

CANCER IN THE CONTRALATERAL BREAST AFTER RADIOTHERAPY FOR BREAST CANCER

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Abstract Background. Patients with breast cancer have a threefold increase in the risk that a second breast cancer will develop. Radiation treatment for the initial cancer can result in moderately high doses to the contralateral breast, possibly contributing to this heightened risk.

Methods. We conducted a case-control study in a cohort of 41,109 women diagnosed with breast cancer between 1935 and 1982 in Connecticut. We reviewed the medical records of 655 women in whom a second breast cancer developed five or more years after the initial tumor and compared their radiation exposure with that of 1189 matched controls from the cohort who did not have a second cancer. The dose of radiation to the contralateral breast was estimated from the original radiotherapy records. Among the exposed women, the average radiation dose to the contralateral breast was 2.82 Gy (maximum, 7.10).

Results. Overall, 23 percent of the women who had a second breast cancer and 20 percent of the controls had

received radiotherapy (relative risk of a second breast cancer associated with radiotherapy, 1.19). Among women who survived for at least 10 years, radiation treatment was associated with a small but marginally significant elevation in the risk of a second breast cancer (relative risk, 1.33); the risk increased significantly with the dose of radiation. An increase in risk in association with radiotherapy was evident only among women who were under 45 years of age when they were treated (relative risk, 1.59) and not among older women (relative risk, 1.01).

Conclusions. Radiotherapy for breast cancer contributes little to the already high risk of a second cancer in the opposite breast. Fewer than 3 percent of all second breast cancers in this study could be attributed to previous radiation treatment; the risk, however, was significantly increased among women who underwent irradiation at a relatively young age (<45 years). Radiation exposure after the age of 45 entails little, if any, risk of radiation-induced breast cancer, (*N Engl J Med* 1992; 326:781-5.)

BREAST cancer will develop in approximately one woman in nine,¹ and such patients are at very high risk for second cancers in the other breast.² The relatively good survival after treatment for breast cancer (over 70 percent at five years) provides ample opportunity for a new breast cancer to evolve; the development of a new cancer may be related to reproductive or dietary factors, genetic influences, environmental exposure, or treatment for the first tumor. In the past, radiotherapy has been used chiefly in conjunction with extensive surgery to treat primary breast cancer. Today it is common to treat early disease with local excision and irradiation of the breast.³ It is conceivable that scatter or incidental exposure to the contralateral breast, which can amount

to a dose of several grays, contributes to the overall risk of a second cancer.^{4,6} On the other hand, practically all epidemiologic studies indicate that radiogenic breast cancer is exceedingly rare among women who have undergone irradiation after 40 years of age.⁷ To evaluate the risk of contralateral breast cancer in relation to radiotherapy and age at exposure, we undertook a case-control study of women in Connecticut. For women who underwent irradiation, the risk of a second breast cancer was estimated as a function of the radiation dose to the contralateral breast.

M E T H O D S

Study Population

Case patients and controls were selected from a cohort of 41,109 women with histologically confirmed invasive breast cancer whose cancers were reported to the (Connecticut Tumor Registry from 1935 through 1982.³ Case patients were defined as women with breast cancer in whom a second cancer developed in the opposite breast five or more years after the first. The controls were women with breast cancer who did not have a second cancer. Two controls were matched to each case patient on the basis of age (± 5 years) and calendar year (± 5 years) at the initial diagnosis of breast can-

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cer, race, and survival for at least as long as the interval between the initial tumor and the second breast cancer in the case patient.

A total of 1927 second primary breast cancers were reported to the registry two or more months after the initial diagnosis (Table 1); of these, 995 developed within five years of the first breast cancer and were excluded. An additional 42 case patients and 121 controls were excluded because histologic confirmation of cancer was lacking, the diagnoses were made out of state or at an unknown hospital, it was unknown whether they were treated with radiation, or matching information was incorrect. Among the women who survived for 10 years, 441 of 465 women with second breast cancers were included. To conserve resources in studying women who survived for five to nine years, 118 of the 353 nonexposed case patients were randomly selected for medical-record abstraction; 108 were eligible for inclusion. Overall, medical records were obtained for 655 cases and 1189 matched controls from 36 hospitals in Connecticut.

Radiation Dose to the Breast

Using a standardized protocol and a common abstract form, we abstracted information on radiation and other treatments for breast cancer, gynecologic and medical histories, risk factors for cancer, and body measurements from medical and radiotherapy records. Data for the case patients were abstracted only until the time of diagnosis of the second cancer. Photocopies of all radiotherapy records were obtained to allow the estimation of the radiation dose to the opposite breast for each woman. Details of the overall treatment plan, including the type of machine used and the actual daily doses of radiation administered, were also gathered. Calculations of doses included all adjuvant radiotherapy and any additional radiation treatments given within three years after the diagnosis of the first breast cancer. Only 69 women received radiotherapy in more than one calendar year.

Postoperative radiotherapy after radical mastectomy usually consisted of irradiation of the lateral and medial tangential breast fields, anterior and posterior supraclavicular fields, and an anterior internal mammary (mediastinal) field. In a simulation of actual treatment conditions, the dose to the contralateral breast was measured by thermoluminescent dosimeters placed in an Alderson anthropomorphic phantom composed of human skeleton and wax to simulate soft tissue. The dosimetric techniques we used were similar to those described elsewhere.⁸ The dose of radiation to the contralateral breast was estimated as the average of five measured values — i.e., the dose at the center of each quadrant of the breast at a depth of 2 cm, and the dose at the nipple at a depth of 1 cm. All the women were considered to be of average size, and the individual patients' contours were not considered.

A quality score was assigned to the available dosimetric information for each subject. A score of "very good" indicated that radiotherapy records were complete and sufficient to obtain reproducible estimates of the dose to various organs (Table 2). Problems were classified as minor or major, depending on the extent of missing

Table 2. Characteristics of Women with Contralateral Breast Cancer (Case Patients) and Matched Controls.*

CHARACTERISTIC	CASE PATIENTS		CONTROLS	
	NO.	%	NO.	%
All patients	655	100	1189	100
Time after first breast cancer (yr) [†]				
5-9	214	33	398	33
10-14	215	33	386	32
≥15	226	35	405	34
Year of diagnosis				
1935-1949	138	21	271	23
1950-1959	213	33	383	32
1960-1969	240	37	448	38
1970-1975	64	10	87	7
Age at diagnosis (yr)				
<45	200	31	369	31
45-54	204	31	363	31
≥55	251	38	457	38
Stage of first breast cancer				
Localized	383	58	790	66
Regional	217	33	311	26
Distant	0	0	4	<1
Unknown	55	8	84	7
Histologic type of breast cancer (ICD-O code) [‡]				
Carcinoma, NOS (8010)	249	38	554	47
Adenocarcinoma (8140)	106	16	171	14
Infiltrating duct (8500)	196	30	322	27
Other	104	16	142	12
Positive nodes				
Yes	196	30	288	24
No	350	53	776	65
Unknown	109	17	125	11
Total irradiated	206	31§	243	20
Type of radiotherapy [¶]				
Orthovoltage (200-400 kVp)	77	37	100	41
Cobalt-60	73	35	72	30
Megavoltage	16	8	24	10
Unknown	40	19	47	19
Quality of information on radiotherapy [¶]				
Very good	106	51	131	54
Good (only minor problems)	18	9	18	7
Fair (major problems)	44	21	58	24
Incomplete information	6	3	7	3
No information	32	16	29	12
Radiotherapy other than for breast cancer	64	10	140	12
Family history of breast cancer				
Yes	67	10	70	6
No	307	47	642	54
Unknown	281	43	477	40
Full-term pregnancy				
Yes	255	39	498	42
No	86	13	142	12
Unknown	314	48	549	46

*Characteristics and treatment descriptions refer to the first cancer. Because of rounding, percentages do not always total 100.

[†]For case patients, this is the length of time between the first and second diagnoses of breast cancer. For controls, it is the interval equivalent to that for the case patients to whom they were matched.

[‡]ICD-O denotes the *International Classification of Diseases for Oncology*, and NOS not otherwise specified.

[§]After adjustment for the sample of nonexposed case patients whose records were not abstracted, approximately 23 percent of case patients who survived at least five years received radiation to treat their initial breast cancer.

[¶]Percentages are of the total number who underwent irradiation.

Table 1. Patients with Contralateral Breast Cancer (Case Patients) and Matched Controls from the Connecticut Tumor Registry (CTR), 1935 through 1982.

TIME AFTER FIRST BREAST CANCER	CASES IN CTR COHORT	CASE-CONTROL STUDY	
		CASE PATIENTS	CONTROLS
yr		number	
<5	995	0	0
5-9	467	214*	398
≥10	465	441	791
Total	1927	655	1189

*Of the 353 nonexposed patients with a second breast cancer, 118 were randomly selected for medical-record abstraction, and 108 of these were eligible for inclusion in the case-control study. The other 106 case patients in this category were exposed to radiation therapy.

treatment details and the availability of similar records within the same hospital from which probable treatment variables could be estimated. Approximately 84 percent of the 449 women who underwent radiotherapy had sufficient information available in their medical records to be included in the dose-response analyses. The quality of data on the doses did not differ significantly between case patients and controls. Approximately 10 percent of the case patients

and 12 percent of the controls received radiotherapy for conditions other than breast cancer, such as bursitis, that contributed negligible amounts of radiation to the breast.

Statistical Analysis

The measure of association between radiation therapy and the development of a second breast cancer was the relative risk, approximated by the odds ratio, which compares the odds of exposure of case patients with that of the control patients. A relative risk equal to 1.0 would imply that radiotherapy was not associated with an increased risk of a second breast cancer; a 95 percent confidence interval for the relative risk that did not include 1.0 would imply a significant association between radiotherapy and contralateral breast cancer. Conditional logistic-regression methods were used to compare radiation exposure in case patients and individually matched controls. Radiation doses to the contralateral breast were grouped into four categories, and relative risks were computed with the nonexposed group as the reference category. Tests for trend were based on the score test. Multivariate analyses were conducted to evaluate other risk factors, such as a family history of breast cancer, but these data were largely incomplete. Population-attributable risks were approximated by the method described by Whittemore.¹⁰ In the context of our study, the population-attributable risk is an estimate of the proportion of second cancers attributable to radiation therapy that could be prevented if all such exposures were eliminated.

For subjects in whom contralateral breast cancer was diagnosed five to nine years after the first cancer, a one-in-three random sample of nonexposed case patients and a complete sample of exposed case patients were selected for study. Exposure status was known beforehand from records available in the central cancer registry. Since nonexposed case patients are underrepresented in this sampling scheme, uncorrected relative risks would be biased upward by a factor of three. Unbiased estimates of the relative risk and confidence intervals were obtained by incorporating the threefold increase due to the sampling scheme into the model to be fitted for subjects in the five-to-nine-year period.

Pathological Review

To evaluate the possibility that metastatic lesions might have contributed to the reporting of second breast cancers among long-term survivors, a pathological review was conducted for a 10 percent random sample of the bilateral cancers. Histologic material was obtained for both the first and the second breast cancers in 49 of 74 patients. For 18 additional women, slides were available only for the second cancer, but pathology reports and hospital records that adequately described the first cancer were found. No histologic information was uncovered for seven of the case patients. Among the 67 cases evaluated, the pathological diagnoses for 63 (94 percent) were in agreement with the diagnoses recorded in the Connecticut Tumor Registry; 2 were different, and in 2 cases the pathologist was not able to make a determination.

If irradiation is causally related to the incidence of contralateral breast cancer, there should be a tendency to observe more second tumors in the area of the opposite breast that received the higher dose — i.e., the medial portion. Unfortunately, information on the exact location of the second breast cancer was missing for most of the case patients, and meaningful analyses therefore could not be conducted.

R E S U L T S

The average age of the women in our study when breast cancer was diagnosed was 51.7 years. More than half the diagnoses were made before 1960 (Table 2). Nearly all the patients had localized or regional disease. The average radiation dose to the contralateral breast was estimated to be 2.82 Gy (3.02 Gy for the case patients and 2.67 Gy for the controls); the maximal dose was 7.10 Gy. Taking into account the frac-

tion of nonexposed case patients sampled, approximately 23 percent of the women in whom a second breast cancer developed and 20 percent of the controls received radiation to treat the initial cancer (relative risk, 1.19; 95 percent confidence interval, 0.94 to 1.50) (Table 3). The proportions of women who underwent radiotherapy did not differ among those followed from 5 to 9 years (24.8 percent of the case patients vs. 24.9 percent of the controls; relative risk, 0.99), but a marginally significant difference was found among the women who survived for 10 or more years (22.7 percent of the case patients vs. 18.2 percent of the controls; relative risk, 1.33; 95 percent confidence interval, 0.99 to 1.78). An increase in risk was apparent only among patients who were less than 45 years of age when they were treated (relative risk, 1.59; 95 percent confidence interval, 1.07 to 2.35).

Dose-response analyses were conducted according to age at the time of treatment and length of time after exposure (Table 4). A significant trend was seen among women who survived for at least 10 years and who were less than 45 years of age when they underwent irradiation. There was little suggestion of a risk due to radiation among those who were 45 or older at the time of treatment or among those followed for less than 10 years.

Although the available data were limited, we evaluated nulliparity, family history of breast cancer, menopause, nodal status, and weight as independent risk factors for second breast cancers, as well as for their influence on the risk associated with radiation. Among women who survived for 10 years, only family history was linked to a significant increase in the risk of a second breast cancer (relative risk, 1.8). Adjusting for all risk factors simultaneously had a negligible effect on the estimate of risk associated with radiation.

Table 3. Relative Risk (RR) of the Development of Contralateral Breast Cancer after Radiotherapy, According to Age at Exposure and Time after Exposure.*

VARIABLE	No. EXPOSED/ TOTAL No.†	RR (95% CI)
No. of patients	206/655	1.19 (0.94–1.50)
Time after treatment (yr)		
5–9	106/214	0.99 (0.68–1.43)
10–14	59/215	1.98 (1.29–3.06)
≥15	41/226	0.93 (0.62–1.40)
≥10	100/441	1.33 (0.99–1.78)
Age at treatment (yr)‡		
<45	78/200	1.59 (1.07–2.36)
45–54	58/204	0.85 (0.56–1.30)
≥55	70/251	1.18 (0.79–1.78)
Age at treatment for 10-yr survivors (yr)		
<45	45/143	1.85 (1.15–2.97)
≥45	55/298	1.08 (0.74–1.57)

*CI denotes confidence interval.

†Numbers refer to case patients.

‡For women less than 35 years of age at the time of treatment, RR = 2.26 (95 percent confidence interval, 0.89 to 5.74); for women 35 to 44 years of age, RR = 1.46 (95 percent confidence interval, 0.94 to 2.26); for women ≥45 years of age, RR = 1.01 (95 percent confidence interval, 0.76 to 1.35).

Table 4. Relative Risk (RR) of the Development of Contralateral Breast Cancer among Women Exposed to Various Doses of Radiation, According to Age at Exposure and Time after Exposure.*

VARIABLE	RADIATION DOSE TO CONTRALATERAL BREAST (Gy)				P VALUE†
	0	0.01-1.99	2.00-3.99	≥4.00	
All patients					
Average dose (Gy)	0	1.11	2.82	5.04	—
No. of case patients	449	51	66	51	—
RR	1.0	1.02	1.07	1.35	0.14
Time after treatment (yr)					
5-9	1.0	0.77	0.82	0.93	0.56
10-14	1.0	1.68	1.70	2.72	0.003
≥15	1.0	0.86	0.89	1.39	0.46
≥10	1.0	1.14	1.33	1.96	0.006
Age at treatment (yr)					
<45	1.0	1.43	1.66	1.64	0.03
45-54	1.0	0.74	0.72	0.84	0.36
≥55	1.0	1.02	0.97	1.67	0.24
Age at treatment for 10-yr survivors (yr)					
<45	1.0	1.54	2.61	2.35	0.003
≥45	1.0	0.97	0.82	1.86	0.23

*The reference category is no exposure to radiation. Patients with missing or incomplete information on the dose of radiotherapy have been excluded.

†P value for trend.

The increase in the overall risk of a second breast cancer attributable to radiation — that is, the population-attributable risk expressed as a percentage — was approximately 2.7 percent (95 percent confidence interval, 0.0 percent to 7.1 percent); it was 11.1 percent (95 percent confidence interval, 2.6 percent to 19.7 percent) for women who underwent irradiation before the age of 45. The estimated relative risk of a second breast cancer at a radiation dose of 1 Gy was 1.07 for all the women and 1.21 for those exposed before the age of 45. Our crude estimate of the absolute excess risk, based on the distribution of person-years in the cohort study for five-year survivors of breast cancer who did not receive radiotherapy,² was about 4.4 cases per 10,000 person-years per gray.

DISCUSSION

Each year, a new primary cancer develops in about 14 of every 1000 women with breast cancer, and half of these cancers occur in the contralateral breast.² Current treatment for early-stage breast cancer couples conservative surgery (also called lumpectomy, quadrantectomy, and partial mastectomy) with radiotherapy in a cumulative dose of approximately 50 Gy to the whole breast.³ The dose of radiation delivered to the opposite breast by therapy intended to preserve the breast can be several grays,⁴ and the dose is equivalent to levels found to induce breast cancer in young women.⁷ In our population-based series of women treated for breast cancer between 1935 and 1982, fewer than 3 percent of all second breast cancers could be attributed to radiotherapy after radical mastectomy. The risk associated with radiation was significantly elevated, however, for women treated before the age of 45 who survived for more than 10 years. Radiotherapy did not contribute to the high risk of second breast

cancers among women whose first cancers occurred after they reached 45 years of age.

During the years when the patients in our study were treated, radiotherapy was frequently used as an adjuvant to radical mastectomy, especially when the axillary nodes were positive. With the advent of combined chemotherapy and hormonal therapy in the 1970s and 1980s, along with the knowledge that radiation therapy after radical mastectomy had little effect on patients' survival, such treatment became less popular.¹¹ Today, conservative surgery followed by radiation therapy has become an accepted treatment for the majority of women with Stage I or II breast cancer.^{3,12,15} Current radiotherapy techniques also differ from those used earlier, which encompassed much wider radiation fields, and megavoltage radiation therapy has essentially replaced the use of orthovoltage therapy (200 to 400 kVp). The results of this study can therefore be generalized to current practice only to the extent that the doses of radiation to the contralateral breast are similar. Given the general awareness that radiation can induce as well as cure breast cancer, it is reassuring that our data indicate a low risk of a second breast cancer after doses of several grays to the opposite breast. Nonetheless, it seems prudent to minimize exposure of the contralateral breast whenever possible,^{4,5} particularly for women under 45 years of age.

Previous studies of cancer in the contralateral breast have for the most part found no association with radiotherapy,^{6,14-18} although a possible link was suggested in an earlier analysis of data from Connecticut.¹⁹ Several recent reports focus on women treated with conservative surgery and radiation, but the numbers of patients were small and the follow-up relatively short.¹⁹⁻²² In only one study did the investigators attempt to compute individual doses to the contralateral breast.⁶ None of the previous studies were large enough for investigators to conduct dose-response analyses over broad categories of age at the time of exposure and length of time after exposure; thus, a small risk among young women followed for long periods of time would have been difficult to detect.

Age at the time of radiation exposure appears to be the most important determinant of the risk of radiation-induced breast cancer. Among patients with tuberculosis who were examined fluoroscopically,^{7,23} women treated with radiation for postpartum mastitis,²⁴ and atomic-bomb survivors,²⁵ breast cancer has been found to develop at a higher-than-expected rate. Exposure after the age of 40 appears to entail less risk than exposure at earlier ages.^{7,26} One study of a series of patients who underwent irradiation reported an increased risk of cancer at older ages, but the underlying condition being treated (benign breast disease), rather than the treatment itself, may have been related to the excess breast cancers.²⁷

In our study, women were grouped according to their age at the time of treatment (<45, 45 to 54, or ≥55 years) in order to obtain relatively equal numbers

in each category; these groupings were also consistent with the categories used in previous reports.² Additional analyses were conducted with different age groupings, and similar risk patterns were seen. The highest risk was observed among the 35 case patients and 73 controls who had breast cancer before the age of 35 (relative risk, 2.26; 95 percent confidence interval, 0.89 to 5.74). For women who were 35 to 44 years of age at the initial diagnosis, the association between radiotherapy and contralateral breast cancer was also strong (relative risk, 1.46; 95 percent confidence interval, 0.94 to 2.26).

We compared our estimates of the radiation risk in this study with estimates from studies of women without a history of breast cancer. On the basis of data from patients with tuberculosis who were examined fluoroscopically,⁷ a relative risk of 1.18 for breast cancer would have been predicted among women an average of 52 years of age who received a dose of 2.82 Gy to the breast — a figure that is close to the relative risk of 1.19 that we observed. Among women who were 35 to 44 years of age when they were treated, the predicted relative risk was 1.45; we observed a relative risk of 1.46. For women under the age of 35, the predicted relative risk was 1.95; we observed a relative risk of 2.26. Thus, although women with breast cancer are unquestionably at very high risk for second cancers, their relative risk of radiation-induced breast cancer did not differ from that of women without breast cancer. Because of their higher underlying risk, however, this similarity in relative risk implies a higher absolute excess risk of radiation-induced breast cancer.

Risk due to radiation was not elevated among the very-long-term survivors — those who lived for more than 15 years. Because of the relatively small number of women who underwent irradiation in this group, we considered the observed decrease in risk to be consistent with a chance occurrence. It is conceivable that the induction of breast cancers may be accelerated among women with a propensity for the development of mammary cancer when they are exposed to radiation, as is seen in some animal models.²⁸ Alternatively, women with breast cancer may check more carefully for an occurrence in the second breast. Thus, radiation-induced breast cancers that would have come to clinical attention 15 or more years after treatment might have been detected earlier because of more intense surveillance.

Overall, although increased surveillance is desirable in women who have had a first breast cancer,²⁹ the risk of radiation-induced cancer in the other breast is small and should not be a factor in the selection of treatment for breast cancer.

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