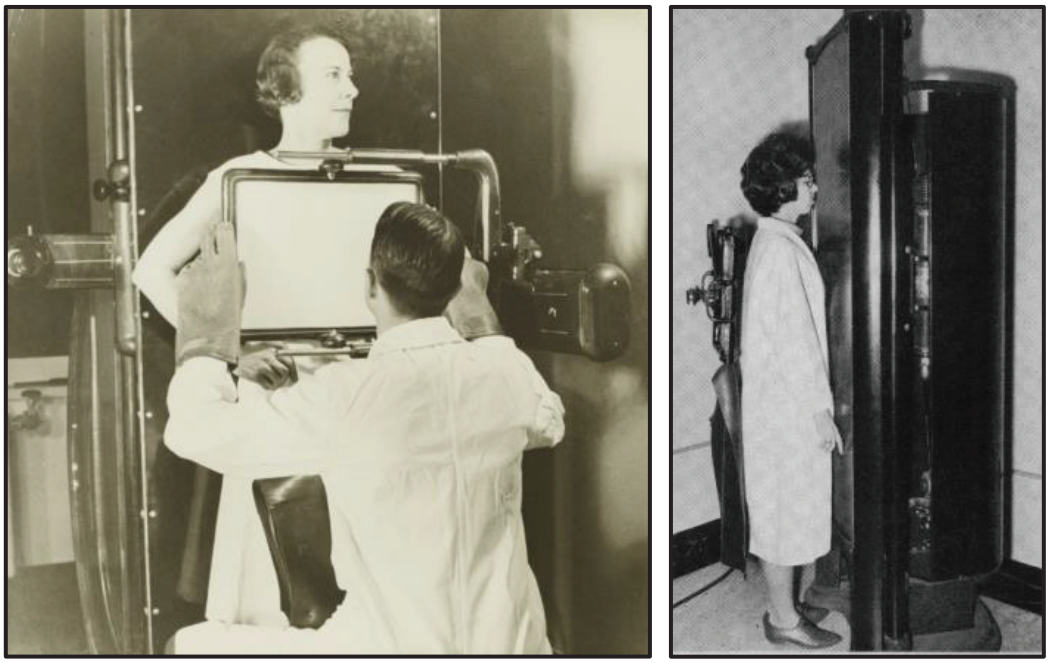

FIG. 2. Typical fluoroscopy examinations of the chest were carried out in PA orientation (left side panel, Columbia University), but AP orientation was preferred in sanatoria in Nova Scotia [right side panel (*6*)]. ''Women's Health Examination Portfolio – Fluoroscope.'' circa 1947. New York: Rare Book and Manuscript Library, Columbia University, Community Service Society Collection (https://bit.ly/3sqs2ap).

org/10.1667/RADE-20-00212.1.S1). FLUXOR was programmed in Analytica® version 5.3.3 programming environment [Lumina Decision Systems Inc., Los Gatos, CA; www.lumina.com(*17*)].

Quantification of Uncertainties

Ideally, doses to CFCS patients would be calculated from patient-specific information regarding the medical procedure and specific machine settings used in each examination. However, details of fluoroscopic or radiographic examinations were not included in abstracted medical records for any patients, and are not known to have existed in medical charts from sanatoria in Canada during the period of interest.

Number of medical procedures involving radiation exposures was also missing for some patients. Partially or completely missing data on start or end treatment dates, and/or treatment information (number of procedures, prescribed treatment rate or both) in medical records were imputed based on average treatment rates and treatment durations estimated for each medical procedure from patients in the cohort for whom the treatment records were complete. For each procedure type, patients were grouped into one of nine uncertainty categories according to the amount of information available, with category 1 including patients who had complete records, up to category 9 which includes patients for whom all dates, numbers of procedures and treatment rate information were missing. For each procedure type (pneumothorax, pneumoperitoneum, chest aspirations), more than 65% of patients were in uncertainty categories 1 through 4 (complete and nearly complete data), and more than 85% of patients were in categories 1 through 6 (complete, nearly complete and containing essential information), while 1% or fewer patients were part of category 9. Probability distributions describing the uncertainty assigned to the imputed number of procedures for patients in the nine categories are provided in Supplementary Information, Appendix A (https://doi.org/10.1667/RADE-20-00212.1.S1).

In the absence of patient-specific details on fluoroscopic and radiographic exams, probability distributions were used to represent uncertainties in the unknown true, average value of each dosimetry parameter. Probability distributions were developed using professional judgment, guided by a statistical analysis of physician interview data and a review of similar data from literature. The distributions for dosimetry parameters selected in this analysis are summarized in Table 3. Details about uncertainties in technical parameters and uncertainties in dose conversion coefficients, including uncertainties in body masses and heights of patients, are discussed in Supplementary Information, Appendix A (https://doi.org/10.1667/RADE-20-00212.1.S1). To propagate uncertainties, Monte Carlo sampling from assumed probability distributions was used to generate 1,000 alternative realizations of possibly true and unbiased average values of all parameters. Uncertainties were shared across all patients within specific subgroups of the cohort defined by: 1. region (Nova Scotia or other provinces); 2. type of medical procedure (pneumothorax, pneumoperitoneum, chest aspirations, GI series fluoroscopy, and chest radiographs); 3. a patient's sex and age (adults or children of various ages); and 4. the time period when treatment occurred. The sampled parameter values were combined using the equations in Appendix B (Supplementary Information) to calculate 1,000 alternative realizations of estimated average doses per procedure of a given treatment type, which were then multiplied by the reported or estimated average number of procedures for that treatment type. In each realization, a sampled parameter value was used in estimating doses to all patients in the cohort subgroup to which it applied; i.e., all uncertainties were shared among those patients. Doses to all patients in each subgroup were estimated first, and doses in all subgroups were then combined to produce a set of average doses for the entire cohort of 63,715 patients. This process was repeated to obtain 1,000 alternative sets of 63,715 dose estimates. A set of doses (one to each patient) is referred to here as a ''cohort dose vector.'' For each of the 1,000 dose vectors, doses are summarized in this article by taking averages across the entire cohort or across members of the cohort exposed to particular procedures (e.g., pneumothorax only, all procedures involving fluoroscopy, all fluoroscopic and radiographic

TABLE 3
Descriptions of Probability Distributions for Dosimetric Parameters Used in FLUXOR

Parameter	Probability distributions[a] (95% CI)	
	Pneumothorax	Pneumoperitoneum/ chest aspirations
Tube voltage (kV)[b]		
All provinces		
Adult	Normal (78, 4.0)	Normal (78, 5.0)
Ages 10 years to adult	Normal (73, 4.0)	Normal (73, 5.0)
Ages 1 to 10 years	Normal (68, 4.0)	Normal (68, 5.0)
Tube current (mA)[b]		
All provinces	Normal (4.0, 0.4)	Normal (4.0, 0.5)
Tube output[c]		
All provinces		
Variability among machines		
No added filtration	Normal (1.0, 0.24)	Normal (1.0, 0.24)
Added filtration	Normal (1.0, 0.12)	Normal (1.0, 0.12)
Uncertainty in tube-to-panel distance	Triangular (0.85, 1.0, 1.15)	Triangular (0.85, 1.0, 1.15)
Tube filtration (added 1-mm filter)		
All provinces	Probability of added filtration (95% CI) Before 1942: 0.0 Between 1942 and 1951: increases by 0.1 per year After 1951: 1.0	
Exposure duration (s)		
All provinces	Uniform (10, 24)	Uniform (8, 26)
Orientation (fraction AP)[d]		
Nova Scotia	Triangular (0.50, 0.65, 0.95)	Triangular (0.50, 0.65, 1.0)
Other provinces	Triangular (0.0, 0.08, 0.16)	Triangular (0.0, 0.08, 0.20)
Shuttering (fraction used)[e]		
Nova Scotia	Uniform (0, 0.02)	Uniform (0, 0.02)
Other provinces	Uniform (0.03, 0.23)	Uniform (0.03, 0.23)
Fluoroscopies after refill (no. per procedure)[f]		
Nova Scotia	1 + Uniform (0.95, 1.0)	1 + Uniform (0.95, 1.0)
Other provinces	1 + Triangular (0.06, 0.18, 0.30)	1 + Triangular (0.06, 0.18, 0.30)
Body weights and heights[g]		
All provinces	Triangular (0.80, 1.0, 1.2)	Triangular (0.80, 1.0, 1.2)

[a] Values provided are: 1. Mean and standard deviation for a normal (Gaussian) distribution; 2. Minimum and maximum for a uniform distribution; or 3. Minimum, mode and maximum for a triangular distribution. All distributions are sampled independently between medical procedures and between Nova Scotia and other provinces, with the exception of filtration.

[b] For each procedure and region, distributions for tube voltage are sampled correlated among ages. Distributions for tube voltage and tube current are correlated with an assumed correlation coefficient of –0.5, for all ages.

[c] The uncertainty in tube output (i.e., exposure rate in air at skin entrance) is given by the uncertain tube voltages and by the multiplicative uncertainty factors listed in this table and described in Supplementary Information (Appendix A; https://doi.org/10.1667/RADE-20-00212.1.S1).

[d] Fraction PA is calculated as one minus fraction AP.

[e] Shuttering was used to restrict the beam to one lung. In pneumoperitoneum procedures, both lungs were kept in the beam; thus the fraction used is set equal to zero.

[f] Not applicable for chest aspirations, as these procedures do not involve refills with air.

[g] Multiplicative factor describing the uncertainty in dose conversion coefficients related to uncertainty in body masses and heights. Further uncertainties in dose coefficients account for uncertainties in tube voltage and tube current, for uncertainties in the relative positions of beam and organs (e.g., shifts in beam position or shifts of organs due to lung collapse), and for statistical uncertainties in radiation transport calculations. Details about these uncertainties are provided in Supplementary Information (Appendix A).

procedures), with resulting uncertain averages being presented as a mean and 95% confidence intervals (CI) across the 1,000 realizations.

Sampling uncertainties shared across all patients within specific subgroups and generating alternative sets or cohort dose vectors using uncertainties in estimated average doses to all patients in each subgroup is a process analogous to the production of alternative realizations of ''conditional'' individual mean doses, used in other dose reconstructions and based on the two-dimensional Monte Carlo method (*18–20*). Each cohort dose vector is a possibly ''true'' vector of average doses that are estimated based on average parameter values assigned to all patients in defined subgroups about which unknown ''true'' individual values vary at random. Each alternative cohort dose vector can be used to evaluate a dose response under the assumption of a potential underlying Berkson error structure (*21*).

Given the absence of individual-specific data on dosimetry parameters, the inter-individual variability of true dose remains unknown. In this approach, no attempt is made to quantify random, unshared uncertainty. Because of the large number of parameters used in estimating individual doses, it is highly likely that such an attempt would result in an overestimation of inter-individual variability of true doses among individuals, due to compounding uncertainties, potentially leading to a bias toward underestimation of the slope of a linear dose response.

TABLE 4
Estimates of Cohort Average Organ Doses (mGy)

Medical procedure	No. of patients[a] (both sexes)	Mean (95% CI)[b] Lungs	Active bone marrow	Heart wall	No. of patients[a] (females)	Mean (95% CI)[b] Female breast
Averaged across all members of the cohort[a] (63,715 patients; 31,787 females)						
Pneumothorax	24,961	300 (140, 530)	83 (40, 150)	170 (87, 320)	13,128	230 (100, 420)
Pneumoperitoneum	4,214	20 (8.3, 37)	6.3 (2.5, 13)	13 (5.5, 26)	2,083	19 (7.2, 41)
Aspirations	5,832	6.5 (3.1, 12)	1.6 (0.71, 2.9)	4.7 (2.1, 8.8)	2,665	5.2 (2.3, 10)
GI series	3,706	0.065 (0.011, 0.23)	0.77 (0.12, 2.7)	0.085 (0.013,0.31)	1,805	0.10 (0.015,0.34)
All fluoroscopies[a,c]	30,130	320 (160, 560)	91 (47, 160)	190 (100, 340)	15,435	250 (120, 450)
Chest radiographs	60,835	1.2 (0.62, 2.1)	0.53 (0.27, 0.94)	0.43 (0.21, 0.79)	30,618	0.19 (0.089, 0.35)
All procedures[a,c]	61,644	**320 (160, 560)**	**92 (47, 160)**	**190 (100, 340)**	30,996	**250 (120, 450)**
Averaged across only the patients who received the listed procedure[a,d]						
Pneumothorax	24,961	760 (360, 1,400)	210 (100, 380)	450 (220, 820)	13,128	550 (240, 1,000)
Pneumoperitoneum	4,214	300 (130, 560)	96 (38, 200)	200 (84, 390)	2,083	290 (110, 630)
Aspirations	5,832	71 (34, 130)	18 (7.8, 32)	52 (23, 96)	2,665	62 (27, 120)
GI series	3,706	1.1 (0.18, 3.9)	13 (2.1, 46)	1.5 (0.22, 5.3)	1,805	1.7 (0.26, 6.0)
All fluoroscopies[a,c]	30,130	690 (350, 1,200)	190 (98, 340)	410 (220, 720)	15,435	510 (240, 940)
Chest radiographs	60,835	1.3 (0.65, 2.2)	0.56 (0.28, 0.99)	0.46 (0.22, 0.86)	30,618	0.20 (0.092, 0.36)
All procedures[a,c]	61,644	**340 (170, 580)**	**95 (49, 160)**	**200 (100, 350)**	30,996	**260 (120, 470)**

[a] Doses were averaged across all patients in the cohort (63,715 patients and 31,787 females; top panel), or across patients who received the listed procedure (bottom panel; numbers of patients in left-most column).

[b] Mean and 95% CI of estimated cohort average doses from 1,000 alternative realizations using Monte Carlo sampling techniques (values rounded to two significant digits).

[c] *All fluoroscopies*: Includes individuals with any fluoroscopic procedures; *All procedures*: includes individuals with any fluoroscopic or radiographic procedures. Averages are taken across all patients in the top panel, and across all patients with fluoroscopies or radiographic procedures in the bottom panel.

[d] Patients could have had one or multiple procedures of any given type; thus, the numbers of patients for *all fluoroscopies* and *all procedures* combined are smaller than the sum of the number of patients for each procedure type.

RESULTS

Cohort doses for the four organs of interest (lungs, female breast, active bone marrow and heart wall) are summarized in Table 4 as averages across the entire cohort (63,715 patients; 31,787 females for breast) and across exposed patients only, and include doses from all fluoroscopic examinations (pneumothorax, pneumoperitoneum, chest aspirations and GI series examinations), and from chest radiographs. Pneumothorax had the largest contribution to cohort average doses (across all patients) for any of the four organs (~90%), followed by pneumoperitoneum (~7%), chest aspirations (~2%), chest radiographies (<1%) and GI series (<1%); percentages in parenthesis are based on mean doses in Table 4.

Table 5 shows that, for all organs, approximately 60% of all patients had mean-estimated doses (mean across 1,000 realizations) of less than 10 mGy. These include patients who had exposures to chest radiographies or to one or two fluoroscopies. Approximately 10% of patients received between 10 and 100 mGy, 25% between 100 and 1,000 mGy, and 5% above 1,000 mGy. Patients with doses greater than 100 mGy had 10 or more medical procedures involving fluoroscopic exams.

TABLE 5
Percentage (%) of Cohort Patients with Mean Organ Doses in Selected Categories

Organ	Dose[a] category (mGy) <10	10 to 100	100 to 1,000	>1,000
Lungs	57	7	25	11
Female breast	57	8	30	5
Active bone marrow	60	13	26	1
Heart wall	59	9	28	4

[a] Doses from all fluoroscopic and radiographic exams.

Doses to Lungs

Figure 3 shows 1,000 alternative cohort lung doses to 30,130 patients who received medical procedures involving fluoroscopy, indicating that doses varied among patients by more than six orders of magnitude. The uncertainty in cohort average doses from all fluoroscopies, described as an uncertainty factor defined as the ratio of the 97.5th and 2.5th quantiles,[2] is about a factor of 3.4 for lungs (Table 4). The uncertainty factors in doses to lungs in individual patients, shown in Table 6, are larger than a factor of three for patients exposed to fluoroscopy procedures, with uncertainty factors of 3 to 5 in 45% of patients, 5 to 10 in 46% of patients, and more than 10 in 9% of patients.

[2] The magnitude of uncertainty can also be represented by ratios of the 97.5 quantile to the mean. Such ratios can be obtained from Table 4, or taken to be approximately equal to the square root of the uncertainty factors defined here as the ratio of the 97.5th and 2.5th quantiles.

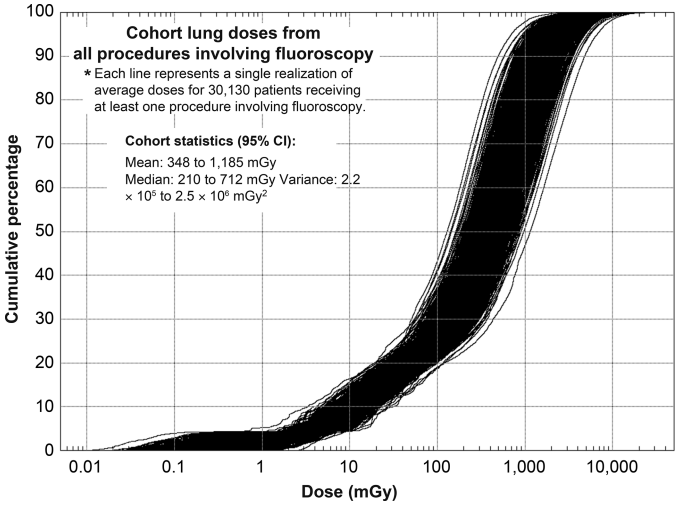

FIG. 3. Probability plot presenting 1,000 alternative realizations of average cohort lung doses in patients exposed during procedures involving fluoroscopy.

Doses to Female Breast

Orientation of patient relative to the X-ray tube has a major impact on doses to breast tissue, because the breast is shielded by the body in PA orientation. The differences between breast doses in AP and PA orientations were larger in adults than in children, because the larger body size of adults provides greater shielding. Because of the importance of patient orientation, uncertainty factors in cohort average doses to female breast are approximately 4.0, larger than uncertainty factors in lung cohort average doses. Uncertainty factors in doses to individual patients are also significantly higher than those in lung doses, having values from 3 to 5 in 5% of patients, 5 to 10 in 75% of patients, and more than 10 in 20% of patients (Table 6).

Doses to Active Bone Marrow

In general, doses to active marrow were estimated to be 3 to 4 times lower than doses to the lungs, primarily because much of the skeletal system and active marrow were outside of the field of view of an incident beam. Uncertainty factors in cohort average doses to active bone marrow from all fluoroscopies are about 3.4, similar to the uncertainty factors in lung doses, with uncertainty factors in doses to individual patients of 3 to 5 in 49% of patients, 5 to 10 in 42% of patients, and more than 10 in 9% of patients (Table 6).

Doses to Heart Wall

Estimated doses to the heart wall per medical procedure were higher than doses to lungs for patients treated in Nova Scotia, who received an average of 65% of their exams in AP orientation, but lower than doses to lungs for patients in other provinces where 92% of exams were carried out in PA orientation. In AP orientation, the heart is located close to the entrance surface and is only partly shielded by the sternum, while the bones in the spinal column provide more protection in PA orientation. Since approximately 90% of patients were treated in provinces other than Nova Scotia, the cohort average doses to the heart wall in Table 4 are lower than cohort average doses to lungs. Patient orientation is an important parameter for doses to heart wall, although not as important as for female breast. Uncertainty factors in doses to the heart wall to individual patients are larger than in lung doses but lower than in breast doses, with values of 3 to 5 in 28% of patients, 5 to 10 in 60% of patients, and more than 10 in 12% of patients (Table 6).

TABLE 6
Percentage (%) of Patients by Level of Uncertainty in Individual Doses from Fluoroscopy Procedures

Uncertainty factor[a]	Lungs	Female breast	Active bone marrow	Heart wall
3 to 5	45	5	49	28
5 to 10	46	75	42	60
>10	9	20	9	12

[a] Ratio of 97.5th to 2.5th percentiles of individual average dose to the listed organ.

DISCUSSION

The new dosimetry system (FLUXOR) allows estimation of absorbed doses to a range of organs and tissues in CFCS patients who received medical procedures involving fluoroscopic and radiographic exams. FLUXOR incorporates available patient-specific information on the types of medical procedures, ages at the time of each procedure, duration of treatment, sex, number of procedures and region (Nova Scotia or other provinces in Canada). FLUXOR has the capability of estimating doses to more than 50 organs and tissues of interest for epidemiologic analyses of radiation effects with respect to mortality and incidence in the CFCS. Here, we present a description of the dosimetry models, and estimated doses and their uncertainties to lungs, female breast, active bone marrow and heart wall.

Comparison with Other Studies

Average individual doses to lungs and female breast, without uncertainties, were previously estimated for the CFCS patients by Howe, and Howe and McLaughlin (*9, 12*), respectively. These doses accounted only for exposures from fluoroscopies associated with induction and maintenance of artificial pneumothorax, but not fluoroscopies associated with pneumoperitoneum, chest aspirations or GI series, or exposures from radiographic examinations (*9, 12*). The average lung dose among patients with estimated doses >10 mGy after pneumothorax was 1,020 mGy (*9*). The 95% CI of pneumothorax average doses of (363, 1,352) mGy estimated in this study (see Table 4) encompasses the previously estimated value, while our overall mean of 761 mGy, taken across all 1,000 alternative realizations of

cohort average doses and including patients with doses 1–9 mGy, is approximately 25% lower than the average dose reported by Howe (*9*). When accounting only for patients receiving >10 mGy, our pneumothorax doses to lungs range from 400 to 1,370 mGy (95% CI) and have an overall mean of 791 mGy (22% lower). Similarly, the previously estimated cohort average doses to breast from pneumothorax procedures in CFCS patients with doses >10 mGy is 890 mGy (*12*) and is contained within the 95% CI of average doses to the breast from pneumothorax procedures of (242, 1,024) mGy estimated in this study, with our overall mean of 545 mGy (Table 4) being about 40% lower. When accounting only for patients receiving >10 mGy, our doses to breast range from 277 to 1,069 mGy (overall mean 588 mGy; 34% lower). These differences are primarily due to the use of the most up-to-date dose conversion coefficients based on age- and gender-specific computerized phantoms, scaled to the Canadian population during the relevant time frame (*14*) and to a lesser degree due to differences in assumptions about technical parameters (primarily tube current, patient orientation and number of fluoroscopies per procedure). Our earlier published work (*14*) provides details about the up-to-date phantoms. Compared to the phantoms used in previously published studies (*9, 12*), the new phantoms include improved and more realistic descriptions of anatomy, size and position of organs for all ages and both genders. For the particular exposure conditions of this cohort, the new phantoms produced lower dose conversion coefficients than those reported in past studies, in particular for the PA orientation which was used preponderantly in all provinces of Canada (except Nova Scotia), where about 90% of patients in the cohort were treated.

The Canadian Fluoroscopy Cohort Study is positioned to address critical gaps in knowledge of the long-term health risks of diagnostic imaging procedures, given the particular exposures received by the CFCS patients: long-term fractionated external exposures to (only) X rays. Why is this important? The rise of computed tomography (CT) and radiological imaging is remarkable, with over 85 million examinations per year performed in the U.S. alone (*22*). Assessments of risks from CT scan exposures are based, in large part, on studies of Japanese atomic bomb (A-bomb) survivors, who experienced acute exposures to mostly high-energy gamma rays (*23*). These assessments require assumptions about the application of risk estimates from single acute exposures to cases of multiple CT examinations spread over time, which are common in medical practice (*24*). Recently published analyses indicate that X rays may exhibit an enhanced biological effectiveness in inducing cancer, relative to the high-energy gamma radiation received by the Japanese A-bomb survivors (*25–28*). A-bomb survivors also differ significantly from the U.S. population with respect to a number of lifestyle factors, in particular, diet, alcohol consumption and smoking, which have been shown to be independent risk factors for lung and breast cancers and leukemia. Incidence rates of these cancers differ between the U.S. and Japan, particularly within different age strata, but are much more similar between the U.S. and Canada (*29*).

Table 7 shows a comparison of estimated doses to lungs, active bone marrow, female breast and heart wall, for large radio-epidemiological cohorts. Direct studies of the association between multiple CT scans in children and subsequent cancer risk have been published (*30, 31*), but concerns have been raised about the absence of individual dosimetry and about the possibility of confounding by indication or reverse causation (*32, 33*). In particular, no doses were calculated in the Australian CT scan study, and risks were reported per additional CT scan (*30*). Further concerns include reported excess risk of brain cancer after CT scans of parts of the body remote from the brain and reported excesses of cancers known to be, at best, only weakly associated with exposure to radiation, while there was no excess of radiosensitive breast cancer among those exposed (*30*). It is also noteworthy that in two recently published studies, in France (*34*) and in Germany (*35*), no significant excess cancer risk from CT scans was found, once adjustments were made for conditions that prompted the scan, family history, or other predisposing factors known to be associated with increased cancer risk. These studies should be interpreted with caution due to the small number of cases and possible methodological issues (*36, 37*).

Studies of nuclear workers have generally limited statistical power due to low cumulative exposures (*38*). Similarly to the A-bomb studies, they include cohorts exposed to gamma rays (with possible contributions from neutrons or internal alpha emitters), while CT scans expose patients to X rays only (*26, 39*). In addition, the information these studies provide is only relevant to risks of radiation exposures in males of working age.

International groups tasked with assessing the effects of radiation and with setting safety standards, have pointed out that despite the large number of data on radiation risks, the transfer of risk estimates derived from one population to a different population remains an important source of uncertainty (*23*). Epidemiological studies based on the CFCS cohort would provide risk estimates for a Caucasian population directly, eliminating the need of a risk transfer from Japanese A-bomb survivors, as is most commonly done in current risk assessments.

The CFCS cohort can bring clarity to these issues because of the large size, long follow-up, a dosimetry system that addressed uncertainties in average doses and the similarity in radiation exposures between fluoroscopies and CT scans. Uniquely, the CFCS cohort is comprised of men and women of all ages, exposed over a prolonged period of time, and it includes a substantial group of patients (33,585 or 53%) who were not exposed to radiation from fluoroscopic examinations, that could be used as an internal comparison group.

TABLE 7
A Comparison of Average Doses to Main Organs of Interest in Large Epidemiological Studies

Study	Description of radiation exposure	Cohort size	Cohort-averaged dose (mGy) (95% CI)			
			Lungs	Female breast	Bone marrow	Heart wall
Canadian Fluoroscopy Cohort Study (this study)	X rays, moderate doses, low dose rate (fractionated)	63,715	690[a] (350, 1,200)	510[a] (240, 940)	190[a] (98, 340)	410[a] (220, 720)
Massachusetts Fluoroscopy Cohort Study (*43, 44*)	X rays, moderate doses, low dose rate (fractionated)	13,385	840	740	90	–[b]
U.S. Scoliosis Cohort Study (*45*)	X rays, low doses, low dose rate (fractionated)	3,010	–[b]	132	–[b]	–[b]
CT scans pediatric patients (*46*)	X rays, low doses, low dose rate (fractionated)	178,602	–[b]	–[b]	19[c]	–[b]
U.S. Radiological Technologists (*47, 48*)	X rays, low doses, low dose rate (chronic)	110,374	17	37	8.7	22
U.S. nuclear workers (*49*)	Gamma rays, low doses, low dose rate (chronic)	53,698	25.7[d]			
Canadian nuclear workers (*50*)	Gamma rays, low-to-moderate doses, low dose rate (chronic)	45,316	21.6[d]			
INWORKS nuclear workers (*51–53*)	Gamma rays, low-to-moderate doses, low dose rate (chronic)	308,297	22.8	5.6	16.0	–[b]
A-bomb survivors (*54–56*)	Gamma rays, low-to-moderate doses, high dose rate (acute)	113,011	230[e]	260[e]	230[e]	209[e]

[a] Averaged across patients who received any fluoroscopic examination.
[b] Not estimated.
[c] Dose to patients with disease (leukemia/MDS); dose to patients without disease was 12 mGy.
[d] Equivalent dose averaged over all organs across the entire cohort (mSv).
[e] Averaged across subjects with doses >5 mGy.

Sensitivity Analyses

Major contributors to uncertainty in estimated doses per procedure for the four organs of interest, determined using the method described in Supplementary Information, Appendix B (https://doi.org/10.1667/RADE-20-00212.1.S1), are the uncertainties in exposure duration, tube output, tube voltage, and patient orientation relative to the X-ray tube. The uncertainty in exposure duration was most often the dominant contributor (accounting for 50% or more of uncertainty in doses per procedure). Uncertainty in patient orientation was important for doses to female breast (up to 50%), and to a lesser degree (up to 20%) for doses to heart wall. The uncertainty in number of exams was an important contributor to uncertainty for ~ 30% of patients. Organ doses per procedure (Supplementary Table C1, Appendix C; https://doi.org/10.1667/RADE-20-00212.1.S1), varied with the position of the incident beam, with doses to organs in the chest cavity being lower in pneumoperitoneum procedures, or GI series, where the beam was centered in the abdominal area, than in pneumothorax procedures where the beam was centered on the lungs.

Other Dosimetry Considerations

The complexities of the FLUXOR dosimetry system are due, in part, to the variety of data sources, including interviews with physicians who performed treatments during the period of interest, contemporary data on machine settings obtained from literature, and information on procedures from medical records. FLUXOR accounts for the type of treatment procedure, the location where treatment was received (Nova Scotia or other provinces), the time period when treatment was received, and a patient's sex and age at the time of treatment. Ideally, doses to patients would be calculated based on patient-specific information on parameters used in each examination. However, details of fluoroscopic or radiographic examinations were not included in the abstracted medical records for any patients, and they were not recorded in the original medical records for any sanatoria operating in Canada during the period of interest. In the absence of patient- and examination-specific data, doses were estimated using probability distributions describing the uncertainty in average parameter values representative to all patients who were part of different subgroups of the cohort. Monte Carlo methods were used to propagate uncertainties, resulting in organ doses organized in a two-dimensional structure, comprised of 1,000 sets of alternative average doses to 63,715 individuals, suitable for different types of dose-response analyses (*20, 40, 41*).

Estimated doses to CFCS patients account for exposures received during the treatment of tuberculosis in sanatoria

and in hospitals with specialized tuberculosis units, but do not include doses that a patient may have received for purposes of tuberculosis diagnosis before being referred for treatment, or doses from other medical procedures not related to tuberculosis (if any), in the years after treatment in sanatoria, as no information about such exposures exists. Diagnostic procedures carried out before a patient arrived in a sanatorium were most likely chest radiographs which would have produced doses on the order of 1 mGy or lower, much lower than doses from fluoroscopic examinations received during treatment. Unaccounted radiation doses from diagnostic radiation exposures after tuberculosis treatment, such as CT scans and X rays, could lead to underestimation of total doses. For example, doses to the lungs from a single CT scan in the chest region [~20 mGy; (*42*)] are similar to doses from pneumothorax procedures estimated in this study (6–25 mGy depending on exposure conditions), but CFCS patients received, on average, 92 pneumothorax procedures, leading to much larger average doses to lungs (760 mGy; 95% CI: 360, 1,400; Table 4).

CONCLUSIONS

We developed a new dosimetry system (FLUXOR) to estimate organ doses and their uncertainties from exposures to X rays from fluoroscopic and radiographic exams. Age-, sex- and organ-specific absorbed doses were estimated in 63,715 tuberculosis patients in the Canadian Fluoroscopy Cohort Study who received fluoroscopic and chest radiographic examinations in the course of treatment, during the period 1930 to 1969. Doses from fluoroscopic procedures far exceed doses received from radiographic examinations. Multiple alternative realizations of average individual doses in the cohort were used to describe the uncertainty in dosimetry. Absorbed doses to lungs, female breast, active bone marrow and heart wall from fluoroscopic procedures varied among exposed patients from a few mGy to several Gy, with cohort-averaged doses having means from approximately 200 to 700 mGy and uncertainty factors (ratio of upper to lower bounds of a 95% CI) up to 4.0, depending on organ. The estimated organ doses and their uncertainties will be used for evaluation of incidence and mortality from cancer and noncancer diseases in the study cohort. The Canadian Fluoroscopy Cohort is an important addition to existing radio-epidemiological cohorts, given the moderate-to-high doses received fractionated over several years, the type of irradiation (external exposure only), radiation type (X rays only), the balanced combination of people of both genders, and inclusion of all age categories.

SUPPLEMENTARY INFORMATION

Appendix A. FLUXOR parameter values and their uncertainty.

Fig. A1. Measured tube output at fluoroscope panel, for different tube voltages and added filtrations.

Appendix B. Mathematical formulation.

Appendix C: Table C1. Additional results. Average doses (mGy) from a single medical procedure.

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