Breast Cancer in Women After Repeated Fluoroscopic Examinations of the Chest [1, 2]

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ABSTRACT—A follow-up study of 1,764 female patients, discharged alive from two tuberculosis sanatoria in Massachusetts between 1930 and 1954, was conducted. In the course of air collapse therapy of the lung (pneumothorax and pneumoperitoneum), 1,047 women were fluoroscopically examined an average of 102 times over a period of several years. A comparison group of 717 women with tuberculosis received other treatments that did not require fluoroscopic monitoring. A 1975 mailing address or a death certificate was obtained for 93.6% of the study subjects, and 78% of 1,146 living patients responded to a mailed questionnaire. An excess of breast cancer (41 observed and 23.3 expected) was seen among the fluoroscopically examined women, whereas no excess (15 observed and 14.1 expected) was apparent among the comparison women. When age was considered, the greatest absolute excess breast cancer risk occurred among exposed women who were first treated between the ages of 15 and 19 years. Among those women 30 years of age and older at the time of first exposure, no elevated breast cancer risk was detected; the failure to observe an excess, however, may be a matter of sampling variation inasmuch as a 50% increased risk could not be excluded. The concentration of excess breast cancer cases among women initially exposed before the age of 30 years suggests that young women may be particularly sensitive to radiation injury. Breast cancer excess risk was also seen to increase with increasing radiation dose, and a linear dose-response relationship is consistent with the data. The excess breast cancer risk did not appear until 15 years after initial exposure and was present at the end of 40 years of observation. The radiation risk estimate for the women living 10 years or more after first exposure is 6.2 excess breast cancer cases per million woman-year-rad.— J Natl Cancer Inst 59:823-832,1977.

The screening of asymptomatic women by mammography and physical examination appears to be of value in reducing breast cancer mortality (*1*). There is concern, however, that repeated X-ray exposures may be harmful *(2–4)*. Atomic bomb survivors *(5-8)*, tuberculosis patients who were exposed to many fluoroscopic chest examinations in the course of pneumotherapy (air collapse treatment of the lung) *(9-12)*, and postpartum mastitis patients who received radiation therapy (*13*) have been shown to be at an increased risk for breast cancer.

The radiation risk estimates *(5, 14,15)* obtained from these populations are between 2 and 8 induced breast cancer cases per million WY-rad.[6] The average ages of these populations were, however, all under 35 years; if age at exposure is associated with breast cancer risk, these risk estimates are not applicable to women over 35 years of age. [7]

Evidence from other epidemiologic studies (*16,17*) indicates that events occurring during the early years of a woman's life have a significant effect on lifetime breast cancer risk. Increased breast cancer risk is associated with early onset of menses, increased age at first full-term delivery, nulliparity, and decreased frequency of artificial menopause. In addition, the female breast undergoes a period of growth during adolescence, and proliferating breast tissue may be more sensitive to ionizing radiation. For these reasons, radiation exposure during early life possibly may be more harmful than irradiation at older ages.

The purpose of the present investigation is to examine the reported association between repeated fluoroscopic X-ray examinations of the chest and breast cancer and to determine whether age at exposure modifies the radiation effect. In contrast to other studies of institutionalized tuberculosis patients, in the present study, a sanatorium that treated children and adolescents exclusively was included (*9–12,* 18).

SUBJECTS AND METHODS

Study population.— Subjects exposed to repeated fluoroscopic examinations were identified by a review of approximately 10,000 hospital discharge records between the years 1930 and 1954 from two Massachusetts tuberculosis sanatoria. Both sanatoria were situated in Middlesex County; one sanatorium treated children and adolescents under 17 years of age exclusively, whereas the other treated adults. Eligible subjects were all females who were discharged alive and who received either pneumothorax or pneumoperitoneum treatments. These procedures, involving the injection of air into the pleural or peritoneal cavity to permit collapse of the lung, were widely used in the treatment of pulmonary tuberculosis at the time. Periodic fluoroscopic inspection of the degree of the lung collapse was required, which resulted in considerable X-ray exposure to the breast.

A comparison group was chosen from among sanatorium patients who did not receive pneumotherapy. To be in-

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ABBREVIATIONS USED: WY = woman-year(s); PAS = *p*-aminosalicylic acid; INH = isoniazid.

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[1] Received December 28, 1976; accepted March 28, 1977.

[2] Supported in part by Public Health Service (PHS) center grant 5 P1O ES00002 from the National Institute of Environmental Health Sciences and by PHS contract 223-75-6014 from the Bureau of Radiological Health of the Food and Drug Administration (FDA).

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[5] This investigation was suggested by Dr. Shields Warren, and we are grateful for his support throughout its execution. We are grateful also to Professor George B. Hutchison for his advice and continued support, to Mr. Peter Smith and Mrs. Anitra Webster for their assistance in computer analysis, and to Mrs. Judy Constantian and Mrs. Dorothy Bowen who so successfully traced the patients.

[6] A shorthand used to present absolute risk estimates will be (excess cases)/10^6 WY-rad. The units of cases per population-unit time-unit dose are specific for the interval of follow-up years and the dose range experienced irrespective of the underlying dose-response relationship.

[7] Recent atomic bomb studies can provide age-specific risk estimates, as a radiogenic breast cancer risk has been observed at all ages (6).

eluded in the comparison group, a patient had to be female, discharged alive, at least 13 years of age at the time of discharge, and positively diagnosed as having tuberculosis. Most of the patients in the children's sanatorium were less than 13 years of age and did not receive air collapse therapy. Nearly all the pneumotherapy patients, however, were 13 years of age and older at discharge.

This sampling scheme resulted in the selection from the two sanatoria of an exposed group of 952 women and a comparison group of 902 women. Upon review of medical histories, 90 comparison women were excluded from study because of nontuberculosis diagnoses, 76 comparison women were found to have received pneumotherapy at other sanatoria, and 19 comparison women were found to have been incorrectly classified. Reclassification of these latter two groups as pneumotherapy patients resulted in a final population of 1,047 women exposed to repeated fluoroscopic examinations during pneumotherapy and 717 women who received other treatments.

Table 1 shows the distribution of demographic and tuberculosis treatment characteristics for all study subjects. No important differences are apparent between exposed and comparison groups with regard to year of birth, age at tuberculosis diagnosis, age at discharge, religion, or race. However, differences were seen with regard to tuberculosis stage and treatment. In addition to receiving air collapse therapy, the exposed group had more serious tuberculosis disease and received more vigorous treatments, including chemotherapy and surgery. The average number of fluoroscopic X-ray exposures received among the pneumotherapy subjects was 102 examinations. Air collapse therapy was continued for an average of 3 1/3 years, and patients averaged 31 fluoroscopic examinations per year during this time.

TABLE 1.—*Study subject characteristics and tuberculosis history from records of sanatoria*

Parameter	Exposed group	Comparison group
No. of women	1,047	717
Average year of birth	1915.6	1916.9
Average age at tuberculosis diagnosis, yr	23.9	22.7
Average age at discharge, yr	26.2	24.6
Religion		
Catholic	64.4%	64.2%
Protestant	32.4%	33.1%
Jewish	1.2%	1.5%
Other	2.0%	1.2%
Race		
White	98.1%	96.1%
Nonwhite	1.6%	2.9%
Unknown	0.3%	1.0%
Previous medical history		
Cancer	0.3%	0.7%
Diabetes	1.9%	1.7%
Pleurisy	20.2%	19.1%
Thyroid problems	0.9%	0.7%
Heart disease	2.4%	2.4%
Stage of tuberculosis		
Childhood, hilum	0.2%	20.8%
Minimal	16.4%	32.3%
Moderately advanced	43.5%	27.9%
Far advanced	39.6%	15.9%
Unknown	0.3%	3.1%
Tuberculosis treatment		
Bed rest only	—	72.8%
Chemotherapy, any	34.0%	22.7%
Streptomycin	18.4%	18.1%
PAS	14.2%	14.1%
INH	25.2%	11.7%
Surgery, any	34.4%	13.4%
Thoracoplasty	18.8%	8.4%
Lobectomy	3.5%	5.2%
Pneumonectomy	1.5%	1.4%
Phrenicectomy	11.5%	4.0%
Pneumotherapy		
Pneumothorax	96.3%	—
Pneumoperitoneum	3.7%	—
Average No. fluoroscopy examinations	102	—

Follow-up methods. —A 1975 mailing address or a death certificate was sought for all 1,764 study subjects. The following location procedures were performed without knowledge of exposure status:

1) Outpatient records. Only the adult sanatorium was still in existence with available outpatient records. A search of these records resulted in location of 24% of the study patients, 270 alive and 148 dead.

2) Vital statistics. The Massachusetts Department of Vital Statistics was contacted, and marriage certificates were sought for all patients likely to have married after hospital discharge. Death records for subjects not found alive were searched for. If a subject moved out of Massachusetts, inquiries were written to vital statistics departments of the State or country to which the subject moved. For subjects found dead, copies of death certificates were obtained and causes of death were classified according to the seventh revision of the International Classification of Disease, Injuries and Causes of Death (*19*) by a physician who was unaware of the study hypotheses and of the exposure status. Approximately 15 % of the study population was located in this manner.

3) City directories. Most cities in Massachusetts annually publish "Residents' Lists" (20). All household members 20 years of age and over are listed along with age, occupation, and previous year's address. Study subjects were followed for many years in these lists. They were also located through the use of telephone directories and R. L. Polk and Company city directories (21).

4) Relatives. After exhausting all the above sources available to locate the study women, we sought and contacted relatives. A useful method of locating relatives was to search for death certificates of parents of study subjects and to acquire the name and address of the informant.

5) Other methods. We located subjects by writing to State tuberculosis agencies; contacting town halls and election boards; searching divorce records; requesting information from the Internal Revenue Service, the Motor Vehicle Bureau of Massachusetts, and military record agencies; and contacting hospitals, former physicians, friends, places of employment, school districts, college alumni associations, or any institution or individual mentioned in the medical records.

These follow-up procedures resulted in location of 93.6% of the study patients; 65 % were alive, 28.6 % were dead, and 6.4 % were lost to follow-up. No meaningful differences were observed between the exposed and comparison groups with respect to follow-up rates (table 2).

Patient questionnaire. —All women found alive were

TABLE 2.—*Number of subjects found alive, found dead, and lost to follow-up by exposure category*

Status	Exposed group (%)	Comparison group (%)	Total subjects (%)
Alive	673 (64.3)	473 (66.0)	1,146 (65.0)
Dead	320 (30.6)	185 (25.8)	505 (28.6)
Lost	54 (5.2)	59 (8.2)	113 (6.4)
Total	1,047 (100)	717 (100)	1,764 (100)

mailed a questionnaire. Of the former sanatorium patients known to be alive, 80 % were residing in Massachusetts. The overall questionnaire response rate after three mailings and telephone contact was 78.1 % for the 1,146 women sent questionnaires. The response rate was 80.5 % for the exposed group and 74.4% for the comparison group.

Distributions of medical problems, menstrual and marital characteristics, surgical histories, and breast cancer risk factors for those responding to the questionnaire are presented in table 3. Twice as many exposed women reported having had a mastectomy. A slight cancer excess also reported among the exposed was accounted for entirely by an excess of breast cancer. No significant differences existed between exposed and comparison subjects with regard to menstrual and marital characteristics or any of the other breast cancer risk factors examined. Pneumotherapy patients reported having more thoracoplasty procedures performed and having INH, an antimicrobial drug, prescribed more frequently.

TABLE 3.—*Medical history and breast cancer risk factors from questionnaire responses*

Parameter	Exposed group	Comparison group
No. of women	543	352
Average age at response, yr	56.7	54.5
Medical history		
Asthma	4.4%	5.4%
Allergies	11.6%	16.8%
Diabetes	4.1%	4.0%
Heart problems	6.6%	7.7%
Thyroid problems	7.6%	7.1%
Cancer, any	8.1%	6.0%
Breast cancer	3.9%	1.4%
Surgical history		
Tonsillectomy	50.4%	57.1%
Appendectomy	39.3%	43.2%
Thoracoplasty	20.7%	9.9%
Lobectomy	6.1%	10.5%
Pneumonectomy	2.4%	2.3%
Mastectomy	4.2%	2.0%
Chemotherapy, any	44.7%	37.5%
Streptomycin	24.2%	25.3%
PAS	22.3%	24.5%
INH	29.0%	17.4%
Never smoked	54.8%	54.6%
Breast cancer risk factors		
Family history of breast cancer	6.1%	6.3%
History of benign breast disease	15.5%	13.9%
Average age at menarche, yr	13.3	13.4
No longer menstruating	83.6%	73.6%
Average age at menopause, yr	46.4	45.8
Hysterectomy	22.7%	27.3%
Nulliparous	28.4%	24.1%
Ever married	86.9%	89.5%
Average No. of children	2.6	2.6
Average age at birth of first child, yr	27.3	26.5
First birth before 30 yr of age	75.2%	81.6%

Ascertainment of breast cancer cases. — Breast cancer cases were ascertained from medical records, mail questionnaire responses, and death certificates. In addition to the medical records from the two study sanatoria, medical records of most other Massachusetts sanatoria were also available. Hospitals where study subjects transferred were visited and additional medical histories as well as follow-up and exposure information obtained. Information on all causes of death was abstracted from death certificates; hospitals where study subjects died were queried for autopsy reports and/or discharge summaries and asked to complete a brief questionnaire regarding any previous history of cancer. Initially, 61 presumed breast cancer cases were ascertained.

We sought histologic confirmation by contacting all hospitals in which a mastectomy or breast cancer diagnosis occurred; 5 cases were subsequently reclassified as not being cancer. Three patients were found to have had chronic cystic mastitis, 1 patient had a mastectomy for a colloid cyst, and 1 patient had fibrocystic breast disease concurrently with metastatic lung cancer. Three of the 5 patients excluded were exposed subjects and 2 were in the comparison group. Of the 56 confirmed breast cancer diagnoses, we ascertained 23 from death certificates, 29 from questionnaire responses, and 4 from medical records. The date of mastectomy or of breast cancer diagnosis was obtained for all cases.

Assessment of radiation dose to the breast. —The methodology developed to estimate the radiation dose to the breasts of patients who received repeated fluoroscopic chest examinations during air collapse therapy has been reported (22). The numbers of pneumotherapy treatments were obtained from the medical records of the two sanatoria studied and from the sanatoria to which patients transferred. Dose estimates were derived by abstraction of information from medical records, physician interview, patient contact, exposure measurements on representative fluoroscopes, and application of an absorbed dose calculation scheme employing a Monte Carlo radiation transport technique (23). Estimated radiation doses to the breast were obtained and applied to the population of Massachusetts women who received pneumotherapy.

Data analysis. —Two methods of analysis were used, one in which breast cancer incidence rates of Connecticut were used and the other in which rates determined from the comparison group were used. Unless stated to the contrary, expected numbers based on Connecticut rates are presented:

1) Connecticut rates. Expected breast cancer cases were determined with the use of age-calendar year specific incidence rates of Connecticut (24, 25), a neighboring State whose cancer registry has been in existence since 1935. The years at which a woman was at risk for breast cancer development (i.e., the years after sanatorium admission or fluoroscopy exposure) were computed separately for each 5-year age group, each 5-year period since start of observation, and each quinquennium from 1930 through 1934 to 1970 through 1974 and for the 6-month period from January 1975 through June 1975. Multiplication of the age-calendar year specific WY at risk by the corresponding Connecticut incidence rates determined the number of expected breast cancers. Ratios of observed to expected cases (stan-

dard morbidity ratios) and absolute risks (observed minus expected cases divided by WY at risk) were calculated, and 90 % one-sided lower confidence limits were determined with the use of the procedure outlined by the National Academy of Sciences (*14*) for Poisson distributed variables. One-sided confidence limits are presented because the hypothesis being tested is that radiation increases the risk of breast cancer. [8]

2) Comparison group. Measures of radiation effect, i.e., ratios of adjusted risks, were also determined with the use of the subjects not given pneumotherapy as the referent population.

For stratified data, we estimated summary risk ratios by means of the method of maximum likelihood when the risk ratio was assumed the same for all strata. If a chi-square test for "heterogeneity" indicated that the risk ratio was not uniform for all strata, a summary risk ratio was estimated by a standardization procedure described by Miettinen (26). Tests of significance were made with use of the Mantel-Haenszel procedure (27), and trends were evaluated by means of a method described by Armitage (28).

The start of the period of risk for breast cancer development was taken as the date of first fluoroscopic examination for the exposed subjects and the date of first sanatorium admission for the comparison subjects not given pneumotherapy. The end of the period of risk was regarded as the date of cancer diagnosis for those women found to have had breast cancer. Among women without breast cancer, the end of the period of risk was selected as the date of death for those who died; July 1, 1975, for those found alive; and the date last known to be alive for those lost to follow-up.

RESULTS

Observed and expected breast cancers and WY at risk for all study subjects are presented in table 4. Fifty-six breast cancer cases were ascertained among all study subjects. Among women exposed repeatedly to fluoroscopic chest examinations existed a significant *(P = 0.0006)* excess of breast cancer cases, 41 observed and 23.3 expected; whereas no excess was apparent among the comparison subjects, 15 observed and 14.1 expected. The breast cancer crude incidence rate was almost twice as great in the exposed subjects (1.5/1,000 WY) as in the subjects not given pneumotherapy (0.8/1,000 WY).

If the exposed women who were lost to follow-up were assumed alive at the common closing date instead of being withdrawn at the time of loss, the relative risk measure changed only slightly, from 1.76 to 1.69. Contrasting the fluoroscopically examined patients with the comparison women and adjusting for age at first treatment and duration of follow-up resulted in a summary risk ratio of 2.01.

TABLE 4.—*Observed and expected breast cancers and WY at risk for all study subjects*

Parameter	Exposed group	Comparison group
No. of women	1,047	717
Breast cancer cases		
Observed	41	15
Expected[a]	23.3	14.1
Observed/expected ratio	1.76	1.06
WY at risk	28,011	19,025
Incidence rate	1.5/1,000 WY	0.8/1,000 WY

[a] Expected breast cancers were determined with the use of Connecticut age-calendar year specific incidence rates.

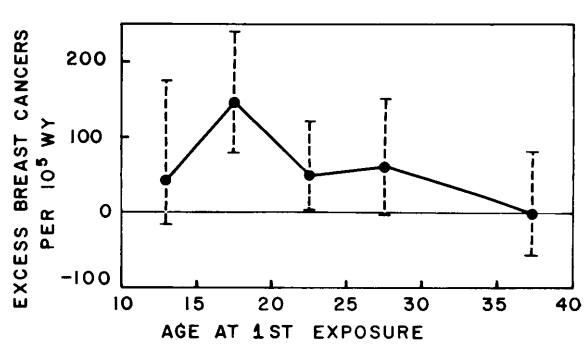
Exposed and comparison subjects differed significantly in seriousness of tuberculosis disease, INH drug usage, and thoracoplasty operations (tables 1, 3). Although associated with pneumotherapy, INH usage, thoracoplasty operations, and extent of tuberculosis disease were not found to be confounding because they were not associated with breast cancer within categories of exposure (29).

Breast Cancer and Age at Exposure

When breast cancer risk was examined by age at first fluoroscopic exposure (table 5), the greatest excess of breast cancer cases was seen among women whose first X-ray exposure occurred between the ages of 15 and 19 years (13 cases observed and 3.4 expected). An excess was also seen in women between the ages of 20 and 29 years (18 observed and 10.9 expected). Among those patients 30 years and older at the time of first exposure, no excess breast cancer cases were detected (8 observed and 8.1 expected). Text-figure 1 shows the absolute excess breast cancer risk by age at first exposure. By means of the method of least squares, the slope of the absolute risk as a function of age was determined to be −3.8 cases/10^5 WY/year of age. The negative slope suggested that the absolute excess breast cancer risk decreased with increasing age at first exposure; however, this decrease was not statistically significant [χ^2_1 (trend) = 2.5, P = 0.11].

Breast Cancer and Number of Fluoroscopic Examinations

The distribution of observed and expected breast cancers



TEXT-FIGURE 1.—Excess breast cancer cases/100,000 WY at risk by age at first exposure, (observed, 0 − expected, E)/10^5 WY; 80% confidence limits are presented.

[8] A one-sided test may be justified when, before the onset of a study, the investigator can state with assurance that the true value of the parameter to be measured is above (or below) the value that would be expected under the null hypothesis. Because we generally accept that radiation induces breast cancer and since to assume that radiation prevents breast cancer has little meaning, one-sided tests are presented. A lower 90 % confidence limit implies that, if repeated samples were evaluated, 90 % of the observed values would be above the lower confidence limit value. A one-sided 90 % limit is equivalent to an 80 % two-sided limit.

TABLE 5.—*Observed and expected breast cancers and WY at risk by age at first fluoroscopic exposure*[a]

Parameter	Age at first exposure, yr							
	<15	15–19	20–24	25–29	30–34	35–39	40+	Total
No. of women	99	242	263	200	105	75	63	1,047
Breast cancer cases								
Observed	2	13	9	9	4	2	2	41
Expected	0.9	3.4	5.4	5.5	3.3	2.5	2.3	23.3
Observed/expected ratio	2.1	3.8	1.7	1.6	1.2	0.8	0.9	1.8
WY at risk	2,510	6,497	7,268	5,708	2,774	1,871	1,383	28,011
Excess breast cancer cases/10^5 WY	42.2	147.6	50.1	61.1	27.0	−28.9	−20.2	63.2
Average No. of fluoroscopic exams	95	111	108	98	89	90	55	102
Excess breast cancer cases/10^6 WY/fluoroscopy	4.4	13.3	4.6	6.2	3.0	−3.2	−3.7	6.2
(90% lower bound)	(−1.7)	(7.3)	(0.1)	(−0.1)	(−6.1)	(−11.9)	(−23.0)	(3.4)

[a] Expected breast cancer cases and WY at risk were computed to two decimal places (for WY, follow-up days were converted to years) and these unrounded values were used in the calculation of the presented results; because rounded values are presented, some results cannot be exactly reproduced.

TABLE 6.—*Observed and expected breast cancer cases and WY at risk by number of fluoroscopy examinations*[a]

Parameter	No. of fluoroscopy examinations						
	0	1–49	50–99	100–149	150–199	200+	Unknown
No. of women	717	395	178	195	122	134	23
Breast cancer cases							
Observed	15	8	8	14	6	5	0
Expected	14.1	8.2	3.6	4.9	3.3	2.8	0.5
Observed/expected ratio	1.1	1.0	2.2	2.9	1.8	1.8	—
WY at risk	19,025	9,242	4,696	6,030	3,632	3,825	585
Incidence of breast cancer/10^3 WY	0.8	0.9	1.7	2.3	1.7	1.3	—
Excess breast cancer cases/10^5 WY	4.5	−1.7	93.3	150.7	74.6	57.3	—
(90% lower bound)	(−20.2)	(−37.9)	(22.1)	(75.6)	(−3.8)	(−9.9)	

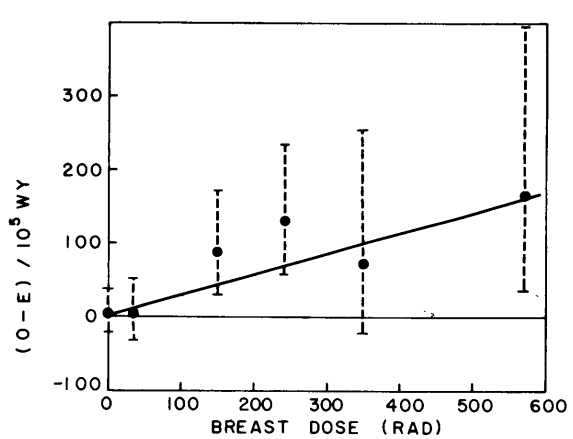
[a] *See* footnote, table 5.

and WY at risk by number of fluoroscopic examinations are given in table 6. No excess breast cancer cases developed among subjects receiving fewer than 50 fluoroscopic examinations (8 cases observed and 8.2 expected). The radiation effect, as measured by the absolute excess risk, increased with increasing numbers of fluoroscopic examinations up to 100-149 examinations, and a decrease in risk after 150 or more fluoroscopic examinations was suggested. A linear increase, however, could not be excluded [χ_1^2 (trend) = 4.1, P = 0.04; χ_4^2 (departure from linearity) = 6.9, P = 0.14].

Breast Cancer and Radiation Dose

Text-figure 2 and table 7 present the excess breast cancer risk by the estimated cumulative radiation dose to the breast in rads (29). No decrease in excess risk was apparent in the highest dose category (574 rads, average), and a dose-response relationship consistent with linearity down to the lowest dose category was observed [χ_1^2 (trend) = 9.4, P = 0.002; χ_4^2 (departure from linearity) = 1.6, P = 0.80]. Among those patients receiving fewer than 100 rads, 10 breast cancers were observed versus 9.6 expected (32 rads, average).

The difference in appearance between the data in tables 6 and 7 reflected the fact that all "examinations" did not result in equal radiation dose to the breast. Examinations after 1947 were performed with additional aluminum filters in the X-ray beam and resulted in less radiation dose to breast tissue. A peritoneum examination differed from a pneumothorax examination in that the breasts were unlikely to be in the direct X-ray beam. Patients who faced the X-ray tube received greater radiation doses to the breast than those who had their backs to the tube, and patients with



TEXT-FIGURE 2.—Excess breast cancer cases/100,000 WY at risk by estimated average dose to breast, (observed, 0 − expected, E)/10^5 WY. Best fitting least-squares line and 80% confidence limits are presented.

TABLE 7.—*Observed and expected breast cancer cases and WY at risk by cumulative breast dose*[a]

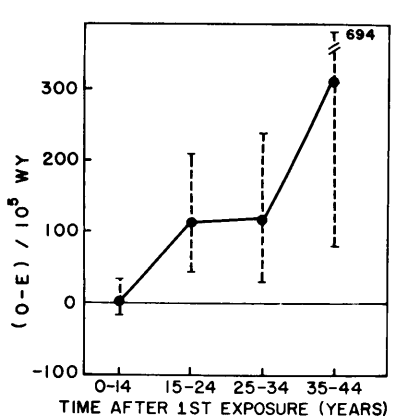
Parameter	Average dose to breast (rads)						
	0	1-99	100-199	200-299	300-399	400+	Total[b] 1+ rads
No. of women	717	469	251	177	65	62	1,047
Breast cancer cases							
Observed	15	10	12	12	3	4	41
Expected	14.1	9.6	5.7	4.8	1.5	1.1	23.3
Observed/expected ratio	1.06	1.04	2.1	2.5	1.9	3.6	1.8
WY at risk	19,025	10,990	7,097	5,584	2,020	1,735	28,011
Incidence of breast cancer/10^5 WY	79	91	169	215	149	231	146
Standardized incidence/10^5 WY[c]	79	109	165	225	144	354	159
Excess breast cancer cases/10^5 WY	4.5	3.6	88.6	129.5	72.3	166.0	63.2
(90% lower bound)	(−20.2)	(−30.8)	(29.8)	(54.8)	(−21.7)	(36.0)	(34.8)

[a] *See* footnote, table 5.
[b] Includes unknown dose category.
[c] The exposed patients were compared with the comparison patients; adjustment was made for age at exposure and duration of follow-up.

bilateral disease received greater total radiation doses than those with unilateral disease. Finally, because of a smaller breast size, an adolescent would receive a greater average radiation dose to the breast than an adult given a comparable external exposure (22). All these factors contributed to the distribution presented in text-figure 2; the main consequence of these adjustments was the shifting of adults who were in the high examination categories to lower dose categories.

Breast Cancer and Duration of Follow-Up

The average length of follow-up for both the exposed and the comparison subjects was 25.6 years. When we examined breast cancer risk by period of observation after first exposure (table 8), no excess breast cancer risk was apparent during the first 15 years of observation (5 breast cancers observed and 4.9 expected). After 15 years, however, the breast cancer excess risk appeared and was present for at least 40 years after the initial X-ray exposure. Excess breast cancer risk by years after first exposure is shown in text-figure 3. A substantial increase in the absolute risk in women living 35 years after first exposure was suggested.



TEXT-FIGURE 3.—Excess breast cancer cases/100,000 WY at risk by number of years after initial fluoroscopic exposure, (observed, 0 − expected, E)/10^5 WY; 80% confidence limits are presented.

Breast Cancer by Age at Observation

The average age at breast cancer diagnosis among the exposed subjects was 48.4 years. The average time from exposure to diagnosis was 24.4 years. Table 9 shows the distribution of observed and expected breast cancer cases and WY at risk by age at observation. Interestingly, while the incidence rate of breast cancer increased with age at observation, the observed-to-expected ratio decreased. An excess breast cancer risk was seen at all ages over 20 years, and the greatest risk appeared among women 40-49 years of age. Few women under 25 years of age at first exposure, however, had reached their 50th birthday (29).

Breast Cancer by Age at First Treatment, Number of Fluoroscopic Examinations, and Duration of Follow-Up

Table 10 presents observed and expected breast cancer cases and WY at risk by age at first treatment, number of fluoroscopic examinations, and duration of follow-up. The greatest risk for breast cancer (24 cancers observed and 8.4 expected) occurred 15 or more years after first exposure among women 15-29 years old who received more than 50 fluoroscopies, approximately 75 rads. An excess breast cancer risk was suggested among exposed women over 30 years of age, only in those who received more than 50 fluoroscopes, though the excess was limited to the first 15 years of follow-up (4 observed and 1.6 expected). The only indication of a low-dose effect was among subjects 15-29 years old at first exposure who received fewer than 50 examinations (7 cancers observed and 4.3 expected). This effect at low doses was concentrated among those women 15-19 years old in whom 4 breast cancer cases were observed and 0.8 was expected (29).

Breast Cancer and Side of Lung Collapse

Comparison between the breast in which the cancer occurred and the lung receiving air collapse treatment (table 11) suggested a slight concordance between the side of the

TABLE 8.—*Observed and expected breast cancer cases and WY at risk by period of observation after first exposure*[a]

Parameter	Period of observation after first exposure, yr								
	0–4	5–9	10–14	15–19	20–24	25–29	30–34	35–39	40–45
No. starting interval	1,047	942	877	836	806	701	504	320	95
Breast cancer cases									
Observed	1	2	2	5	11	8	6	5	1
Expected	0.9	1.5	2.5	3.6	4.6	4.4	3.5	1.8	0.4
Observed/expected ratio	1.1	1.3	0.8	1.4	2.4	1.8	1.7	2.7	2.7
WY at risk	4,983	4,517	4,260	4,106	3,838	2,999	2,108	1,017	183
Incidence of breast cancer/10^3 WY	0.2	0.4	0.5	1.2	2.9	2.7	2.8	4.9	5.5
Excess breast cancer cases/10^5 WY	2.2	10.4	−10.8	33.1	166.0	119.7	117.6	309.9	344.3
(90% lower bound)	(−15.7)	(−22.1)	(−45.3)	(−29.4)	(62.3)	(8.2)	(−17.5)	(57.3)	(−144.6)

[a] *See* footnote, table 5.

TABLE 9.—*Observed and expected breast cancers and WY at risk by age at observation*[a]

Parameter	Age at observation, yr					
	<20	20–29	30–39	40–49	50–59	60+
Breast cancer cases						
Observed	0	1	6	18	10	6
Expected	0.0	0.2	2.8	8.6	7.5	4.2
Observed/expected ratio	—	4.3	2.2	2.1	1.3	1.4
WY at risk	1,174	5,134	7,455	7,401	4,753	2,093
Incidence of breast cancer/10^3 WY	0	0.2	0.8	2.4	2.1	2.9
Excess breast cancer cases/10^5 WY	0	15.0	43.1	126.6	52.4	87.1
(90% lower bound)		(−2.4)	(4.9)	(56.6)	(−27.1)	(−49.1)

[a] *See* footnote, table 5.

TABLE 10.—*Observed and expected breast cancer cases and WY at risk by number of fluoroscopy examinations, age at first treatment, and period of observation*[a]

No. of fluoroscopy examinations	Age at first treatment, yr	Breast cancer cases	Period of observation, yr		
			0–14	15+	Total
0	<15	Observed	0	3	3
		Expected	0.05	2.3	2.4
		WY at risk	2,577	3,273	5,850
	15–29	Observed	1	6	7
		Expected	0.8	5.1	5.9
		WY at risk	4,352	4,440	8,792
	30+	Observed	4	1	5
		Expected	2.3	3.6	5.8
		WY at risk	2,382	2,001	4,383
1–49	<15	Observed	0	0	0
		Expected	0.0	0.2	0.2
		WY at risk	352	327	680
	15–29	Observed	1	6	7
		Expected	0.6	3.7	4.3
		WY at risk	2,980	2,970	5,949
	30+	Observed	0	1	1
		Expected	1.4	2.2	3.6
		WY at risk	1,418	1,195	2,613
50+	<15	Observed	0	2	2
		Expected	0.03	0.7	0.7
		WY at risk	862	968	1,830
	15–29	Observed	0	24	24
		Expected	1.2	8.4	9.6
		WY at risk	6,129	6,935	13,064
	30+	Observed	4	3	7
		Expected	1.6	2.8	4.4
		WY at risk	1,730	1,559	3,289

[a] *See* footnote, table 5.

TABLE 11.—*Comparison between the specific breast in which the cancer occurred and the specific lung collapsed*

Lung collapsed	Cancerous breast			
	Left	Right	Bilateral	Total
Left	10	8	0	18
Right	4	7	1	12
Bilateral	6	5	0	11
Total pneumotherapy	20	20	1	41

pneumothorax and the side of the affected breast. Seventeen concordant breast–lung pairs were observed versus 12 discordant pairs. Although not statistically significant, these data suggested that slightly more radiation was received on the same side of the body as the lung being collapsed. A large concordance would not be expected under a causal hypothesis inasmuch as 69 % of the physicians, who administered the pneumotherapy, when interviewed reported fluoroscoping with the machine shutters fully open (exposing both breasts); 81 % always scanned the opposite lung to determine whether the tuberculosis had spread.

Radiation Dose to the Breast and Risk Estimation

The average dose to the breast associated with one fluoroscopic examination was estimated to be 1.5 rads, and the pneumotherapy-treated patients received an average cumulative dose to the breast of 150 rads (22). The radiation risk estimate derived from the Massachusetts women in this study living 10 or more years after first exposure was 6.2 excess breast cancer cases per million WY-rad, (38–20.85)/(18,511 WY) (150 rads). The uncertainty due to sampling variability was such that the true value was estimated to lie between 2.8 and 10.7 cancers/ 10^6 WY-rad (90% Poisson confidence limits). If the expected cases of breast cancer were computed with the use of rates observed in the patients not given pneumotherapy, specific for age at first treatment and duration of follow-up (excluding the first 10 yr of follow-up), the risk estimate would have been 5.6 cancers/ 10^6 WY-rad.

In the computation of the risk estimates above, no assumption as to the shape of an underlying dose-effect relationship was made. If linearity was assumed over the range of all doses, the age-adjusted regression risk estimate would have been 2.9 cases/ 10^6 WY -rad; however, if the excess risk decreased at high doses, this estimate would have underestimated the risk at lower doses. The regression estimate over the dose range from 0 to 300 rads was 8.2 cases/ 10^6 WY-rad.

The dose to the breast differed significantly with respect to whether the patient faced the X-ray fluoroscopy tube or the fluoroscopist.[9] Responses to the patient questionnaire indicated that about one-fourth of all the fluoroscopic examinations in both the child and the adult sanatoria were performed with the patient facing the X-ray tube, and interviews with the former physicians administering the pneumotherapy confirmed this figure. No difference among age categories with respect to X-ray beam orientation was reported.

[9]The estimated breast dose per 1 R entrance skin exposure would be 480 mrads if the patient faced the X-ray tube versus 20 mrads if her back was to the tube (29).

DISCUSSION

The data reported in this study are consistent with the hypothesis that a woman's lifetime risk of breast cancer is in large part determined during the early years of life (*16*). In addition, multiple low-dose radiation exposures of the female breast appear to convey a breast cancer risk that is proportional to the cumulative total dose received, and the dose-response relationship for breast cancer induction is consistent with linearity. Increased breast cancer risk after radiation exposure also seems permanent, lasting at least 40 years after initial exposure.

Age

The appropriate measure of radiation effect when age categories are compared is the absolute risk as estimated by the excess number of breast cancer cases per WY of observation. The large absolute risk among women 15-19 years of age at first exposure and the failure to observe a radiation effect among those over 30 years of age (table 5, text-fig. 1) suggest that radiation exposure during early life is more harmful than exposure later in life.

In women over 30 years of age, our findings are consistent with the previous Nova Scotia fluoroscopy study. Myrden and Hiltz (*11*) found no breast cancers among 66 Canadian women who were 30 years of age and older at first fluoroscopy; however, they observed 22 breast cancers among 234 women who were under 30 years of age at first fluoroscopy. In a recent study of atomic bomb survivors, over 200 breast cancer cases were observed between 1950 and 1969 and ratios of observed to expected cases were found to be significantly higher for younger women than for older. A recent analysis of these data indicates that, among females over age 10 years at exposure, the greatest radiogenic breast cancer risk, as measured in absolute terms, occurred among females 10-19 years of age at exposure, whereas women over age 35 experienced the least risk (5, 6).

In contrast to the fluoroscopy and atomic bomb studies, a recent follow-up of the women who received radiation therapy for acute postpartum mastitis (*13*) indicates that women over 30 years of age at exposure were at the same or perhaps greater risk for breast cancer development than women under 30 years old (30). This suggests that the sensitivity of breast tissue to radiation may be related to the condition of the breast at the time of exposure. The different results might also reflect differences in the age distributions of the exposed populations. Of the tuberculous women, 33 % were initially exposed under age 20 years, the period of apparent increased sensitivity, whereas only 4 % of the mastitis patients were under 20 years of age when irradiated.

The data from the tuberculosis studies should not be interpreted to mean that women over 30 years of age when exposed are at *no* radiation risk. In addition to the mastitis patients, a breast cancer risk has also been observed among atomic bomb survivors at all ages (6, 7) including those over age 30 at the time of exposure. Because of the small number

(243) of pneumotherapy-treated women who were 30 years of age or over at first exposure, a radiogenic breast cancer risk possibly exists but the sample size may have been too small to detect it.

Dose Response

The distribution of breast cancer excess risk by estimated cumulative breast dose in rads is consistent with a linear relationship down to the lowest dose category (text-fig. 2). When the exposed patients are contrasted with the comparison patients and adjustments are made for age at exposure and duration of follow-up, the standardized incidence rate for the women receiving less than 100 rads (32 rads, average) is $109/10^5$ WY compared to $79/10^5$ WY for the comparison women. Although suggestive of an increased risk at these low doses, this difference is not statistically significant *(P = 0.5)*. At high doses, a decrease in excess breast cancer risk was seen among women receiving more than 150 fluoroscopic examinations; however, this decrease was not as apparent when adjustment was made for the most important factors contributing to breast dose: type of examination, breast size, patient orientation, X-ray beam size, the addition of aluminum filtration, exposure time, and machine physical parameters (table 7).

The use of the term "nonexposed" was avoided in description of the tuberculosis patients not given pneumotherapy. Although they did not receive repeated fluoroscopic examinations to the same extent as the pneumotherapy-treated patients, they were subject to more frequent X-ray examinations than the general population. Many diagnostic chest X-ray examinations were performed, and fluoroscopic examinations were occasionally made for reasons other than pneumotherapy surveillance. The comparison group of patients not given pneumotherapy is in fact a "minimally exposed" group, and the absence of any excess breast cancers is of interest.

Duration of Effect

The persistent injurious effect of radiation exposure, present at the end of 40 years of observation (table 8, text-fig. 3), suggests that, unlike bone marrow exposure and leukemia risk (14), excess breast cancer risk does not decrease with time after reaching some maximum value. The data, in fact, indicate that the greatest risk occurs among those living 35 years after first exposure. If radiation-induced breast cancers are manifest at the same time as nonradiogenic breast cancers (i.e., in later life) and not before, then the observed duration of effect may reflect the youthful average age (25 yr) of the population at first exposure. Many years may have been necessary for the population to age sufficiently to the time when breast cancers would be expected to occur. The observation of an effect 35 years after initial exposure is then consistent with the hypothesis that a woman's lifetime risk for breast cancer development is largely determined during her younger years.

Although the start of follow-up was chosen to be the date of first fluoroscopy exposure, air collapse therapy lasted an average of 3.3 years, and other dates could have been selected, e.g., the date of last treatment or the midpoint between the dates of initial and final treatments. Selection of alternate dates to begin the period at risk for breast cancer development would not affect the conclusions suggested above but would indicate a minimum "latent period" (between breast exposure and manifestation of disease) of less than the 15-year period determined by use of the date of first fluoroscopy.

Risk Estimation

In addition to sampling variability, the greatest uncertainty associated with the risk estimate of 6.2 excess breast cancers/ 10^6 WY-rad is the estimation of radiation dose. Not only is radiation dose to breast a function of machine parameters such as beam quality (kVp), tube current, and aluminum filtration, but also it is a function of human parameters such as patient breast size and patient orientation with respect to the X-ray tube. The time required for the physician to perform the fluoroscopic examination is also an important determinant of radiation dose to breast. To account for these factors, an extensive methodology was developed to estimate cumulative radiation dose to the breast. When we allowed for the assumptions concerning actual fluoroscopic conditions to vary, the best estimate of excess breast cancer risk was seen to be accurate within the limits of sampling variation (3-11 cases/ 10^6 WY-rad) (22). Although dose was estimated as thoroughly as possible, the numerous uncertainties involved with the retrospective assessment of fluoroscopic doses and procedures should be kept in mind when the derived risk estimate is evaluated.

Table 12 compares the current study with the three previously published studies. The risk estimate for the

TABLE 12.—*Comparisons with other radiation-induced breast cancer studies*

Study group	No. irradiated	Ages at irradiation yr (mean)	Mean dose to the breast rads	Period after irradiation on which risk estimates based, yr	Excess breast cancers per 10^6 WY-rad
Atomic bomb survivors[a] *(7, 14, 31)*	11,968	10+ (34)	61.4	5–24	2.5
Nova Scotia fluoroscopy series *(11, 14)*	243	0–60+ (26)	1,215	10–30	8.4
Mastitis patients *(13, 14, 30)*	606	15–44 (27)	247	10–34	8.3
Current study	1,047	5–59 (25)	150	10–44	6.2

[a] Women over 10 yr of age at irradiation who received a breast kerma dose of greater than 9 rads.

Massachusetts patients was comparable with the two studies of Western women but three times larger than the estimate from the atomic bomb survivors. This apparent discrepancy, however, may have been the result of computation of the risk with the use of different years of follow-up: The A-bomb survivor estimate was computed for years 5-24 of follow-up; the fluoroscopy patient estimate was for follow-up years 10-44. The absolute risk estimate for the Massachusetts fluoroscopy-treated patients, computed for years 5-24 of follow-up, was *3.1* cases/ 10^6 WY-rad, in close agreement with the A-bomb survivor estimate of 2.5 cases/ 10^6 WY-rad for the same years of follow-up. Alternatively, the different risk estimates may have reflected different genetic susceptibilities for radiation injury, differences in the age distributions of the two populations, or simply a chance occurrence.

Because cell repair and repopulation may occur when radiation exposure is distributed over several years, we might expect that repeated fluoroscopic exposures would produce fewer deleterious effects than a single exposure of the same total dose. This does not appear to be the case inasmuch as repeated exposures to low radiation doses appear to act in a cumulative manner. That the four studies involving different radiation modalities, dose rates, dose fractionations, and total doses result in breast cancer risk estimates that are so similar is perhaps noteworthy.

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