

Cancer Mortality After Multiple Fluoroscopic Examinations of the Chest^{1,2}

Faith G. Davis,³ John D. Boice, Jr.,⁴ Jennifer L. Kelsey,⁵ and Richard R. Monson^{6,7}

ABSTRACT—Total cancer deaths were not increased among 2,074 women and 1,277 men who were fluoroscopically examined an average of 73 and 91 times, respectively, during lung-collapse therapy for tuberculosis (TB). Patients who did not receive this form of therapy (2,141 women and 1,418 men) and general population rates were used for comparison. All subjects were discharged alive from eight TB sanatoria in Massachusetts between 1930 and 1954; the average follow-up was 23 years. Deaths due to breast cancer were not increased among exposed females [standardized mortality ratio (SMR)=1.0, $n=24$], and SMRS greater than 2.1 could be excluded with 95% confidence. In contrast to other series, our inability to detect a breast cancer excess was likely due to lower breast doses (66 rad) and higher average ages at exposure (28 yr) and thus lower sensitivity. A deficit of lung cancer among exposed males and females was observed (SMR=0.8, $n=26$), even though increased risks have been observed among other populations exposed to similar dose levels. The estimated average lung dose was 91 rad, and SMRS greater than 1.2 for lung cancer could be excluded with 95% confidence. Overall, this study indicates that the radiation hazard of multiple low-dose exposures experienced over many years is not greater than currently accepted estimates for breast and lung cancer. For lung cancer the radiogenic risk may be less than predicted from high-dose, single-exposure studies.—*JNCI* 1987; 78:645-652.

Studies of the biologic effects of radiation exposure in humans have provided estimates of carcinogenic risk. These risks are known to vary by organ, host characteristics, and specific conditions of the exposure (1). Such radioepidemiology has been used in estimating the probability that a specific cancer has been caused by a specific radiation exposure, and further refinements to incorporate factors that modify radiogenic risks are needed (2).

This paper reports the mortality experience of a previously unstudied cohort of Massachusetts TB patients who received multiple chest exposures to fluoroscopic x-rays used to monitor lung volume during air-collapse therapy. While the dose from a single fluoroscopy is small, organs directly exposed could receive a cumulative dose of several hundred rads. Cancers hypothesized to be found in excess were breast, lung, and leukemia. Scatter radiation to contiguous organs outside the radiation fields may also have occurred. In previous studies of female TB patients, an elevated risk of breast cancer incidence (3) and mortality (4, 5) has been observed, and, based on small numbers, elevated risks of cancer at other sites have been suggested. Our study is the first to describe in detail the cancer mortality of male TB patients who experienced multiple chest fluoroscopies.

SUBJECTS AND METHODS

A retrospective cohort study was conducted of 6,910 patients admitted to eight Massachusetts hospitals between 1930 and 1954. These hospitals were the primary TB treatment hospitals in the state and represent 30-40% of the TB beds available at that time. Patients were identified from medical records and were eligible if they had a confirmed diagnosis of pulmonary TB and were alive at the time of first discharge. Sixty-eight subjects for whom follow-up information was not available beyond the date of discharge were excluded.

Information on exposure and other relevant factors was obtained from hospital admission records. Data included demographic variables, medical treatment information, selected cancer risk factors, and information to facilitate follow-up. Risk factors included smoking and alcohol behavior and breast cancer risk factors (age at menarche, type and age at menopause, the birthdate of the first child, and the presence of benign breast disease). In an effort to obtain complete exposure information, multiple admission records for 40% of those patients admitted to several Massachusetts hospitals were obtained. No attempt was made to acquire additional medical records for patients who transferred out of state.

ABBREVIATIONS USED: CI=confidence interval; CRR=crude rate ratio; ICDA-8=International Classification of Diseases Adapted for Use in the United States, 8th revision; RR=relative risk; SMR=standardized mortality ratio; SRR=standardized rate ratio; TB=tuberculosis.

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³ Epidemiology-Biometry Program, School of Public Health, University of Illinois at Chicago, Box 6998, Chicago, IL 60680.

⁴ Radiation Epidemiology Branch, Division of Cancer Etiology, National Cancer Institute, National Institutes of Health, Public-Health Service, U.S. Department of Health and Human Services, Bethesda, MD 20892.

⁵ Division of Epidemiology, School of Public Health, Columbia University, New York, NY 10032.

⁶ Department of Epidemiology, Harvard School of Public Health, 677 Huntington Ave., Boston, MA 02115.

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TABLE 1.—Gender and vital status as of January 1, 1981, as related to category of radiation exposure

Status	Exposed group		Unexposed group		Total	
	No.	%	No.	%	No.	%
Females						
Dead	823	40	793	37	1,616	38
Alive	1,037	50	1,070	50	2,107	50
Lost	214	10	278	13	492	12
Total	2,074	100	2,141	100	4,215	100
Males						
Dead	715	56	963	68	1,678	62
Alive	498	39	390	27	888	33
Lost	64	5	65	5	129	5
Total	1,277	100	1,418	100	2,695	100

Efforts to obtain a date and cause of death for deceased subjects and a current address for living subjects followed methods similar to those outlined previously (6). The primary resources used were State Vital Statistics Division records, motor vehicle registries, city directories, and town residence lists that are unique to Massachusetts. Current vital status was ascertained for 88% of the women and 95% of the men (table 1). Death certificates were requested from the state of last known residence for those subjects known to have died. Death certificates were validated with the use of the subjects' names and dates of birth. Records were not available for 38 of 1,616 female deaths (2.4%) and 20 of 1,678 male deaths (1.2%).

Causes of death were abstracted from death certificates. To verify this information, we requested relevant autopsy, discharge, and pathology reports from hospitals where study subjects had died. In this manner, reported cancer deaths were confirmed for 35 and 28% of the exposed and unexposed groups, respectively. No further information was available on the remaining 67% of cancer deaths. This limited success reflects the fact that only 1,628 (49%) of all the deaths occurred in hospitals that were currently operating.

The cohort was divided into 2 exposure groups: 1) those who received air-collapse therapy with associated fluoroscopy exposure and 2) those with no record of having received this form of therapy. Two estimates of radiation exposure were calculated for the exposed group. First, the total number of air-collapse therapy

examinations, as abstracted from standard pneumotherapy logs in the medical record, were counted. Second, details of each treatment regimen (dates started and stopped, type of collapse, and side of lung collapsed) were applied to a dosimetry model to estimate the average radiation dose that would be absorbed in several target tissue organs. This model was developed for an earlier study and considered the following factors: machine exposure rate, field size, anatomical location of x-ray beam, type and mass of body tissue, and orientation of the patient during the examination (4, 7). The average number of examinations and estimated average tissue doses for the sites of primary interest are shown in table 2.

The appropriateness of the radiation dosimetry assumptions was evaluated by surveying living patients and former TB physicians. In 1981, questionnaires were mailed to all subjects with known current addresses. Up to two additional mailings and one telephone contact were made to nonrespondents, each at approximately 1-month intervals. Former patients were asked whether they had received lung-collapse therapy; how frequently a fluoroscope had been used; and whether they faced the x-ray machine, the physician, or were rotated during the fluoroscopy examination. In addition, eight mail questionnaires from 18 physicians known to have conducted air-collapse procedures in study hospitals over the appropriate time period were obtained.

Physician responses indicated that each fluoroscopy lasted 15 seconds on the average. Patient responses indicated that 25% of all fluoroscopies were performed with the patient facing the x-ray source. These data suggest that air-collapse therapy procedures were similar to those reported in a previous study of female TB patients in Massachusetts and that assumptions regarding factors in the dosimetry model were reasonable. Coefficients used for the breast dose estimations were updated from a previous report [(7) and Davis FG: Unpublished Ph.D. dissertation]. Limitations of dose estimation included a) not having individual data on the position of the patient relative to the x-ray source for that half of the population who died prior to the survey and b) not knowing with accuracy the length of fluoroscopic exposure during each examination.

Mortality analyses were conducted separately for the 4,215 females and 2,695 males eligible for study. Under-

TABLE 2.—Number of fluoroscopy exams and dose estimates, rad, for selected organs

Specification	Cumulative exposures				Total, n=3,099, ^a average
	Females, n=1,892		Males, n=1,207		
	Average	Range	Average	Range	
No. of fluoroscopy examinations	73	1-580	91	1-751	80
Estimated absorbed organ doses, rad					
Breast ^b	66	<1-627	—	—	—
Lungs	81	<1-692	108	<1-911	91
Active bone marrow	10	<1-77	15	<1-112	12

^a 252 of the 3,351 patients having air-collapse therapy had no exposure record.

^b Organ doses for adolescents are assumed to be equal to those of adults, except for female breast tissue.

lying cause of death was coded from death certificates according to the ICDA-8 (8). Person-years of follow-up were calculated with the use of the date of first discharge as entry date. Closing date was defined as the date of death for deceased subjects, date last known to be alive for subjects lost to follow-up, and January 1, 1981, for subjects known to be alive.

Risk estimates were standardized over 5-year age and time intervals. SMRs were calculated with the use of Massachusetts death rates to compute expected values. This was accomplished by multiplying each 5-year age and 5-year calendar time interval of a cause-specific death rate by the comparable person-years experience of the exposed individuals in that stratum and by summing the results over 5-year age and time intervals. For observed values based on 20 or fewer events, 95% Fisher exact confidence limits were computed; otherwise, 95% approximate CIs based on the Poisson distribution are reported (9). For each cause of death, a Mantel-Haenszel chi-square statistic and associated P-value were estimated (10).

Lung and breast cancer mortality data were stratified by time since exposure, age at exposure, and dose level. This analysis was restricted to patients living 10 years or more after discharge because of the long latent periods associated with these radiogenic tumors (1). Stratum-specific SMRs, CCRs (comparing the crude death rate in the exposed to the crude death rate in the unexposed), and overall sex-specific SRRs were estimated. SRRs compared the exposed group to the unexposed group, controlling for age and time at exposure. A stratified analysis was not conducted for leukemia, because few deaths were observed. For the unexposed subjects, times and ages of "exposure" were surrogate measures, estimated from dates of admission.

Proportional hazards modeling was conducted to evaluate breast cancer mortality in relation to radiation exposure, taking into account other breast cancer risk factors and/or possible confounding variables, in addition to survival time (11). Lung cancer was not evaluated by means of this technique because of the incompleteness of information on smoking history.

RESULTS

A total of 103,354 person-years of follow-up were accumulated in females for an average of 24.5 years per person. Males accumulated 56,290 person-years of follow-up for an average of 21.0 years per person. The average age when first given air-collapse therapy was 27.9 years for the 2,074 exposed women and 32.6 years for the 1,277 exposed men. The 2,141 unexposed women were, on the average, slightly older than the exposed women (32 vs. 29 yr) at their date of first discharge. The unexposed males were 11 years older on the average than the exposed males (44 vs. 33 yr) at first discharge.

Exposed females were more likely than unexposed females to have married, to have achieved a higher level of education, and to have smoked (table 3). Smoking and alcohol data, obtained from the medical record,

were missing in unequal proportions of the female exposure groups. Similar proportions of male exposure groups were smokers and users of alcohol at the time of TB hospitalization, although these data are incomplete and may not be indicative of an individual's lifetime experience. Male and female exposure groups tended to be admitted with more advanced TB and to have received more aggressive surgery, a finding consistent with the disease status of a previous Massachusetts female cohort (3). No difference in proportions between study groups was noted for race, chemotherapy treatments such as streptomycin and isoniazid, or other chronic diseases. The cohort was predominately white (96%), and their religious affiliation was mainly Catholic (62%) or Protestant (32%).

The number of deaths experienced by all women (SMR=2.2) and all men (SMR=1.8) in this cohort were higher than the number of deaths expected based on population rates (table 4). As anticipated, TB and respiratory diseases were major causes of death in both exposure groups. In males, significantly higher risks of death from cirrhosis of the liver (exposed group SMR=1.7, $n=16$; unexposed group SMR=2.0, $n=19$) were observed. For causes of death other than nonmalignant respiratory diseases, the mortality of both male and female exposure groups was slightly higher than that of the general population.

Cancer Mortality

There was no apparent elevation of deaths due to all types of cancer in exposed and unexposed women, although increases for some specific cancer sites were noted (table 5). Focusing on those sites of primary interest: Breast cancer mortality was similar to that expected (exposed SMR=1.0, $n=24$; unexposed SMR=1.0, $n=23$), respiratory cancer mortality was slightly elevated in both groups (exposed SMR=1.3, $n=10$; unexposed SMR=1.4, $n=11$), and leukemia mortality was modestly elevated in both groups (exposed SMR=1.8, $n=5$; unexposed SMR=1.5, $n=5$).

The risk of death in males from all cancers was elevated in the unexposed group (SMR=1.5, $n=159$) but not in the exposed group (SMR=0.9, $n=73$). There was no suggestion of an elevated risk from respiratory cancers (SMR=0.7, $n=16$) or leukemia (SMR=0.4, $n=1$) in exposed men. The number of deaths due to esophageal cancer was higher than expected (SMR=4.2, $n=8$), but 2 of these cases were diagnosed at the time of air-collapse therapy. Esophageal cancer was also elevated in the unexposed group and therefore may not be related to radiation exposure during TB treatment (SMR=4.0, $n=10$).

Breast Cancer Mortality

An increased risk of death from breast cancer was not observed. No variation in mortality by time since exposure and dose level was observed (table 6). A modest elevation was suggested for exposure during adolescence

TABLE 3.—Distribution of selected characteristics of TB patients by gender and exposure status

Characteristic	Females, mean		Males, mean	
	Exposed, n=2,074	Unexposed, n=2,141	Exposed, n=1,277	Unexposed, n=1,418
Year of discharge	1943	1943	1944	1946
Age at discharge, yr	28.6	32.3	33.0	44.1
Age at first exposure, yr	27.9	—	32.6	—
Specification	Females, %		Males, %	
	Exposed	Unexposed	Exposed	Unexposed
Marital status				
Never married	33	35	37	27
Married	59	52	54	57
Other	8	13	9	16
Education				
1-8 yr	18	26	15	17
9-12 yr	34	23	25	16
13 yr or more	17	11	13	8
Unknown	31	39	47	59
Smoking history				
Smoker	23	15	41	36
Nonsmoker	35	28	8	7
Unknown	43	57	51	57
Alcohol				
User	15	14	39	42
Nonuser	57	47	34	36
Unknown	28	40	27	22
Stage of TB				
Minimal	15	46	12	30
Moderate	45	31	43	36
Advanced	39	23	45	34
TB treatment				
Thoracoplasty	27	7	25	7
Lobectomy	4	4	3	4
Pneumonectomy	3	1	1	0
Streptomycin	28	30	33	36
Isoniazid	12	13	27	21

TABLE 4.—Number of deaths observed (Obs) and expected among TB patients by gender and exposure group

Causes of death ^a	Females				Males			
	Exposed		Unexposed		Exposed		Unexposed	
	Obs	SMR ^b	Obs	SMR ^b	Obs	SMR ^b	Obs	SMR ^b
All deaths	823	2.6*	793	1.8*	715	1.9*	963	1.7*
TB	424	82.9*	283	60.8*	263	44.4*	256	39.1*
Malignant neoplasms	100	1.1	106	1.0	73	0.9	159	1.5*
Allergic, endocrine, metabolic, and nutritional diseases	5	0.6	12	1.0	11	1.9	8	1.0
Circulatory system diseases	148	1.0	262	1.1*	206	1.0	352	1.1*
Respiratory diseases	5	3.6*	52	2.5*	70	3.0*	94	2.7*
Digestive system diseases	13	0.7	22	1.1	28	1.2	39	1.4*
Cirrhosis of liver	8	0.9	10	1.2	16	1.7*	19	2.0*
Suicide	5	1.5	6	1.9	12	1.5	3	0.4
Other and unspecified	75	2.6*	50	1.4*	52	1.7*	52	1.4*
All deaths minus TB and nonmalignant respiratory ^c	346	1.2*	458	1.1*	382	1.1*	613	1.2*

^a ICDA-8 codes for first nine disease categories are: 010-998, 010-019, 140-209, 240-279, 390-458, 460-519, 520-577, 571, and 950-959.

^b Ratio of observed to expected utilizes expected numbers based on 5-yr age and calendar time-specific death rates from Massachusetts.

^c *P*-value of <.05.

^c Nonmalignant respiratory disease includes ICDA-8 010-019 and 460-519.

TABLE 5.—Number of cancer deaths observed (Obs) and expected among TB patients by gender and exposure group

Cancer type ^a	Females						Males					
	Exposed			Unexposed			Exposed			Unexposed		
	Obs	SMR ^b	95% UB ^c	Obs	SMR ^b	95% UB ^c	Obs	SMR ^b	95% UB ^c	Obs	SMR ^b	95% UB ^c
Buccal cavity and pharynx	0	0.0	2.7	3	2.1	6.1	3	0.9	2.5	11	2.4*	4.3
All digestive	22	0.9	1.3	29	0.9	1.3	27	1.0	1.5	54	1.3	1.8
Esophagus	2	2.8	10.3	0	0.0	4.3	8	4.2*	8.3	10	4.0*	7.4
Stomach	2	0.5	1.9	4	0.7	1.8	1	0.2	0.9	11	1.1	2.0
Large intestine	8	0.7	1.3	13	0.9	1.5	9	1.2	2.2	14	1.2	2.0
Rectum	2	0.7	2.6	6	1.6	3.4	2	0.6	2.1	7	1.3	2.7
Liver	3	1.1	3.2	1	0.3	1.5	3	2.4	6.7	4	2.1	5.4
Pancreas	4	1.0	2.6	2	0.4	1.5	4	0.9	2.4	6	1.1	2.4
Respiratory system	10	1.3	2.4	11	1.4	2.4	16	0.7	1.1	45	1.6*	2.2
Bone	2	4.8	17.3	0	0.0	7.2	2	5.3	18.1	1	1.6	9.3
Breast	24	1.0	1.6	23	1.0	1.4	—	—	—	—	—	—
All genital	20	1.2	1.9	20	1.1	1.8	—	—	—	—	—	—
Cervix uteri	8	1.9	3.7	8	1.8	3.6	—	—	—	—	—	—
Prostate gland	—	—	—	—	—	—	6	1.2	2.6	11	1.1	2.0
Bladder	1	0.9	5.1	1	0.6	3.3	3	1.2	3.7	6	1.4	3.1
Kidney	2	1.5	5.2	1	0.6	3.5	2	1.1	3.8	6	2.5	5.4
Brain and other central nervous system	2	0.8	3.0	3	1.3	3.8	2	0.9	3.1	4	1.9	4.7
Thyroid gland	1	2.5	13.9	1	2.1	11.1	0	0.0	18.4	0	0.0	19.1
Leukemia and aleukemia	5	1.8	4.2	5	1.5	3.2	1	0.4	2.1	5	1.4	3.2
Other and unspecified	11	0.9	1.6	9	0.7	1.3	11	1.0	1.8	16	1.3	2.1
All malignant neoplasms	100	1.1	1.3	106	1.0	1.2	73	0.9	1.2	159	1.5*	1.7

^a ICDA-8 codes are: 140-149, 150-159, 150, 151, 153, 154, 155-156, 157, 160-163, 170, 174, 180-184, 180, 186, 188, 189, 190-192, 193, and 204-207.

^b Ratio of observed to expected utilizes expected numbers based on 5-yr age and calendar time-specific death rates for white Massachusetts females and males. *, *P*-value of <.05.

^c The upper bound (UB) of the 95% confidence limit.

with an SMR of 1.7. This effect was not apparent (CRR= 1.0) when the unexposed women were used as the comparison group.

The SRR for breast cancer mortality was 1.1 (95% CI= 0.6-2.1) when we compared the exposed to unexposed groups and controlled for time since exposure and age at exposure. This estimate is similar to that obtained by means of a proportional hazards model to control for other possible breast cancer risk factors.

Lung Cancer Mortality

When sexes were combined, no overall (SMR= 0.8 with 95% CI=0.5-1.2) or subgroup excesses of lung cancer mortality were observed (table 7). No lung cancer deaths occurred in females within 20 years of discharge. A modest elevation of risk was noted in women 20 years or more after discharge (SMR = 1.5, *n* = 10), an effect that was also suggested in women first exposed after age 20 (SMR= 1.5, *n* = 10). Excess lung cancer deaths were not observed in the male group at any time period following exposure or for any category of age at exposure. An increasing risk for death from lung cancer with increasing radiation dose, as measured by the number of exams or the estimated absorbed lung dose, was not observed in either sex when either population rates or the unexposed group were used for comparison.

The SRR for lung cancer mortality in 10-year survivors, controlling for age at exposure and time since

TABLE 6.—Breast cancer deaths among exposed females surviving 10 years or more by the number of years after discharge, age at first exposure, and estimated exposure levels

Specification	Number ^a	Obs	Exp ^b	SMR ^c	95% CI
No. of years after first discharge					
10-19	1,546	5	5.0	1.0	0.4-2.2
20-29	1,370	12	7.7	1.6	0.8-2.6
30-39	998	5	6.2	0.8	0.3-1.8
≥40	342	1	1.3	0.8	0.0-3.9
Age at first exposure, yr					
5-19	210	3	1.7	1.7	0.4-4.7
20-29	826	10	10.0	1.0	0.5-1.8
30-39	367	7	6.0	1.2	0.5-2.3
≥40	143	3	2.5	1.2	0.3-3.3
No. of fluoroscopy examinations					
1-99	998	15	13.2	1.1	0.7-1.8
≥100	419	6	5.3	1.1	0.5-2.4
Absorbed dose estimate for breast tissue, rad					
1-49	764	11	9.7	1.1	0.6-2.0
50-149	471	8	6.5	1.2	0.6-2.3
≥150	182	2	2.4	0.8	0.1-2.8

^a Number of subjects; in the first section, the number of subjects entering each time interval is shown.

^b Expected values are based on 5-yr age and calendar time-specific death rates for white Massachusetts females.

^c Ratio of observed to expected.

TABLE 7.—Lung cancer deaths among 10-year survivors by gender, the number of years after first discharge, age at first exposure, and exposure levels

Specification	Females			Males			Total			
	Obs	Exp ^a	SMR ^b	Obs	Exp ^a	SMR ^b	Obs	Exp ^a	SMR ^b	95% CI
No. of years after first discharge										
10-19	0	0.9	0.0	4	3.9	1.0	4	4.8	0.8	0.2-2.1
20-29	4	2.7	1.5	4	7.3	0.6	8	10.0	0.8	0.3-1.6
30-39	4	3.1	1.3	4	7.4	0.6	8	10.5	0.8	0.3-1.5
≥40	2	0.7	2.9	1	1.7	0.6	3	2.4	1.3	0.3-3.7
Age at first exposure										
5-19	0	0.7	0.0	0	1.0	0.0	0	1.7	0.0	—
20-29	5	3.8	1.3	2	6.5	0.3	7	10.3	0.7	0.3-1.4
30-39	4	2.2	1.9	6	7.2	0.8	10	9.4	1.1	0.5-2.0
≥40	1	0.8	1.3	5	5.7	0.9	6	6.5	0.9	0.3-2.0
No. of fluoroscopy examinations										
1-99	6	4.8	1.2	4	12.0	0.3	10	16.8	0.6	0.3-1.1
≥100	3	2.0	1.5	6	7.6	0.8	9	9.6	0.9	0.4-1.8
Absorbed dose estimate for lung tissue, rad										
1-49	6	3.0	2.0	4	8.0	0.5	10	11.0	0.9	0.4-1.7
50-149	0	2.6	0.0	1	5.2	0.2	1	7.8	0.1	0.0-0.7
≥150	3	1.2	2.4	5	6.3	0.8	8	7.5	1.1	0.5-2.1

^a Expected values are based on 5-yr age and calendar time-specific death rates for white Massachusetts females and males.

^b Ratio of observed to expected.

exposure, was 1.3 for women (95% CI=0.5-3.4) and 0.7 for men (95% CI=0.3-1.4).

DISCUSSION

The apparent discrepancy between the negative finding for breast cancer mortality in our study and RRs of approximately 1.5 reported in other studies may be due to differences in radiation dose to the breast and in ages at exposure. Average breast doses computed for women with TB in previous studies (7, 12) were nearly twice as large as the 66 rad in our series. Excess breast cancer deaths following exposure to the atomic bomb were evident primarily among women exposed to doses greater than 100 rad (13). Risk of radiogenic breast cancer also appears inversely related to age at exposure (1), and our average age of 28 years was higher than previous series (7, 12). Women first exposed during adolescence had an elevated risk (SMR = 1.7; 95% CI=0.4-4.7). RRs greater than 2.1 can be excluded with 95% certainty, a finding within the range of risks previously reported. It should be kept in mind that incidence data would give a more accurate picture of radiation carcinogenesis. Several incidence series have convincingly demonstrated that radiation is a risk factor for breast cancer, even at levels below 100 rad (1).

That radiation exposure is a risk factor for lung cancer has been established in males and females exposed to different types and levels of radiation (1). For example, RRs on the order of 1.5 have been estimated for spondylitic patients receiving doses of 200 rad and for atomic bomb survivors receiving doses greater than 100 rad (14). In contrast, significant excess risks have not been observed in previous studies of female TB patients receiving doses on the order of 100 rad to the lung (4, 15). The absence of an association in both males and

females in this study is consistent with earlier TB studies and suggests that air-collapse therapy exposures, characterized by repeated, relatively low x-ray doses occurring over several years, may not be as carcinogenic as single or short-term exposures of the same total dose. SMRs greater than 1.2 for lung cancer could be excluded with 95% confidence, but this estimate may be distorted by differential underlying respiratory disease and smoking behavior in the exposure groups. Comparison with population rates likely underestimate risks because TB patients would have less lung tissue at risk for cancer development due to the disease itself or to surgical procedures removing all or portions of a lung. Similarly, comparisons between the exposed and nonexposed could be misleading since the exposed had more advanced disease and more frequent surgical procedures.

Leukemia has frequently been associated with radiation exposure (1). In our series, a modest risk of leukemia was found in exposed females (RR= 1.8, 95% CI= 0.6-4.2) but not in exposed males. Since the average bone marrow dose was low (12 rad) and the number of excess cases expected was small, the study did not have sufficient power to detect an effect with any meaningful precision.

Results based on a cohort defined by an underlying disease such as TB must be interpreted cautiously. An elevated cause-specific death rate in both exposure groups relative to the general population may be due to their common disease experience or some unknown correlate of that experience. In contrast, a similarly elevated rate in the exposed group relative to both the unexposed group and rates in an external population is more likely to be due to the particular experience of the exposed group. Based on very few deaths, elevated ratios for bone, esophageal, and kidney cancer were observed in exposed females relative to both comparison groups.

Increased risks from these three sites were not observed in an earlier TB series of females and, except for bone, risks were not consistent across gender in this cohort (4). While these sites are thought to have relatively low sensitivity to radiation (12), results of other higher dose studies have been mixed (13,14,16,17). Because radiation doses were low to organs outside the x-ray field, it is unlikely that radiation played a role in the etiology of these tumors.

The small nonsignificant excess of thyroid cancer in the females (SMR=2.2, $n=2$) is interesting because this is a very radiosensitive site, and both exposure groups were likely to receive more diagnostic x-rays than the general population.

Smoking is the factor most likely to distort estimates for cancer sites where it is associated with increased risk, such as lung, larynx, oral cavity, esophagus, bladder, pancreas, and liver (18,19). A higher proportion of males (40%) than females (20%) reported smoking in this cohort. These proportions are consistent with the proportion of smokers in the population during the 1930's (19). The absence of an increased risk of lung cancer in our series argues against a strong overall carcinogenic effect attributable to greater cigarette consumption among exposed relative to unexposed, particularly for men. It is possible that greater consumption among unexposed relative to exposed may have masked any radiation effect for smoking-related cancer sites. Although the data in table 3 do not support this scenario, we cannot rule it out because of the large number of subjects with incomplete smoking data.

Heavy consumption of alcohol has been associated with oral, esophageal, liver, and possibly stomach cancer (20, 21). Elevated SMRs for esophageal cancer in both exposed and unexposed males may reflect similarly high alcohol consumption across exposure groups. The modest elevation of liver cirrhosis deaths is also consistent with males being greater than average alcohol consumers (22). Another study of TB patients reported an excess of liver cirrhosis that was concentrated among patients treated with isoniazid, an anti-TB drug that became common in the 1950's (23) and was used by a larger proportion of males than females in this series.

The absence of a dose-response relationship between radiation exposure and breast or lung cancer may be a reflection of the relatively narrow range of doses observed, low average levels of exposure, errors in the estimation of dose, or absence of a radiogenic effect at these dose levels. Errors may include misclassification between exposure groups and/or across categories of dose and errors resulting from the averaging procedures. Estimates of dose are crude inasmuch as assumptions regarding several factors (patient orientation, length of examination, distance from the machine, and other machine factors) were made in the absence of individual information on the complete cohort.

Some subjects may have received air-collapse therapy subsequent to that indicated on the medical records available to us, whereas others contacted during the survey had no recall of documented air-collapse therapy,

TABLE 8.—Agreement between medical record and survey data on the experience of air-collapse therapy

Medical record information	Survey response					
	Exposed group		Unexposed group		Total	
	No.	%	No.	%	No.	%
Females ^a						
Exposed	564	92	47	8	611	100
Unexposed	46	8	519	92	565	100
Males ^b						
Exposed	288	90	32	10	320	100
Unexposed	10	5	193	95	203	100

^a Kappa statistic $K=0.84$, $P<.001$.

^b Kappa statistic $K=0.83$, $P<.001$.

making both data sources imperfect. If the experience of a subset of live subjects (table 8) reflects that of the rest of the cohort, only a modest amount of misclassification between exposure groups occurred. On the basis of discharge summaries, 20% of the exposed group were expected to continue air-collapse therapy, which suggests that average doses may be underestimated. If these errors are random, then overall and dose-response effects will be more difficult to detect (24).

The potential range of error in dose due to the averaging procedures used was explored. If the percent of time spent facing the x-ray source is varied to 15 or 35% (relative to the 25% used), the estimated average dose to breast tissue ranges from 45 to 85 rad. Increasing the average exposure to 30 seconds per examination would double dose estimates for all exposed sites; decreasing the exposure time to 5 seconds per examination would reduce dose estimates by two-thirds.

The crude number of examinations suggests that the levels of radiation received by this exposed group are, on the average, lower than those reported in other TB cohorts (4, 12). Overall estimates of risk observed in this study are consistent with the lower RRs expected when compared to estimates from higher dose series, assuming a dose-response relationship exists.

These results cannot be regarded as supporting the absence of a radiogenic cancer effect because of the limited size of the cohort, lack of available data on potential confounding factors, and the crudity of exposure data. They do, however, exclude large carcinogenic risks for the hypothesized cancer sites at the modest dose levels observed.

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