Acta Radiologica Oncology 25 (1986) Fasc. 4–6

FROM THE DANISH CANCER REGISTRY UNDER THE DANISH CANCER SOCIETY, AND THE DANISH INSTITUTE FOR CLINICAL EPIDEMIOLOGY, COPENHAGEN, DENMARK, AND THE RADIATION EPIDEMIOLOGY BRANCH, NATIONAL CANCER INSTITUTE, BETHESDA, MARYLAND, USA.

BREAST CANCER FOLLOWING MULTIPLE CHEST FLUOROSCOPIES AMONG TUBERCULOSIS PATIENTS

A case-control study in Denmark

H. H. STORM, E. IVERSEN and J. D. BOICE JR

Abstract

A case-control study of breast cancer among tuberculosis (TB) patients in Denmark (1937–1954) was conducted to provide additional information on the radiation risk associated with low-dose chest fluoroscopy exposures. Records of 46013 TB patients were linked to the Danish Cancer Registry and 125 subsequent female breast cancers identified. Medical records were located for 89 (71%) of these women who developed breast cancer and on 390 controls, who were individually matched to cases on age and calendar year of TB diagnosis, and survival. Common risk factors for breast cancer such as nulliparity (relative risk (RR)=2.5) and high relative weight (RR=2.6) were also identified in this population of TB patients. However no risk was evident with exposure to any type of fluoroscopy (RR=0.6; 95% CI=0.2–1.4), or to fluoroscopies performed to monitor lung collapse therapy (RR=0.8; 95% CI=0.5–1.4). Although based on only 7 breast cancers, there was a suggestion of an increased risk among women who received greater than 1 Gy to their breasts (RR=1.6; 95% CI=0.4–6.3). Because of the infrequent use of fluoroscopy in our study, the breast doses were too low, 0.27 Gy on average, to expect to detect a significant elevation in breast cancer risk overall. The findings do suggest, however, that current estimates of breast cancer risk following radiation are not greater than presently accepted, and that a relative excess of 40 per cent can be excluded with reasonable confidence following breast doses on the order of 0.3 Gy.

Key words: Radiation, injurious effects, neoplastic, chest fluoroscopies, breast cancer.

Breast cancer is the most common cancer among women in Denmark (6) and other western countries (31). Among identified factors influencing the breast cancer incidence (e.g. genetic, hormonal, dietary, radiation), at present only the reduction of unnecessary radiation exposure, appears suitable for primary prevention (11, 23, 30). Thus secondary prevention (i.e., early detection and treatment) is considered by many to be the most promising approach to alter the course of the disease. Screening for breast cancer by methods that included mammography has reduced the mortality among healthy women above the age of 50 years (24, 27). The efficacy of mammography screening below age 50 is still disputed, although baseline mammographies at an early age (35–40 years) have been recommended (4). Conceivably, mammography could become the most widespread source of radiation exposure to the female breast in the foreseeable future. Thus it is important that the potential risk associated with fractionated exposure to low-dose radiation, as anticipated in screening programmes using mammography, be accurately estimated and balanced against the benefit afforded by the mammography screening.

The breast is unusually sensitive to the carcinogenic effects of ionising radiation (19), and many epidemiologic studies (1–3, 16, 20, 25, 28) point to a linear relationship between the induction of breast cancer and radiation dose. Age at exposure is the most important modifier of the radiation effect with risk being lowest among older women (13). Assuming a linear dose-response relation, absolute risks for women below the age of 40 at exposure are estimated to be 6.6 excess breast cancers per million women per year per 10 mGy (3); these data are consistent with a 0.5 per cent increase in relative risk (RR) per 10 mGy. There are insufficient data on exposure among women over the age of 40 years to meaningfully quantify

Accepted for publication 1 April 1986.

the apparently low risk previously suggested (13). To provide additional information on the risk of breast cancer following low-dose fractionated radiation exposures, a study among Danish TB patients was conducted, using record-linkage techniques within a well-defined population.

Material and Methods

A record-linkage between the Danish TB registry (1937–1954) and the Danish Cancer Registry (1943–1977) was performed. Both registries are population based and cover the entire Danish population. Since 1943 the Cancer Registry has collected information on all malignant tumors and certain tumor-like conditions in Denmark. The Registry is based on notifications from multiple sources, including yearly linkage with the Death Registry (10). A high degree of completion and diagnostic reliability has been reached (10, 22, 26). Respiratory tuberculosis has been a reportable disease by law ever since April 1905. The Danish TB Registry was established in 1920 and is based on the compulsory notification to the National Board of Health of cases of respiratory tuberculosis from hospitals, clinics, general practitioners, and death certificates. The TB Registry is computerized from 1937 onward and contains information on all newly diagnosed cases and some relapses. Detailed information on treatment, however, is not available on the computer tapes, and medical records had to be abstracted to obtain data on fluroscopies associated with lung collapse therapy and on other breast cancer risk factors.

Study population. Excluding TB patients known to have died prior to the start of the Cancer Registry in January 1943, 46 013 TB patients were available for record linkage with the Cancer Registry. Variables used in the computerized matching procedure included date of birth, sex and first letter of current or maiden name. The computerized procedure was followed by a visual determination of true matches based on the complete name or maiden name. This linkage method has proven reliable in past studies (8). Invasive cancers were identified in 1 478 TB patients, and 125 of 135 females with no other cancer prior to the breast cancer were selected for detailed study (10 simultaneous TB and breast cancer diagnoses were excluded). Controls selected were TB patients without cancer matched to cases on age and calendar year at TB diagnosis, residence in or outside Copenhagen, and survival at least as long as the time elapsed between TB and breast cancer diagnosis for the corresponding case. We selected 4 matched controls per case from the TB file. However, because all hospital records from several major TB hospitals had been destroyed (9), we selected 4 additional controls for each case in order not to loose study-power (18). It was thus assured that medical record abstracts could be obtained on average for 4 controls per case.

Retrieval of TB records, rematching. TB clinics for follow-up and screening purposes have been established in all counties in Denmark. These were contacted, using the code for county identified from the TB file, in an attempt to obtain records on patients from that area. The majority of patient records were obtained in this fashion, and information on previous hospitalisations, treatment and follow-up status for TB provided. In addition to the TB clinics, records were also obtained from general hospital and centralized county files for those areas with closed TB sanatoria. Altogether, medical records were obtained on 89 (71%) breast cancer cases, and 235 (66%) of the corresponding controls initially chosen. No difference in the ability to locate hospital records for cases and controls was apparent. Medical records were subsequently obtained on 435 controls when we included the supplementary controls in the abstraction process. Because the TB registry records date of notification rather than date of diagnosis, 18 cases and 37 controls had to be re-matched. Of the 173 controls for whom a breast cancer case record was not available, 128 could be reassigned to cases with available records. A total of 89 cases and 390 matched controls were included in the final analyses.

Data abstraction. Details on known risk factors for breast cancer (nulliparity, family history, menarche, obesity (11)), on TB treatment (bedrest, surgery, chemotherapy, pneumothorax), and the yearly number of fluoroscopies, chest radiograms, and photofluorographic examinations following TB diagnosis were abstracted. Five per cent of the records were reabstracted by a retired TB doctor and no significant discrepancies were found.

Dosimetry. A breast dose associated with all fluoroscopic examinations was calculated as described by Boice et coll. (3). Breast dose coefficients used to convert exposure in R (roentgen unit) to absorbed breast dose in Gy were obtained using a Monte Carlo estimation procedure that accounts for changes in shielding, scattering, and field geometrics (3). Exposure rates in R/min were assumed similar to those reported in North America (3). The coefficients, slightly smaller than previously published (3), were applied to the number of fluoroscopies for the individual patient and fluoroscopy procedures used in Denmark. The exposure procedures commonly used to fluoroscope TB patients were estimated from interviews with 36 Danish TB physicians. The estimated average exposure time was estimated to be 21 seconds, the patients faced the roentgen tube about 12 per cent of the time and uncollimated beams were used 76 per cent of the time. In the analyses we followed the example of others (2) in using the date of first exposure to fluoroscopy in defining the age and latency intervals. Other dates could have been used, e.g., date of last exposure or date of median exposure. Since most fluoroscopies occurred within 5 years of initial treatment and since the latency for radiation-induced breast cancer is measured in decades the choice of these alternate dates would have little effect on the study

Table 1

Characteristics of women who developed breast cancer following TB treatments and their matched controls

Characteristic	Breast cancer cases (n=89) (per cent)	Controls (n=390) (per cent)
Year of TB diagnosis		
1921–1936	11.2	9.0
1937–1946	56.2	57.9
1947–1954	32.6	33.1
Age at TB diagnosis (years)		
<20	5.6	4.1
20–29	29.2	30.8
30–39	34.8	38.7
40–49	11.2	15.4
50–59	5.6	4.9
60+	13.5	6.2
Residence at TB diagnosis		
Captial	47.7	45.7
Provincial towns	46.5	48.7
Rural areas	5.8	5.6
Years of follow-up*		
<10	18.0	5.4
10–19	32.6	5.6
20–29	38.2	24.6
30–39	9.0	48.7
40+	2.2	15.6
TB verification		
a) Radiography only	11.2	9.7
b) Bacteriologic only	1.1	1.8
Both a and b	82.0	84.9
Unknown	5.6	3.6
No. of photofluorographies		
0	48.3	34.4
1–9	33.7	35.9
10–19	12.4	22.6
20+	5.6	7.2
Family history of cancer**		
Yes	11.2	7.7
No	5.6	10.0
Unknown	83.1	82.3
Age at menarche		
11–13	6.7	5.6
14–16	22.5	20.5
17–18	3.4	2.8
Unknown	67.4	71.0
Marital status		
Married	53.9	56.6
Not married	39.9	27.4
Divorced	3.4	6.4
Widow	3.4	8.7
Unknown	0.0	2.1
Parity		
Unknown parity	16.9	16.2
Nulliparous	34.8	19.0
Parous		
Age at first birth		
18–20	3.4	6.7
21–25	20.2	22.3
26–30	10.1	14.4
30+	6.7	11.0
Unknown	7.9	10.4

Table 2

Risk of breast cancer by breast dose

Breast dose (Gy)	0	0.01–0.49	0.50–0.99	1.00–2.74
Average breast dose	0	0.16	0.61	1.44
No. cases	8	71	3	7
No. controls	23	291	65	11
RR (matched)	1.00	0.71	0.15*	1.57
CI 95%	–	0.30–1.72	0.04–0.59	0.40–6.28

* p<0.01.

results. Fluoroscopies given other than in conjunction with pneumothorax treatments, however, were also included in the dose calculation, using the conditions for pneumothorax fluoroscopy. For these later fluoroscopies the exposure times may have been somewhat shorter (5 seconds), and the breast doses consequently slighly overestimated. Radiation dose from photofluorography and chest radiography are 10 per cent or less of the doses received by fluoroscopy (29) and were not considered in the analysis.

Analysis. Comparisons between the cases and their matched controls were made by the conditional logistic regression method using a computer program developed by Lubin (15). Continuous variables were grouped into 'categories', i.e., non-overlapping intervals, and calculations of relative risks between each category and a chosen reference category were made using dummy indicator variables for the categories. The breast doses were grouped into four categories, as were weight indices, for body mass analysis (12). The effect of latency since first exposure was considered in the categories 10+, 15+ and 25+ years. The breast cancer risk was evaluated for 3 different age groups at first exposure to fluoroscopy (17–29, 30–39, 40–85 years). Other risk factors for breast cancer as parity, number of live births and age at first birth were evaluated.

Results

Cases and controls were diagnosed with TB as early as 1921 and were followed on average for 30 years (Table 1). Only 4 per cent of the population was below age 20 at time of TB diagnosis and 25 per cent were over age 40. Approximately half of the patients had bilateral lung tuberculosis. Most patients (80%) were treated primarily with bedrest; 43 per cent received pneumothorax treatment; 48

* For the controls this represents the interval between the date of TB diagnosis and date of last known vital status. For the breast cancer cases this represents the interval between date of TB diagnosis and date of breast cancer. On average, cases were followed 26.9 years and controls 31.0 years to date of last known vital status.

** Among cases, 3 breast cancers occurred in first degree relatives. None of the controls had breast cancers among relatives.

Table 3

Risk of breast cancer by exposure to fluoroscopy by time since—and age at TB diagnosis

	RR (matched)	CI 95%	No. of observations
Time since TB diagnosis (years)			
>10	0.76	0.26–2.19	400
>15	0.72	0.22–2.41	317
>25	0.95	0.20–4.47	169
Age at exposure (years)			
17–29	0.33	0.07–1.51	167
30–39	0.70	0.15–3.32	179
40–85	0.81	0.18–3.63	133
Total	0.58	0.24–1.40	479

Table 4

Risk of breast cancer by number of live birth

	No. of live birth		
	0	1–2	3+
Cases	31	32	11
Controls	74	156	97
RR (matched)	1.00	0.52*	0.27*
CI 95%	–	0.30–0.93	0.11–0.63

* p<0.05.
p (trend) = 0.005.

Table 5

Risk of breast cancer by body mass index (Quetelet)

	Quetelet[a]				
	I	II	III	IV	V
Cases	16	18	19	8	15
Controls	80	74	81	38	31
RR (matched)	1.00	1.28	1.18	0.87	2.53*
CI 95%	–	0.57–2.88	0.42–3.34	0.31–2.47	1.06–6.06

* p<0.05.
[a] I: <19.82. II: 19.82–21.75. III: 21.77–23.80. IV: 23.88–26.06. V: 26.07+.

per cent received chemotherapy (streptomycin, PAS and isoniazid in some combination); and 14 per cent had surgery (resection, thoracoplasty, phrenico-exeresis and other). The average number of total fluoroscopies was 50 per person, with the controls receiving slightly more than the patients. The average number of fluoroscopies among patients receiving pneumotherapy, however, was 90. The mean dose to the breast for patients exposed to fluoroscopy was estimated to be 0.27 Gy. The average number of chest radiographies was 20 and the average number of photofluorographic examinations was 15 among those receiving at least one such examination.

The relative risk of breast cancer associated with multiple chest fluoroscopies was 0.6 (95% CI; 02–1.4). The relative risk among the patients receiving pneumothorax treatment was 0.8 (95% CI; 0.5–1.4). There was no discernible trend in risk by dose over the categories investigated, although those receiving breast doses greater than 1 Gy appeared to be at a somewhat elevated risk (RR=1.6; 95% CI: 0.4–6.3) (Table 2). Women receiving 0.50–0.99 Gy to their breasts were at significantly decreased risk of developing breast cancers. No significant variation was observed by time since exposure or by age at exposure (Table 3).

Nulliparous women were at high risk of breast cancer compared with women who had children (RR=2.47; 95% CI: 1.47–4.15). Among parous women, the number of children was inversely related to breast cancer risks (Table 4). Only women in the high category of relative body mass (Quetelet index>26) at the time of TB diagnosis were at significantly high risk (RR=2.53; CI 95%: 1.1–6.1) (Table 5). Family history of breast cancer and age at menarche could not be considered because of the high rate of missing information.

Discussion

No increased risk for breast cancer among TB patients treated with pneumothorax (RR=0.8) or exposed to any fluoroscopy (RR=0.6) was observed in our study. This finding is similar to one Canadian study (7) but unexpected considering that other studies of TB patients treated by pneumothorax have reported RR on the magnitude of 1.6–2.8 (2, 5, 16, 20). The mean breast dose in our study, however, was lower (0.27 Gy) than in most other investigations. Breast doses were 1.5 Gy in the Massachusetts fluoroscopy study (3), 2.47 Gy in the New York mastitis study (25), and 0.61 Gy among the atomic bomb survivors (14, 21). The reason for the lower breast dose in our study versus other TB studies was because the average number of fluoroscopies was lower, e.g., 50 versus 102 in the Massachusetts series (3), and Danish patients rarely faced the roentgen tube during fluoroscopy (12% versus 25% of the time). At the breast dose of 0.27 Gy observed in our study, a RR of only 1.14 would have been predicted based on current risk estimates (3). Since only 89 cases were available for study, our investigation was too small to detect a statistically significant breast cancer radiation effect at this dose level. The statistical variations was such that relative risks greater than 1.4 could be excluded with 95% confidence.

The decreased risk following exposure to 0.50–0.99 Gy most likely appeared by chance, or is an artifact associated with the way in which we chose to group the dose categories. The selection of 0.50–0.99 Gy was arbitrary and the significance of the deficit is not apparent for those receiving more than 0.50 Gy or when the dose categories are chosen in equal thirds based on the distribution of controls, i.e., note that only 3 cases received between 0.50–0.99 Gy whereas 71 cases received less dose to their breast. Furthermore, the breast doses were probably somewhat overestimated since we considered all fluoroscopies including non-pneumothorax fluoroscopies, to have lasted the same time (21 seconds). This exposure time also may have been overestimated by some of the TB physicians, since other studies have reported considerably shorter durations (3, 16, 20). We considered any rotation of the patient equal to facing the roentgen tube (high breast dose) which is not strictly correct. However, these conditions were applied equally in cases and controls and could not account for our findings. On the other hand, if the breast doses were overestimated, our study had even less power to detect an effect of radiation. It should be noted, however, that at the outset we were not aware that the breast doses were going to be so low, and had assumed conditions similar to those in the United States (3) and Canada (16, 20) in our initial estimate of power.

Several sources of bias should be considered. Our inability to locate records for 36 breast cancer may have biased results if these cases were exposed to high radiation doses. If hospital records for patients who had undergone pneumothorax treatment were easier to find, a bias underestimating the risk may have been introduced abstracting 'replacement' controls. However, the unavailable TB records were due to destruction of material from entire hospitals and evenly distributed through most of the country. These records were not concentrated among the high risk group, i.e., adolescents, or associated with the treatment given. The linkage procedure on name and date of birth may have missed some young women, since they would change their name after marriage. The low percentage (4,4%) of persons below age 20 at TB diagnosis in our study add some support to this possibility as 9.9% was expected based on the age-distribution of prevalent TB patients in 1955 (17). However, maiden name is usually available in the Cancer Registry records as a matching factor, and loss of approximately 4 (e.g. 4.5%) adolescent cases would not influence the overall results.

Although we were not able to link fluoroscopy radiation as an important risk factor for breast cancer among Danish TB patients, our study was able to identifty other known risk factors. Nulliparity increased breast cancer risk, and the protective effect of having many children was observed. Obesity, taken as body mass index at TB diagnosis, was associated with a significantly increased risk of breast cancer, an interesting finding considering the mean age of TB patients (36 years) and the underlying disease, TB, that is not correlated with obesity

ACKNOWLEDGEMENTS

The study was supported by grants Nos 1234/70 and 1241/55 from the Danish Medical Research Council, contract No. 263-MD-203379 from the National Cancer Institute, U.S. Public Health Service, USA, and by the Danish Cancer Society who also supports the Danish Cancer Registry. We wish to acknowledge Mrs Bente Riisberg and Dr Kirsten Storm for abstracting the data. Dr Kai Stein, our TB consultant, and TB-doctors in Denmark for their helpful cooperation. Bob Weinstock, ORI, Cathy Drzyzgula, IMS and Svend Bang ISA for computer assistance.

Request for reprints: Dr Hans H. Storm, The Danish Cancer Registry, Landskronagade 66, DK-2100 Copenhagen, Denmark.

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