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Original Contribution

Potential Increased Risk of Ischemic Heart Disease Mortality With Significant Dose Fractionation in the Canadian Fluoroscopy Cohort Study

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Risks of noncancer causes of death, particularly cardiovascular disease, associated with exposures to high-dose ionizing radiation, are well known. Recent studies have reported excess risk in workers who are occupationally exposed to low doses at a low dose rate, but the risks of moderately fractionated exposures, such as occur during diagnostic radiation procedures, remain unclear. The Canadian Fluoroscopy Cohort Study includes 63,707 tuberculosis patients exposed to multiple fluoroscopic procedures in 1930–1952 and followed-up for death from noncancer causes in 1950–1987. We used a Poisson regression to estimate excess relative risk (ERR) per Gy of cumulative radiation dose to the lung (mean dose = 0.79 Gy; range, 0–11.60). The risk of death from noncancer causes was significantly lower in these subjects compared with the Canadian general population ($P < 0.001$). We estimated small, nonsignificant increases in the risk of death from noncancer causes with dose. We estimated an ERR/Gy of 0.176 (95% confidence interval: 0.011, 0.393) ($n = 5{,}818$ deaths) for ischemic heart disease (IHD) after adjustment for dose fractionation. A significant ($P = 0.022$) inverse dose fractionation effect in dose trends of IHD was observed, with the highest estimate of ERR/Gy for those with the fewest fluoroscopic procedures per year. Radiation-related risks of IHD decreased significantly with increasing time since first exposure and age at first exposure (both $P < 0.05$). This is the largest study of patients exposed to moderately fractionated low-to-moderate doses of radiation, and it provides additional evidence of increased radiation-associated risks of death from IHD, in particular, significantly increased radiation risks from doses similar to those from diagnostic radiation procedures. The novel finding of a significant inverse dose-fractionation association in IHD mortality requires further investigation.

cardiovascular disease; dose fractionation; ionizing radiation; ischemic heart disease; noncancer diseases; radiation dose-response relationship

Abbreviations: CI, confidence interval; CT, computed tomography; CVD, cardiovascular disease; ERR, excess relative risk; ICD, *International Classification of Diseases*; ICD-9, *International Classification of Diseases, Ninth Revision*; IHD, ischemic heart disease; LSS, Life Span Study; SMR, standardized mortality ratio.

The relationship between exposure to ionizing radiation and subsequent development of cancer has been firmly established in many studies (1). Therapeutic doses of ionizing radiation to the heart and large arteries have long been shown to be associated with several noncancer causes of death, particularly coronary heart disease, myocardial infarction, and stroke, in studies of patients treated with radiotherapy for breast cancer (2–5), Hodgkin disease (6–8), and peptic ulcer (9), as well as in childhood cancer survivors (reviewed by Stewart (10)). More recently, and controversially, there have been emerging reports of excess mortality and morbidity from circulatory disease—both cardiovascular disease (CVD) and cerebrovascular disease—in a number of groups exposed to moderate and low doses, in particular in the Life Span Study (LSS) of Japanese atomic bomb survivors (11), but also in a number of occupationally exposed cohorts (reviewed by Little et al. (12)). However, the complicated, multifactorial nature of CVD and possible contributions from unmeasured

confounders and errors in dose estimates inevitably raise concerns over whether the observed associations are causal (12).

It is still not clear whether the CVD risks in occupational settings, characterized by small daily dose fractions, are associated with lower risks than those for acute, high-dose exposure in the way that would be expected for cancer (12, 13). Even less is known about the risks of diagnostic low-dose radiation imaging technologies such as computed tomography (CT), radiation doses from which are sometimes higher than cumulative lifetime occupational exposures (14). Given the tripling in use of CT scans in the United States since 1993 (14), it is important to understand the risks of such exposures received over a protracted time period. However, very limited epidemiologic data exist to examine how dose fractionation modifies noncancer risks (15).

The Canadian and US cohorts that administered fluoroscopic x-rays as part of treatment of tuberculosis have been studied in relationship to cancer (16–19), but noncancer diseases have not been examined. In light of the potential importance of such an association for radiological protection of the general population, further epidemiologic studies, particularly those that quantify dose and its fractionation, are needed (20). The Canadian Fluoroscopy Cohort Study includes all 63,707 tuberculosis patients admitted to medical institutions in Canada who received widely varying cumulative doses of highly fractionated ionizing radiation. In this article, we assess noncancer disease mortality between 1950 and 1987. We decided a priori to concentrate on the relationship between cumulative lung tissue dose and several noncancer causes of death in organs in the direct path of the fluoroscopic beam, with particular emphasis on radiation-associated risks of CVD and dose-fractionation associations.

MATERIALS AND METHODS

Cohort characteristics and follow-up

The methods used to assemble the cohort have been described previously (18) and are summarized briefly below. The medical records from all Canadian institutions that treated tuberculosis patients in 1930–1952 were examined to extract information on patient identification and treatment for tuberculosis, including a detailed history of any artificial pneumothorax (110,088 patient records from 46 institutions). Multiple admissions to different institutions were identified by computerized record linkage of the patient records (21), resulting in 92,707 patients.

Deaths in the cohort were ascertained via computerized record linkage with the Canadian Mortality Database. Because information on cause of death is available only since 1950, we included in the cohort only those known to be alive at the beginning of 1950. Exclusions were made for those with incorrect age ($n = 1,653$), invalid last contact status or year ($n = 850$), age of more than 100 years at the end of follow-up ($n = 2,392$), and other record irregularities ($n = 6$), leaving a cohort of 63,707 patients for analysis (24,932 radiation-exposed subjects and 38,775 unexposed subjects).

The underlying causes of death were recoded from the original *International Classification of Diseases* (ICD) codes in use at the time of death to those of the *International Classification of Diseases, Ninth Revision* (ICD-9). The analysis focuses on diseases involving organs that were in the direct path of the fluoroscopic beam, including all respiratory diseases (ICD-9 codes 460–519) and CVDs. All CVDs (ICD-9 codes 390–448) were split into hypertensive disease (ICD-9 codes 401–405), ischemic heart disease (IHD) (ICD-9 codes 410–414 and 429.2), and other cardiovascular nonstroke diseases. Stroke (ICD-9 codes 430–438) was excluded because the relevant organs are largely out of the direct path of the beam.

Dosimetry

Absorbed lung doses from fluoroscopy were estimated for each patient for each year since first admission for treatment for tuberculosis, as described by Miller et al. (22). Briefly, the following 4 components were used to estimate total dose: 1) counts of the number of fluoroscopic procedures each patient underwent in each calendar year; 2) data on the output of typical fluoroscopes used during the relevant period; 3) data from human phantom experiments on the estimated organ dose per unit of surface exposure, depending on shuttering used and whether or not filtration was added to the x-ray beam (23); and 4) interviews with 91 physicians who administered artificial pneumothorax during the relevant period to ascertain contemporary fluoroscopy practices. Previously, average parameters estimated from these interviews were used in dose estimation models (18). In the current analysis, for each lung dose to be estimated, 100,000 simulations were carried out. In each simulation, a value of each parameter was chosen at random from among the 91 physicians who administered artificial pneumothorax, weighted by their years of experience. The dose was then estimated as the arithmetic mean of all simulations as the most appropriate for fitting a linear dose-response relationship, somewhat analogous to regression calibration (24).

We used the lung dose as a central dose measurement of interest because it should be a reasonable surrogate for doses to the heart and associated major blood vessels. The lung tissue doses were estimated as organ-absorbed doses in Gy. A typical fluoroscopic examination delivered an average lung dose of 0.0125 Gy (range, 0.010–0.016) at a dose rate of approximately 0.6 mGy/second (18).

Statistical analysis

Each patient contributed person-years at risk from the later of the start date of treatment or the start date of follow-up, defined as January 1, 1950, to the exit date of December 31, 1987, or the date of death, whichever occurred earlier. The person-years at risk were classified by sex, Canadian province of most admissions, type of tuberculosis diagnosis (pulmonary/nonpulmonary), stage of tuberculosis (minimal, moderate, advanced, or not specified), smoking status (unknown, nonsmoker, or smoker), age at first exposure (0–4, 5–9, 10–19, or 20–87 years), attained age (0–24, 25–29, . . . 80–84, or 85–100 years), calendar year at risk (1950–1954, 1955–1959, . . . 1980–1984, or 1985–1987), duration of fluoroscopy screenings (0, 0.04–1, or 1–30 years), and cumulative lagged lung dose. Doses were lagged by

10 years, a minimal latent period that has been used in several studies of long-term risks of radiation exposure on cancer and noncancer mortality risk (12, 20); additional analyses were conducted by using latent periods of 5 and 15 years. In contrast to studies by Howe (18) and Howe and McLaughlin (19), which treated doses as instantaneous exposures, we used time-dependent person-year–weighted mean cumulative dose in each cross-classified cell in the regression analyses.

The first series of analyses compared the cohort with the general Canadian population. Standardized mortality ratios (SMRs) were estimated by using sex-, attained age–, and calendar year–specific Canadian general population mortality rates for 1950–1987. Additional analyses examined variation of SMRs by radiation dose categories (nonexposed, exposed to 0–0.99 Gy, or exposed to 1.00–11.60 Gy).

In the second series of analyses, we used Poisson regression as follows:

$$R(D) = R_0 \times \left(1 + \beta D \exp\left(\sum_i \gamma_i Z_i\right)\right) \qquad (1)$$

where $R(D)$ is the disease rate at dose D, R_0 is the background (0 dose) parametric rate that depends on various possibly confounding factors, β is the excess relative risk (ERR) per 1 Gy of lung dose (ERR/Gy), and γ_i are regression estimates for association-modifying factors, Z_i, such as age at first exposure or dose fractionation. Because of the observed differences in background rates by sex, attained age, calendar year, province of admission, type and stage of tuberculosis, and duration of fluoroscopy screenings, all subsequent analyses were adjusted for these variables by stratification.

The number of deaths used in the dose-response analysis is smaller than that in the standardized mortality ratio analysis because of different cutoff linkage weights used for computerized linkage of the cohort with the Canadian Mortality Data Base. A lower cutoff value is used in the standardized mortality ratio analysis in order for the cohort to be as comparable as possible to the Canadian population. The increased cutoff point for the internal dose-response analysis was used to avoid dilution of any association due to the presence of false positives (i.e., false linkages); it would not be expected to bias estimates of relative risk.

Dose fractionation was calculated as a continuous variable by using the ratio of cumulative lung dose and overall duration of fluoroscopy treatments and expressed in Gy/year. In all subsequent analyses, dose fractionation was used as a proxy for radiation dose protraction. The variable was not time dependent and was centered so that the dose-association parameter corresponded to the risk for a person with radiation exposures at 0.2 Gy/year (~16 fluoroscopic procedures/year).

The primary model used to evaluate the dose response assumes a linear dose-response relationship, but we also evaluated several alternative forms, including linear-quadratic and linear-exponential relationships. We also examined a nonparametric model allowing the dose response to vary by dose categories (0, 0–0.14, 0.15–0.49, 0.50–0.99, and 1.00–11.60 Gy), which were chosen to evenly distribute cases.

Maximum likelihood techniques (25) were used to fit the model via EPICURE software (HiroSoft International Corporation, Seattle, Washington). All tests were 2-sided with a specified type I error of 0.05, and confidence intervals for risk estimates were derived by the profile likelihood. Because of the form of equation 1, the possible values of β are limited by the requirement that the corresponding relative risk should not be negative. If the likelihood optimum being sought for a point or bound estimate attempted to converge below this limiting value, the minimum value for β was used, given by $-1/D_{\max}$, where $D_{\max}$ was the maximum dose.

Table 1. Study Characteristics of the Canadian Fluoroscopy Cohort Study ($n = 63{,}707$), 1950–1987

Characteristic	No.	Mean	Median	Range
Person-years of follow-up	1,902,252			
Follow-up, years		31		0–37
Age at end of follow-up, years		65		1–99
Time since first exposure, years		39		0–57
Number of fluoroscopic procedures[a]			64	1–2,041
Duration of fluoroscopy screenings, years[a]			2	0–35
Dose fractionation, Gy/year[a]			0.36	0–7.30
Total dose, Gy[b]		0.79		0–11.60

[a] Exposed subjects only.
[b] Cumulative person-time–weighted lung dose.

RESULTS

Table 1 presents characteristics of the 63,707 subjects in the Canadian Fluoroscopy Cohort Study by exposure status. Radiation doses from fluoroscopic procedures were generally accumulated over a protracted period, with the majority of patients (85%) receiving doses over a period of less than 3 years (data not shown) (median, 2 years) (Table 1). The mean cumulative person-time–weighted lung dose for the entire cohort was 0.79 Gy. Among exposed patients, the mean lung dose was 0.92 Gy (data not shown), and the median dose fractionation was 0.36 Gy/year.

Table 2 demonstrates that the cohort was evenly split between men and women. Overall, 24,932 subjects (39% of the cohort) were exposed to at least 1 fluoroscopic procedure in association with artificial pneumothorax.

Approximately 21% of the nonexposed subjects did not have pulmonary tuberculosis, whereas almost all of the exposed subjects had pulmonary tuberculosis (Table 2). Rates of smoking among those with smoking information were similar for exposed and nonexposed subjects (76% and 74%, respectively). Because background mortality rates for all noncancer diseases and CVD did not differ significantly between smokers and nonsmokers after adjustment for radiation dose, smoking was not used as an adjustment factor in further analyses.

Based on 14,884 noncancer deaths (Table 3), the mortality rate in the cohort was similar to that of the sex-, attained age–, and calendar year–comparable Canadian general population

Table 2. Characteristics of Subjects in the Canadian Fluoroscopy Cohort Study, 1950–1987

Characteristic	Nonexposed ($n = 38,775$)		Exposed ($n = 24,932$)		Total ($n = 63,707$)	
	No.	%	No.	%	No.	%
Sex						
Men	20,116	51.9	11,804	47.3	31,920	50.1
Women	18,659	48.1	13,128	52.7	31,787	49.9
Birth year						
1853–1899	6,827	17.6	1,599	6.4	8,426	13.2
1900–1909	6,466	16.7	4,092	16.4	10,558	16.6
1910–1919	9,273	23.9	8,892	35.7	18,165	28.5
1920–1929	10,900	28.1	8,850	35.5	19,750	31.0
1930–1939	4,112	10.6	1,476	5.9	5,588	8.8
1940–1949	1,197	3.1	23	0.1	1,220	1.9
Year of first admission						
1930–1934	2,389	6.2	1,932	7.7	4,321	6.8
1935–1939	3,938	10.2	4,766	19.1	8,704	13.7
1940–1944	9,370	24.2	7,689	30.8	17,059	26.8
1945–1952	12,957	33.4	8,184	32.8	21,141	33.2
Age at first admission, years						
0–9	2,292	5.9	161	0.6	2,453	3.9
10–19	6,499	16.8	5,297	21.2	11,796	18.5
20–29	13,167	34.0	12,399	49.7	25,566	40.1
30–39	7,259	18.7	4,830	19.4	12,089	19.0
40–89	9,558	24.6	2,245	9.0	11,803	18.5
Province of most admissions						
Nova Scotia	2,494	6.4	1,914	7.7	4,408	6.9
Other	36,281	93.6	23,018	92.3	59,299	93.1
Type of tuberculosis						
Pulmonary	8,121	20.9	288	1.2	8,409	13.2
Nonpulmonary	30,654	79.1	24,644	98.8	55,298	86.8
Stage of tuberculosis						
Minimal	11,703	30.2	3,561	14.3	15,264	24.0
Moderate	11,012	28.4	11,684	46.9	22,696	35.6
Advanced	7,143	18.4	9,110	36.5	16,253	25.5
Not assigned	8,917	23.0	577	2.3	9,494	14.9
Smoking status						
Nonsmoker	1,928	5.0	1,528	6.1	3,456	5.4
Smoker	5,441	14.0	4,731	19.0	10,172	16.0
Unknown	31,406	81.0	18,673	74.9	50,079	78.6

(SMR = 0.96, 95% confidence interval (CI): 0.94, 0.97, $P < 0.001$). Of the CVD endpoints, IHD showed significantly reduced SMRs compared with the general population. The SMRs for each cause of death were similar for men and women (results not shown). When the SMRs were examined in 3 dose groups (unexposed, 0–0. 99 Gy, and 1.00–11.60 Gy), we observed a 10% excess of CVD deaths in those with any fluoroscopy exposure compared with those with no exposure, but there appeared to be no dose-response relationship (Table 3).

In the categorical analysis, risks of all noncancer and IHD mortality were nonsignificantly increased compared with those with dose 0 (Table 4, which also shows numbers of deaths and person-years by dose category). Table 5 further demonstrates that there were few indications of trends of noncancer disease mortality with radiation dose.

Table 3. SMRs for Various Causes of Death Compared With Canadian Population Rates, Canadian Fluoroscopy Cohort Study, 1950–1987

Cause of Death	Nonexposed			Exposed to Dose[a] of 0–0.99 Gy			Exposed to Dose[a] of 1.00–11.60 Gy			Entire Cohort		
	No. of Observed Deaths	SMR[b]	95% CI	No. of Observed Deaths	SMR[b]	95% CI	No. of Observed Deaths	SMR[b]	95% CI	No. of Observed Deaths	SMR[b]	95% CI
All causes	16,811	1.28	1.26, 1.30	6,022	1.37	1.34, 1.41	9,930	1.40	1.37, 1.43	26,741	1.32	1.30, 1.34
All noncancer[c]	9,505	0.92	0.90, 0.93	3,364	1.03	1.00, 1.07	2,015	1.04	1.00, 1.09	14,884	0.96	0.94, 0.97
All CVDs	6,580	0.88	0.85, 0.90	2,361	1.01	0.97, 1.05	1,362	1.00	0.95, 1.06	10,303	0.92	0.90, 0.94
Hypertensive	58	0.66	0.50, 0.85	38	1.31	0.93, 1.79	18	1.03	0.61, 1.63	114	0.85	0.70, 1.02
Ischemic heart disease	4,285	0.89	0.87, 0.92	1,585	1.03	0.98, 1.08	890	0.98	0.92, 1.05	6,760	0.93	0.91, 0.96
Stroke	1,054	0.74	0.70, 0.79	344	0.85	0.76, 0.95	187	0.83	0.71, 0.93	1,585	0.77	0.74, 0.81
Other (nonstroke) CVDs	1,183	0.98	0.92, 1.03	394	1.09	0.98, 1.20	267	1.27	1.12, 1.43	1,844	1.03	0.99, 1.08
All respiratory diseases	1,852	1.80	1.72, 1.88	638	2.01	1.86, 2.17	438	2.39	2.17, 2.63	2,928	1.91	1.85, 1.98
All infectious diseases	2,959	19.38	18.69, 20.10	1,180	21.53	20.32, 22.80	793	22.22	20.70, 23.82	4,932	20.28	19.72, 20.86
All tuberculosis	2,872	31.53	30.39, 32.71	1,154	34.57	32.60, 36.62	773	35.38	32.93, 37.96	4,799	32.80	31.88, 33.74
Other infectious diseases	87	1.41	1.13, 1.74	26	1.21	0.79, 1.78	20	1.44	0.88, 2.23	133	1.37	1.15, 1.63
All solid cancers	3,002	1.02	0.99, 1.06	1,018	0.94	0.88, 1.00	1,807	1.01	0.96, 1.05	4,809	1.02	0.99, 1.05

Abbreviations: CI, confidence interval; CVD, cardiovascular disease; SMR, standardized mortality ratio.

[a] "Dose" refers to the cumulative person-time–weighted lung dose.

[b] Standardized by sex, attained age, and calendar year.

[c] Excludes deaths attributed to tumors that were benign or of uncertain nature, infectious diseases, and external causes.

Table 4. Relative Risks for Noncancer Causes of Death From the Categorical Analysis, Canadian Fluoroscopy Cohort Study, 1950–1987

Dose[a] Category, Gy	Mean Dose, Gy	Person-years	All Noncancer Deaths[b]			Ischemic Heart Disease Deaths		
			No.	RR[c]	95% CI	No.	RR[c]	95% CI
0	0	1,231,110	8,299	1		3,716	1	
0.01–0.14	0.06	144,709	1,149	1.25	0.97, 1.60	526	1.35	0.92, 1.97
0.15–0.49	0.32	146,841	1,081	1.23	0.96, 1.58	492	1.33	0.91, 1.93
0.50–0.99	0.74	157,004	964	1.17	0.91, 1.51	456	1.23	0.84, 1.82
1.00–11.60	2.40	222,590	1,442	1.20	0.93, 1.55	628	1.20	0.81, 1.76
Total	0.79	1,902,254	12,935			5,818		

Abbreviations: CI, confidence interval; RR, relative risk.
[a] "Dose" refers to the cumulative person-time–weighted lung dose.
[b] Excludes deaths attributed to tumors that were benign or of uncertain nature, infectious diseases, and external causes.
[c] All analyses are adjusted for categories of sex, attained age, calendar year, Canadian province of admission, type (pulmonary vs. nonpulmonary) and stage of tuberculosis diagnosis, and duration of fluoroscopy screenings by stratification.

By contrast, models with adjustment for modification by dose fractionation had generally larger ERR/Gy estimates and, for IHD, this was statistically significant ($P = 0.031$, ERR/Gy = 0.176, 95% CI: 0.011, 0.393). The trend was linear; tests for quadratic and exponential deviations from the linear dose response were not significant ($P = 0.178$ and $P = 0.241$, respectively, results not shown). When analyses were restricted to patients with cumulative doses of less than 0.5 Gy, we estimated an ERR/Gy of 0.149 (95% CI: −0.284, 0.670) based on 4,734 IHD deaths among 61,063 subjects (results not shown). The modifications by dose fractionation, age at first exposure, and time since first exposure were not statistically significant in this subset (all $P > 0.2$, results not shown).

Results of analyses using 5- and 15-year lags in lung doses are presented in Appendix Table 1. Similar trends were observed in analyses with adjustment for dose fractionation, although the findings for IHD were no longer significant. The ERR/Gy of all respiratory diseases increased with increasing lag time.

Table 6 shows estimated risks for noncancer outcomes separately for 3 categories of dose fractionation. Dose fractionation was a significant modifier of risks of IHD mortality (P for heterogeneity = 0.022). The highest risks were estimated for those with dose fractionation of 0–0.14 Gy/year or 0–11 fluoroscopic procedures/year (ERR/Gy = 0.592, 95% CI: 0.004, 1.400), and lower risks were estimated for those exposed to doses fractionated at 0.15–0.29 Gy/year (ERR/Gy = 0.145, 95% CI: 0.007, 0.320) and 0.30–7.30 Gy/year (ERR/Gy = 0.010, 95% CI: −0.043, 0.078). There were similar trends of higher risks with increasing dose fractionation for all CVDs and all noncancer outcomes combined, but they were not statistically significant. In the whole cohort, cumulative person-time–weighted lung radiation dose was only moderately associated with dose fractionation (Pearson's $r = 0.314$).

In the analysis of radiation dose–modifying associations (Table 7), we observed a significant decrease in ERR of IHD with increasing time since first exposure ($P = 0.013$) and increasing age at first exposure ($P = 0.004$). The

Table 5. Excess Relative Risks per Gy for Noncancer Causes of Death, Canadian Fluoroscopy Cohort Study, 1950–1987

Cause of Death	No. of Deaths	ERR/Gy[c]	95% CI	*P* Value[a]	Dose-Fractionation Adjusted ERR/Gy[c,d]	95% CI	*P* Value[b]
All noncancer[e]	12,935	0.032	−0.006, 0.078	0.104	0.042	<−0.087, 0.159	0.779
All CVDs	8,877	0.020	−0.025, 0.074	0.413	0.069	−0.050, 0.219	0.472
Ischemic heart disease	5,818	0.007	−0.044, 0.072	0.800	0.176	0.011, 0.393	0.031
Hypertensive and other (nonstroke) CVDs	1,697	0.027	−0.064, 0.167	0.609	0.034	<−0.087, 0.161	0.464
All respiratory	2,658	0.081	−0.002, 0.197	0.058	0.060	<−0.087, 0.259	0.551

Abbreviations: CI, confidence interval; CVD, cardiovascular disease; ERR, excess relative risk.
[a] *P* for departure of ERR/Gy from 0.
[b] *P* for significance of dose-fractionation modification.
[c] All analyses are adjusted for categories of sex, attained age, calendar year, Canadian province of admission, type (pulmonary vs. nonpulmonary) and stage of tuberculosis diagnosis, and duration of fluoroscopy screenings by stratification.
[d] Additionally adjusted for continuous dose-fractionation modifications (i.e., ERR/Gy at 0.2 Gy/year or 16 fluoroscopic procedures/year).
[e] Excludes deaths attributed to tumors that were benign or of uncertain nature, infectious diseases, and external causes.

Table 6. Excess Relative Risks per Gy for Noncancer Causes of Death by Categories of Dose Fractionation, Canadian Fluoroscopy Cohort Study, 1950–1987

Cause of Death	Dose Fractionation, Gy/year[a]										P Value[b]
	0		0.0004–0.14			0.15–0.29			0.30–7.30		
	No. of Deaths	No. of Deaths	ERR/Gy[c]	95% CI	No. of Deaths	ERR/Gy[c]	95% CI	No. of Deaths	ERR/Gy[c]	95% CI	
All noncancer[d]	8,299	810	0.168	−0.179, 0.617	940	0.069	−0.017, 0.173	2,886	0.034	−0.006, 0.080	0.569
All CVDs	5,696	569	0.281	−0.139, 0.848	650	0.089	−0.017, 0.219	1,962	0.021	−0.025, 0.077	0.241
Ischemic heart disease	3,716	391	0.592	0.004, 1.400	442	0.145	0.007, 0.320	1,269	0.010	−0.043, 0.078	0.022
Hypertensive and other (nonstroke) CVDs	1,078	106	0.381	<−0.198, 1.953	120	−0.069	<−0.099, 0.187	393	0.035	−0.059, 0.177	0.447
All respiratory diseases	1,694	179	0.645	<−0.200, 2.114	186	−0.0002	<−0.117, 0.225	599	0.093	0.006, 0.214	0.299

Abbreviations: CI, confidence interval; CVD, cardiovascular disease; ERR, excess relative risk.

[a] The 4 dose fractionation groups are equivalent to the following numbers of fluoroscopic procedures per year: 0, >0–11, 12–23, and 24–584.

[b] *P* for heterogeneity from the likelihood ratio test.

[c] All analyses are adjusted for categories of sex, attained age, calendar year, Canadian province of admission, type (pulmonary vs. nonpulmonary) and stage of tuberculosis diagnosis, and duration of fluoroscopy screenings by stratification.

[d] Excludes deaths attributed to tumors that were benign or of uncertain nature, infectious diseases, and external causes.

estimates for dose fractionation after adjustment for age at first exposure and time since first exposure were still significant ($P = 0.061$ and $P = 0.007$, respectively) (results not shown). Risks did not differ by sex, type or stage of tuberculosis, attained age, or smoking status (all $P > 0.2$).

DISCUSSION

In this analysis based on the largest cohort of patients exposed to low-to-moderate fractionated doses of ionizing radiation, we found that risks of all CVDs and individual outcomes generally were somewhat lower or similar to those of the general Canadian population. However, subjects with any fluoroscopy exposure had a small, statistically nonsignificant excess CVD mortality risk compared with those with no exposure. Significantly increased radiation-related risks of IHD were estimated for dose fractionation below 0.3 Gy/year (<24 fluoroscopic procedures/year). We estimated a statistically significant inverse dose-fractionation association for IHD (i.e., the highest radiation risks were observed for the highest dose fractionation). Radiation-related risks of IHD decreased significantly with increasing time since first exposure and age at first exposure.

In light of the importance of an observed association for radiological protection of the general population exposed to potential risks of CT scans and other radiation diagnostic techniques, it is important to understand the mechanism of the association between low-dose ionizing radiation and IHD. IHD is the leading cause of death in the United States (26) and worldwide (27), so even small elevations in relative risk caused by low-level exposure may be of considerable public health concern. Approximately a quarter of the Canadian Fluoroscopy Cohort Study subjects with at least 1 fluoroscopy procedure ($n = 144{,}709$ person-years) were exposed to doses of less than 0.15 Gy and thus provide direct evidence of risks from low-dose exposures such as CT scans, which, for an appreciable proportion of the US population, are in excess of 0.05 Gy/year (28). Although a typical dose to the lung from fluoroscopic examination (0.0125 Gy) is similar to a lung dose from a chest CT scan (0.0224 Gy) (29), the maximum dose in our study, 11.60 Gy (Table 1), is much higher than any expected from CT scans. We estimated a significantly increased risk of IHD among those exposed at a rate of 0–11 fluoroscopic procedures per year (ERR/Gy = 0.592, 95% CI: 0.004, 1.400).

This study has a number of strengths. The results are based on a long-term follow-up of a very large cohort of subjects of both sexes exposed at different ages. We were able to evaluate the risks of low-to-moderate radiation doses protracted over time. To account for various uncertainties in radiation dose estimation, we estimated lung doses by using Monte Carlo simulation techniques, which sampled from probability distributions of various data sources and should provide a reasonable estimate of radiation doses to the lung and heart. This analysis focuses on those organs that would have been in the direct path of the fluoroscopic beam and for which the lung tissue doses should be reasonable surrogates for the relevant organ dose, in particular for IHD and nonmalignant respiratory diseases. The outcome and exposure information

Table 7. Summary of Results for Risk Models with Interaction Terms for Ischemic Heart Disease, Canadian Fluoroscopy Cohort Study, 1950–1987

Dose-Response Modifier	No. of Deaths (Total $n = 5,818$)	Person-years ($n = 1,902,252$)	Dose-Fractionation Adjusted		P Value[a]
			ERR/Gy[b]	95% CI	
Sex					
Men	4,217	871,353	0.251	0.028, 0.539	0.298
Women	1,601	1,030,899	0.019	−0.177, 0.406	
Age at first exposure, years					
0–9	23	83,833	0.817	<−0.194, 8.605	0.004[c]
10–19	362	372,174	0.144	−0.153, 0.608	
20–87.4	5,433	1,446,245	0.175	0.006, 0.403	
Time since first exposure, years					
0–19	1,885	1,001,202	0.766	0.204, 1.658	
20–29	1,758	486,066	0.335	0.024, 0.826	0.013[c]
30–39	1,718	347,068	0.053	−0.061, 0.154	
40–57	457	67,916	−0.108	<−0.117, 0.376	
Type of tuberculosis					
Pulmonary	5,077	1,644,842	0.178	0.013, 0.400	0.598
Nonpulmonary	741	257,410	<−0.222	Not estimated	
Stage of tuberculosis[d]					
Minimal	1,105	504,109	0.512	−0.185, 2.263	0.769
Moderate	2,193	697,296	0.150	−0.087, 0.557	
Advanced	1,675	409,286	0.176	−0.024, 0.462	
Attained age, years					
4–49	487	972,902	−0.031	<−0.111, 0.800	0.650[c]
50–69	2,978	763,075	0.162	−0.037, 0.452	
70–98	2,353	166,275	0.262	−0.030, 0.738	
Smoking status[d]					
Nonsmoker	275	108,735	0.166	<−0.101, 0.655	0.389
Smoker	1,214	290,243	0.365	<−0.103, 0.871	

Abbreviations: CI, confidence interval; ERR, excess relative risk.

[a] P for likelihood ratio test for interactions unless otherwise stated.

[b] Analyses are adjusted for categories of sex, attained age, calendar year, Canadian province of admission, type (pulmonary vs. nonpulmonary) and stage of tuberculosis diagnosis, and duration of fluoroscopy screenings by stratification, as well as continuous dose-fractionation modifications (i.e., ERR/Gy at 0.2 Gy/year or 16 fluoroscopic procedures/year).

[c] P for linear trend test.

[d] Results from analyses restricted to those with known stage of tuberculosis and smoking information.

are both register-based, so most biases (e.g., due to misclassification of exposure or outcome) are unlikely.

The most important limitation is the lack of data on potential confounders, particularly socioeconomic status and smoking. Unfortunately, a limited amount of smoking information is available for only approximately 20% of the cohort (Table 2). However, separate analyses of IHD deaths among those who had information on smoking status showed similar radiation-related risks for smokers and nonsmokers ($P = 0.389$, Table 7), suggesting that smoking did not mask an association between radiation and IHD mortality. Our finding is similar to those in the LSS of Japanese atomic bomb survivors (11) and in the study of workers of the Mayak Production Association in the Southern Urals region of the Russian Federation (30), neither of which found an interaction of smoking with radiation-associated heart disease. We also lacked information on other important CVD risk factors, such as family history of heart disease, diabetes, high blood pressure, obesity, and cholesterol plasma levels (31, 32). However, because these factors are unlikely to be associated with radiation dose, they are unlikely to have confounded the observed association. Risk analyses of Mayak workers showed little impact on radiation risk estimates from adjustment for blood pressure and body mass index (weight (kg)/height (m)^2) (30), and there was similarly little evidence of modification of radiation-related risk of IHD by a variety of medical and lifestyle factors in a Nordic cohort of women treated for breast cancer (5).

Another limitation of the results is that there are few grounds a priori for expecting an inverse dose-fractionation association. In general, ERRs per Gy of circulatory disease are similar in groups exposed occupationally to moderate or low doses at low dose rates, in atomic bomb survivors exposed to moderate or low doses at high dose rates, and in medically exposed groups exposed at high doses and high-dose rates (12). This suggests that there should be no large (inverse or positive) dose-fractionation association. The unexpected finding could also be due to multiple comparisons. However, the observation of a clear monotonic decrease in risks with decreasing dose fractionation argues against it being simply a chance finding.

Competing mortality risks could influence the results of the study. For example, if those who were more susceptible to tuberculosis death were also more susceptible to, for example, radiation-induced CVD death, radiogenic excess risks of subsequent radiation-induced CVD could be reduced in the surviving population. However, all analyses were adjusted for confounding by stage of tuberculosis, so bias from this hypothetical mechanism is unlikely. Study findings are limited by the end of follow-up in 1987, although the majority of study subjects were older than 60 years at the end of follow-up, so few extra CVD deaths would be expected were follow-up to be extended. The impact of measurement errors in dosimetry was estimated in previous studies and shown to be relatively small and primarily of Berkson type (19) and therefore unlikely to introduce a substantial bias in risk estimates (24).

Studies of the association of radiation incurred during treatment for cancer and noncancer diseases with the risk of subsequent noncancer diseases have primarily concerned partial-body radiation exposures and subjects exposed to much higher radiation doses than observed in this study. In general, excess CVD risk has been observed in many groups of breast cancer survivors, in which radiation doses to the heart are expected to be high (3–5). Radiation-related risks of IHD were also increased in patients given mediastinal irradiation for Hodgkin disease (7, 8). A cohort study of peptic ulcer patients, in whom exposures would be somewhat lower than in those treated for cancer, found that radiation therapy increased the risk of diseases of the circulatory system, specifically IHD (9). Nearly a quarter of subjects in our study were first exposed before age 20 years. Studies of survivors of childhood cancer have reported increased risks of CVD outcomes, but lower doses were not significantly associated with increased risks (33, 34).

Analysis of the mortality of tuberculosis fluoroscopy patients in Massachusetts showed that death rates from circulatory diseases were similar to those of the US population (17); however, no analyses of dose response were presented, and the "all circulatory disease" group included a large number of stroke deaths, which were unlikely to be radiation associated because the brain and cerebral arteries were not in the path of the fluoroscopic beam.

Recent studies of moderate- and low-dose–exposed groups (doses <0.5 Sv/day and <0.01 Sv/day) from the LSS of Japanese atomic bomb survivors (11) and studies of nuclear workers (35, 36) and uranium miners (37–39) suggest that there are radiogenic excess risks of most major subtypes of circulatory disease. In a recent meta-analysis, in which the authors used a random effects model, an ERR/Gy of 0.10 (95% CI: 0.04, 0.15) for IHD was derived, consistent with the risk derived here (12). When our analyses were restricted to patients with cumulative doses of less than 0.5 Gy, we estimated an ERR/Gy of 0.149 (95% CI: −0.284, 0.670) (results not shown).

Radiation in the present study was fractionated, with doses being received at least 1 day apart and, in some cases, several weeks apart up to a 1-year interval. A quarter of all patients with relapsed tuberculosis returned for artificial pneumothorax treatments years after the initial treatment. Previous analysis of lung cancer mortality in relationship to radiation exposure in this cohort (18) failed to find an association of radiation with lung cancer mortality, in contrast to the findings in the LSS. It was suggested that a dose-fractionation modification of risk for fluoroscopy patients might account for the disparity, but no formal analysis was presented, and, in the analysis, radiation doses were treated as instantaneous. In the current analysis, we used time-dependent radiation doses and estimated a significant inverse dose-fractionation association for IHD mortality in the moderate dose-rate range. In the group of subjects with dose fractionation at 0.15–0.29 Gy/year, risks of IHD (ERR/Gy = 0.15, 95% CI: 0.01, 0.32) were comparable to the risks of all heart disease (ERR/Gy = 0.14, 95% CI: 0.06, 0.23), but not IHD (ERR/Gy = 0.02, 95% CI: −0.10, 0.15) estimated in the LSS cohort exposed instantaneously (11). The estimated risks for those in the dose-fractionation category of less than 0.15 Gy/year were 4-fold higher, although statistically comparable with the risk in the LSS and the meta-analysis of moderate- and low-dose exposed groups described above (12). The apparently contradictory results for IHD are puzzling and may be a consequence of diagnostic misclassification of cause of death; they require further investigation.

The similarity of radiation-related risks of CVD in our study with the risks from instantaneous exposures (in the LSS) and from low-dose, low dose-rate exposures (in occupationally exposed workers) might imply different initiation and/or progression mechanisms. At moderate doses (0.5–5 Gy) in humans and in both in vivo and in vitro experiments, many inflammatory markers are upregulated long after exposure to radiation (40, 41), although for exposures of less than 0.5 Gy, the balance shifts toward antiinflammatory pathways (10, 42, 43), implying that the initiating mechanisms for adverse associations in this dose range would not directly result from inflammation. Dose-related variations in T-cell and B-cell populations in the atomic bomb survivors also suggest that the immune system may be adversely affected (44).

Our results controversially suggest a strong inverse radiation dose-fractionation modification of risk for IHD mortality, which contradicts the currently accepted theory that protracted radiation delivery generally diminishes radiation-related risks (15). However, in the Janus series of animal experiments, γ dose fractionation was shown to modulate risks of cancer and nontumor diseases differentially across different organ systems; risks decreased with fractionation for liver, lung, and kidney tissues, whereas the reverse was seen for the vascular system (45). Differences in tissue responses could be due to differences in cell proliferation rates, with tissues that have a higher proportion of cycling cells having a

higher response to smaller dose fractions and lower dose rates.

In summary, we observed a significant dose-related increase in mortality from IHD when adjusted for dose fractionation and a significant inverse dose-fractionation modification of risk; however, these findings are novel and need to be replicated in other studies. Further study of risks in this well-characterized cohort with respect to mortality and incidence due to low-to-moderate dose and moderate dose fractionation could help clarify many important questions about long-term health risks of radiation and dose fractionation.

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(Appendix follows)

Appendix Table 1. Excess Relative Risks per Gy for Noncancer Causes of Death With Lags of 5 and 15 Years, Canadian Fluoroscopy Cohort Study, 1950–1987

Cause of Death	No. of Deaths	Lag of 5 Years						Lag of 15 Years					
		ERR/Gy[a]	95% CI	*P* Value[b]	Dose-Fractionation Adjusted		*P* Value[c]	ERR/Gy[a]	95% CI	*P* Value[b]	Dose-Fractionation Adjusted		*P* Value[c]
					ERR/Gy[a]	95% CI					ERR/Gy[a]	95% CI	
All noncancer[d]	12,935	0.036	−0.002, 0.082	0.068	0.036	<−0.107, 0.127	0.972	0.039	−0.001, 0.087	0.055	0.038	−0.001, 0.140	0.962
All CVDs	8,877	0.024	−0.020, 0.079	0.315	0.032	<−0.107, 0.172	0.812	0.023	−0.023, 0.079	0.352	0.031	<−0.010, 0.183	0.858
IHD	5,818	0.011	−0.040, 0.075	0.692	0.078	−0.070, 0.277	0.378	0.003	−0.047, 0.067	0.910	0.115	<−0.042, 0.312	0.063
Hypertensive and other (nonstroke) CVDs	1,697	0.034	−0.059, 0.179	0.528	0.035	−0.045, 0.269	0.536	0.056	−0.049, 0.219	0.346	0.050	<−0.035, 0.237	0.487
All respiratory diseases	2,658	0.085	0.000, 0.201	0.050	0.063	−0.003, 0.279	0.595	0.107	0.016, 0.233	0.017	0.081	0.012, 0.330	0.636

Abbreviations: CI, confidence interval; CVD, cardiovascular disease; ERR, excess relative risk; IHD, ischemic heart disease.

[a] All analyses are adjusted for categories of sex, attained age, calendar year, Canadian province of admission, type (pulmonary vs. nonpulmonary) and stage of tuberculosis diagnosis, and duration of fluoroscopy screenings by stratification, as well as continuous dose-fractionation modifications (i.e., ERR/Gy at 0.2 Gy/year or 16 fluoroscopic procedures/year). Lung doses are lagged by 5 years.

[b] *P* for departure of ERR/Gy from 0.

[c] *P* for significance of dose-fractionation modification.

[d] Excludes deaths attributed to tumors that were benign or of uncertain nature, infectious diseases, and external causes.