Breast Cancer Following Radiotherapy and Chemotherapy Among Young Women With Hodgkin Disease

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Context Second cancer is the leading cause of death in long-term survivors of Hodgkin disease (HD), with exceptionally high risks of breast cancer among women treated at a young age. Quantitative associations between radiotherapy dose delivered to the breast and administered chemotherapy have not been reported to date in large series, nor has the influence of ovarian exposures on subsequent risk.

Objective To quantify the long-term risk of breast cancer associated with use of radiotherapy and chemotherapy to treat young women with HD.

Design, Setting, and Subjects Matched case-control study of breast cancer within a cohort of 3817 female 1-year survivors of HD diagnosed at age 30 years or younger, between January 1, 1965, and December 31, 1994, and within 6 population-based cancer registries. The study was conducted March 1, 1996, through September 30, 1998.

Main Outcome Measures Relative risk (RR) of breast cancer associated with radiation dose delivered to site of breast cancer or to ovaries and with cumulative dose of alkylating agents.

Results Breast cancer occurred in 105 patients with HD who were matched to 266 patients with HD but without breast cancer. A radiation dose of 4 Gy or more delivered to the breast was associated with a 3.2-fold (95% confidence interval [CI], 1.4-8.2) increased risk, compared with the risk in patients who received lower doses and no alkylating agents. Risk increased to 8-fold (95% CI, 2.6-26.4) with a dose of more than 40 Gy ($P<.001$ for trend). Radiation risk did not vary appreciably by age at exposure or reproductive history. Increased risks persisted for 25 or more years following radiotherapy (RR, 2.3; 95% CI, 0.5-16.5; $P=.03$ for trend with dose). Treatment with alkylating agents alone resulted in a reduced risk (RR, 0.6; 95% CI, 0.2-2.0) of breast cancer, and combined alkylating agents and radiotherapy in a 1.4-fold (95% CI, 0.6-3.5) increased risk. Risk of breast cancer decreased with increasing number of alkylating agent cycles ($P=.003$ for trend). Risk also was low (RR, 0.4; 95% CI, 0.1-1.1) among women who received 5 Gy or more delivered to ovaries compared with those who received lower doses.

Conclusions Hormonal stimulation appears important for the development of radiation-induced breast cancer, as evidenced by the reduced risk associated with ovarian damage from alkylating agents or radiation. The high radiation-related risk, which did not diminish at the highest doses or the longest follow-up, however, suggests the need for lifetime surveillance and programs of patient and public awareness.

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Treatment of Hodgkin disease (HD) represents one of the major medical successes of the 20th century. Fifty years ago, the typical patient survived only a few years,[1] whereas the current 5-year relative survival rate is 85%.[2] In the United States alone, approximately 120 000 survivors of HD[2] are at risk for the serious late sequelae of curative therapies, including the occurrence of new primary cancers.[3,4] Second malignant neoplasms are now the leading cause of death in long-term survivors of HD,[5,6] with breast cancer representing the most frequent solid tumor among women.[7,8]

For editorial comment see p 529.

Estimates of breast cancer risk appear inversely related to age at treat-

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ment, with the largest excesses (6- to 15-fold) consistently reported among women treated at age 30 years or younger.[9-12] Increased rates of breast cancer have been generally attributed to chest irradiation for HD, consistent with the known sensitivity of the breast to ionizing radiation at young ages.[13] However, no large analytic studies of patients with HD have been conducted to date that quantify risk in terms of radiation dose delivered to the area in the breast where cancer developed, or that account for radiotherapy- or chemotherapy-related ovarian dysfunction. Thus, despite concerted efforts to minimize therapeutic doses and the field size of radiotherapy for HD,[14,15] it is unclear whether current levels of reductions in radiation dose and volume will ultimately result in decreases in risk of second cancer.[16] Since excess breast cancers following exposure to ionizing radiation likely occur throughout life,[13] an important question for young women who are long-term survivors of HD is whether the large relative risks (RRs) reported in the first few decades following radiotherapy will persist as they enter the ages when breast cancer occurs more frequently.

Despite the burden of developing a second cancer following HD, descriptive data that address the relative importance of chemotherapy and other factors for the development of breast cancer have been conflicting and sparse.[12,17,18] No large international investigation to date has quantified the long-term risks associated with radiation dose delivered to the site of subsequent breast cancer while simultaneously taking into account the effects of cumulative dose of alkylating agents, age at exposure, age at diagnosis of breast cancer, and radiation dose delivered to the ovaries. To address these issues, we analyzed the risk of breast cancer among 3817 women diagnosed with HD at age 30 years or younger and provide estimates of relative and absolute excess risk in terms of radiation dose delivered to the breast and of number of alkylating agent cycles.

METHODS

Study Patients

A matched case-control study was conducted from March 1, 1996, through September 30, 1998, within a population-based cohort of 3817 women who were treated for HD at age 30 years or younger and who survived for 1 or more years. Women were diagnosed with HD between January 1, 1965, and December 31, 1994, and reported to 1 of 5 population-based cancer registries in Iowa, Denmark, Finland, Sweden, and Ontario,[19] or to affiliated tumor registries in the Netherlands: Netherlands Cancer Institute, Amsterdam; the Dr Daniel den Hoed Cancer Center, Rotterdam; Leiden University Medical Center, Leiden; or the Catharina Hospital, Eindhoven.[20] Record-linkage techniques[21] were used to identify women who developed a second primary breast cancer, which included ductal carcinoma in situ, as in prior series.[17,22] Pathology reports and clinical information were centrally reviewed (L.B.T., M.G.) to confirm the diagnosis of breast cancer. For each documented case, at least 2 controls were selected by stratified random sampling from the cohort. Matching factors were registry, calendar year of HD diagnosis, age at HD diagnosis, and length of survival without a second cancer at least as long as the interval between the diagnoses of HD and breast cancer in the case. In each registry, 2 controls were matched to each case, except in the Netherlands where the 1 to 4 controls selected for each case (who were included in a separate report[20]) were retained for the present analysis. The current study was exempted from institutional review board review because it used only existing anonymous data.

Data Collection

For each patient, demographic and medical record information, including data on all therapy for HD during the matched time interval, were abstracted onto standardized forms. Sources of information included hospitals providing initial treatment, medical centers, radiotherapy facilities, and offices of private physicians. Data on dose and duration of administration were abstracted for all alkylating agents, as recorded for each cycle of treatment; for other cytotoxic drugs, information was limited to dates and duration of administration, as in prior studies.[21,23] Of 171 patients who received alkylating agents, data on cumulative dose were available for 84% (29 of 37 case patients [78%] and 114 of 134 controls [85%]). For the remaining 16% of cases, cumulative dose was estimated based on the duration of therapy or imputed from the median dose in controls. Data on menopausal status at diagnosis of breast cancer (or comparable date in controls) were also collected, with special care given to ensure that temporary treatment-related cessation of menses was not scored as menopause; information on menopausal status was available for 90% of cases and 82% of controls. Because data on the use of hormone therapy were limited (only 8 cases and 42 controls identified as users), this variable was not included in the analysis.

Radiation Dosimetry

Most women (n=360) were treated with radiotherapy, with fields including mantle only (33 cases [32%], 74 controls [29%]); mantle and subdiaphragmatic fields (37 cases [36%], 73 controls [29%]); mantle and additional supradiaphragmatic fields with or without subdiaphragmatic fields (20 cases [20%], 72 controls [28%]); and other sites (14 cases [12%], 34 controls [13%]). For 1% of controls, treatment location was unknown. The mean (SD) treatment doses for mantle radiotherapy were similar for cases (37.7 [4.7] Gy) and controls (37.3 [4.1] Gy). The goal of the radiation dosimetry was to estimate the dose delivered to both the specific location in the breast where cancer developed for each case and the corresponding anatomical site in matched controls.

All records relevant to tumor location (mammograms, computed tomography scans, ultrasound images, mag-

netic resonance images, surgical reports, and clinical notes and diagrams) and original radiotherapy records (daily logs, summaries, field diagrams, and simulation films) were reviewed by a radiation oncologist (M.G.) and a radiation physicist (M.S.) to determine whether the tumor was in a treatment field, under the block used to shape an irregular field, or outside a treatment field.

Dose delivered to tumors within a treatment field was derived using standard radiotherapy techniques.[24] For tumors under the block, the dose was estimated using data calculated by treatment-planning systems.[25] If the tumors occurred outside the nearest treatment field, out-of-beam measurements in a water phantom were used.[26,27] The largest source of uncertainty in estimation of radiation dose was contributed by those breast tumors that occurred in close proximity (within ±2 cm) to the edge of a field, blocked or unblocked, because dose in such areas declines rapidly by a factor of 2. Doses from all radiotherapy treatments were summed to obtain a total radiation dose delivered to the breast. For women who received subdiaphragmatic irradiation, radiation dose delivered to the ovary was estimated using similar techniques.

For patients who initially presented with bilateral breast cancer, dose delivered to the largest tumor was estimated. Since the study end point was the initial diagnosis of breast cancer, data on subsequent tumors were not collected. Information on either radiotherapy or breast tumor location was inadequate to estimate dose for 1 case and 7 controls, for whom dose was imputed using the median dose given to all controls; repeat analyses excluding these patients showed comparable results.

Mean dose of radiation delivered to the specific location in the breast where cancer developed, or to a comparable location in matched control patients, was 25.1 Gy (median, 25.1 Gy; range, 12.0-61.3 Gy) and 21.1 Gy (median, 23.0 Gy; range, <0.1-56.0 Gy), respectively; overall doses were similar for women treated with radiation alone or both radiation and alkylating agents (mean [SD], 22.8 [16.1] Gy and 21.5 [15.2] Gy, respectively). Among case patients who received any type of chest radiotherapy, 51 (49%) of the breast cancers occurred in the unblocked treatment field, whereas 28 (27%) were diagnosed at sites that received lower-dose radiation (25 [24%] under the block and 3 [3%] out of beam); 16 (15%) occurred at the blocked edge and 8 (8%) at the field edge. For 1 case, relative location could not be determined.

Statistical Analysis

Conditional regression analysis was conducted to obtain maximum likelihood estimates of the RR of breast cancer associated with specific treatments by comparing the exposure histories of the cases with those of individually matched controls.[28,29] Most analyses were based on a model in which the odds ratio, which closely approximates the RR, was expressed as a log-linear function of variables indicating treatments or other factors of interest. Except where stated otherwise, estimates of RR by categories of radiation dose delivered to the breast were adjusted for the number of cycles of treatment with alkylating agents and the radiation dose delivered to the ovaries, both treated as continuous variables.

Analyses evaluating other risk factors, including therapy with alkylating agents, were also adjusted for the radiation dose delivered to the breast (treated as a continuous linear variable); that is, the RR was given by the expression $\exp(\Sigma_j \alpha_j x_j)[1+\beta z]$, where z indicates the radiation dose delivered to the breast in gray; x_j, the variables measuring other risk factors; and α_j and β, the parameters to be estimated. The linear model was chosen because many studies have indicated that the relation of breast cancer risk to radiation dose is well described by a linear function, with the coefficient β referred to as the excess RR per gray.[13,30] There was no evidence of nonlinearity in the dose response as evidenced by comparing the linear model with a categorical model ($P=.36$) or with a linear-quadratic model ($P>.50$).

Two-sided P values and 95% confidence intervals (CIs) were based on the likelihood ratio statistic. Trend P values test the hypothesis that $\alpha_j=0$ or $\beta=0$ for the continuous variables x_j or z. To test for heterogeneity of the radiation-related risk among categories defined by variables such as age at exposure and time since exposure, we compared the fit of a model having separate estimates of the radiation effect for each category with that of a model having a single estimate for all categories. The analyses were conducted using the PECAN module of the EPICURE software package[29]; $P<.05$ was used to determine statistical significance.

Since virtually all women had been treated with radiotherapy or alkylating agents, it was not possible to form a reference group of untreated patients. Thus, for categorical analyses, the reference group consisted of patients who received a radiation dose of less than 4 Gy delivered to the location in which breast cancer developed, and either non–alkylating agent chemotherapy or no chemotherapy. Categories were defined by dividing the group of control patients with doses exceeding 4 Gy into approximately equal-sized groups.

Women were categorized into mutually exclusive treatment groups according to all administered chemotherapy. The large number of women (n=138) who received mechlorethamine (usually with vincristine, procarbazine, and prednisone in the MOPP regimen)[31] allowed further evaluation of this group, with cumulative dose categories defined by dividing control patients into 4 approximately equal-sized groups. To calculate absolute excess risk for 1000 women followed up for 25 years, we used external rates for the cohort to estimate the number of breast cancers that would be expected in the absence of treatment-related exposure for each 5-year follow-up interval. This number was then multiplied by the excess RR (excess RR=RR−1) for the dose of interest un-

Table 1. Characteristics of Women Aged 30 Years or Younger With Hodgkin Disease Who Developed a Secondary Breast Cancer, and Matched Controls

Characteristic	No. (%)* Cases (n = 105)	Matched Controls (n = 266)
Cancer registry		
Iowa	4 (3.8)	8 (3.0)
Denmark	15 (14.3)	29 (10.9)
Finland	10 (9.5)	19 (7.1)
Ontario	20 (19.1)	40 (15.0)
Netherlands	40 (38.1)	138 (51.9)
Sweden	16 (15.2)	32 (12.0)
Age at diagnosis of Hodgkin disease, y		
13-17	21 (20.0)	47 (17.7)
18-21	29 (27.6)	73 (27.4)
22-25	19 (18.1)	73 (27.4)
26-30	36 (34.3)	73 (27.4)
Year of diagnosis of Hodgkin disease		
Before 1970	34 (32.4)	68 (25.6)
1970-1974	31 (29.5)	101 (38.0)
1975-1979	30 (28.6)	64 (24.1)
1980-1984	5 (4.8)	18 (6.8)
1985-1994	5 (4.8)	15 (5.6)
Stage of Hodgkin disease		
I or II	94 (89.5)	214 (80.5)
III or IV	11 (10.5)	52 (19.6)
Histological type of Hodgkin disease		
Nodular sclerosis	58 (55.2)	170 (63.9)
Mixed cellularity	22 (21.0)	44 (16.5)
Lymphocyte-predominant	7 (6.7)	15 (5.6)
Lymphocyte-depleted	1 (1.0)	7 (2.6)
Not specified	17 (16.2)	30 (11.3)
Interval to breast cancer, y		
1-4	0	NA
5-9	5 (4.8)	
10-14	26 (24.8)	
15-19	33 (31.4)	
20-24	27 (25.7)	
>25	14 (13.3)	
Breast cancer detection		
Patient or spouse	67 (63.8)	NA
Physical examination by physician	15 (14.3)	
Mammography	10 (9.5)	
Other/not specified	13 (12.4)	
Laterality of breast cancer		
Left	53 (50.5)	NA
Right	46 (43.8)	
Bilateral	6 (5.7)	
Location of breast cancer		
Upper outer quadrant	53 (50.5)	NA
Upper inner quadrant	16 (15.2)	
Lower outer quadrant	12 (11.4)	
Lower inner quadrant	12 (11.4)	
Outer half	3 (2.9)	
Areolar/subareolar (central)	3 (2.9)	
Multifocal	2 (1.9)	
Other/not specified	4 (3.8)	
Stage of breast cancer		
DCIS	8 (7.6)	NA
I	42 (40.0)	
IIA	36 (34.3)	
IIB	13 (12.4)	
III or IV	6 (5.7)	
Histological type of breast cancer		
Infiltrating ductal carcinoma	76 (72.4)	NA
Other adenocarcinomas	10 (9.5)	
Comedocarcinoma	8 (7.6)	
Lobular carcinoma, excluding in situ	7 (6.7)	
Other	4 (3.8)	

Abbreviations: DCIS, ductal carcinoma in situ; NA, not applicable
*Percentages may not sum to 100 because of rounding.

der the assumption that the excess RR per gray remained constant over the period of 5 to 25 years. External rates for each participating cohort were provided to the National Cancer Institute by the collaborating population-based registries and reflect the cancer experience of the populations covered by the registries, which produced the cases and controls.

RESULTS

The mean and median age at diagnosis of HD was 22 years, with approximately 20% of the patients younger than 18 years (TABLE 1). Breast cancer occurred in 105 patients with HD who were matched to 266 patients with HD but without breast cancer. Diagnosis of breast cancer occurred a mean of 18.0 years (median, 18.0 years; range, 7-30 years) after diagnosis of HD, and 41 cases were diagnosed 20 or more years afterward. The mean age at diagnosis of breast cancer was 40.7 years (median, 41.0 years; range, 27-57 years). All 105 case patients were in clinical remission from HD at the time of breast cancer diagnosis.

Treatment of HD with radiotherapy alone (≥4 Gy delivered to the area in which subsequent breast cancer developed) was associated with a significantly increased 3.2-fold (95% CI, 1.4-8.2) increased risk of breast cancer compared with the reference group (TABLE 2), while a 1.4-fold (95% CI, 0.6-3.5) increased risk followed both treatment with radiotherapy and alkylating agents ($P = .002$ for difference in RR). This latter risk was similar among women who received combined-modality therapy (RR, 1.4; 95% CI, 0.5-4.2) or those given initial radiotherapy and salvage alkylating agents (RR, 1.3; 95% CI, 0.5-3.6) (median time between use of radiotherapy and alkylating agents, 3.5 years). Women given alkylating agents alone for HD experienced a reduced risk of breast cancer (RR, 0.6; 95% CI, 0.2-2.0).

Increased risks of breast cancer were observed in all radiation dose categories of 4 Gy or more; risk increased with increasing dose to the location in which

the subsequent tumor developed, with 8-fold (95% CI, 2.6-26.4) increased risks for doses of 41 to 61 Gy ($P<.001$ for trend) (Table 2). Risk of breast cancer decreased with increasing number of alkylating agent cycles ($P=.003$ for trend) (Table 2). A 60% deficit was evident among women who received a radiation dose of 5 Gy or more delivered to the ovaries (RR, 0.4; 95% CI, 0.1-1.1; $P=.06$ compared with lower dose).

The risk of breast cancer according to both the number of cycles of alkylating agent chemotherapy and the radiation dose delivered to the ovaries is summarized in TABLE 3. All women receiving doses of 5 Gy or more delivered to the ovaries experienced reduced risks of breast cancer regardless of alkylating agent treatment; however, for women receiving ovarian doses less than 5 Gy, risk depended on alkylating agent therapy, with an RR of 0.2 (95% CI, 0.1-0.5) following 9 or more cycles ($P=.001$ for trend). Breast cancer deficits roughly paralleled the percentage of women who became menopausal after treatment (see Table 3 footnote). Overall, women who became menopausal before age 40 years (12 cases, 66 controls) experienced significant ($P<.001$) reductions in risk of breast cancer compared with women who remained premenopausal (71 cases, 133 controls); the RRs were 0.2 (95% CI, 0.05-0.6), 0.3 (95% CI, 0.1-0.8), and 0.7 (95% CI, 0.2-2.1) for age at menopause younger than 30 years, 30 through 39 years, and 40 years or older, respectively ($P=.16$ for trend). However, even among women not known to have become menopausal, the number of cycles of alkylating agent therapy remained a significant predictor ($P=.03$) of lowered risk of breast cancer.

Risks of breast cancer according to type and cumulative dose of alkylating agents are shown in TABLE 4. Relative risks after chemotherapy that included either mechlorethamine or other alkylating agents were 0.5 (95% CI, 0.3-0.9) and 0.3 (95% CI, 0.1-0.9), respectively. Risk of breast cancer decreased with increasing cumulative dose of either mechlorethamine ($P=.02$ for trend) or procarbazine ($P=.001$ for trend) when evaluated separately; the correlation coefficient for cumulative dose was 0.70 among women who received both drugs.

TABLE 5 shows RRs of radiation-associated (≥4 Gy vs <4 Gy) breast cancer for each of several subgroups defined by age at radiotherapy and other variables. It should be noted that CIs in these subgroups are wide and that the numbers of cases in some of the referent groups are small. The effect of radiation was greatest for women treated for HD between age 13 and 17 years, but differences among exposure age groups were not significant ($P>.50$ for heterogeneity). Breast cancer excesses were evident before women reached age 35 years and did not decrease with increasing age at diagnosis of breast cancer, even among women aged 50 years or older ($P>.50$ for heterogeneity), for

Table 2. Risk of Breast Cancer Among Young Women Diagnosed With Hodgkin Disease, by Treatment*

	No. (%)			
	Cases (n = 105)	Matched Controls (n = 266)	RR (95% CI)	*P* Value
Radiation ≥4 Gy and/or Alkylating Agents				
Treatment				
Neither	9 (8.6)	39 (14.7)	Reference	
Radiation alone	59 (56.2)	93 (35.0)	3.2 (1.4-8.2)	.006
Alkylating agents alone	6 (5.7)	37 (13.8)	0.6 (0.2-2.0)	.42
Both	31 (29.5)	97 (36.5)	1.4 (0.6-3.5)	.51
Combined modality therapy	15 (14.3)	46 (17.3)	1.4 (0.5-4.2)	.51
Initial radiotherapy and salvage alkylating agents	16 (15.2)	51 (19.2)	1.3 (0.5-3.6)	.60
Radiation Delivered to Specific Location in Breast†				
Dose, median (range), Gy				
3.2 (0-3.9)	15 (14.7)	76 (29.5)	Reference	
4.6 (4.0-6.9)	13 (12.7)	30 (11.7)	1.8 (0.7-4.5)	.21
21.0 (7.0-23.1)	16 (15.7)	30 (11.7)	4.1 (1.4-12.3)	.008
24.5 (23.2-27.9)	9 (8.8)	30 (11.7)	2.0 (0.7-5.9)	.22
35.2 (28.0-37.1)	20 (19.6)	31 (12.1)	6.8 (2.3-22.3)	<.001
39.8 (37.2-40.4)	12 (11.8)	31 (12.1)	4.0 (1.3-13.4)	.02
41.7 (40.5-61.3)	17 (16.7)	29 (11.2)	8.0 (2.6-26.4)	<.001
Cycles of Alkylating Agent Chemotherapy				
No. of cycles				
0	68 (64.8)	132 (49.6)	Reference	
1-4	10 (9.5)	20 (7.5)	0.7 (0.3-1.7)	.44
5-8	17 (16.2)	55 (20.7)	0.6 (0.3-1.1)	.12
≥9	4 (3.8)	29 (10.9)	0.2 (0.1-0.7)	.006
Any noncyclic chemotherapy	6 (5.7)	30 (11.3)	0.4 (0.1-1.0)	.05
Radiation Delivered to Ovaries				
Dose, Gy				
<3.0	94 (89.5)	214 (80.5)	Reference	
3.0-4.9	4 (3.8)	13 (4.9)	1.2 (0.3-3.9)	.78
≥5.0	7 (6.7)	39 (14.6)	0.4 (0.1-1.1)	.07

Abbreviations: CI, confidence interval; RR, relative risk.

*Exposure was defined as treatment with alkylating agents for more than 1 month or radiotherapy that resulted in a dose of ≥4 Gy delivered to the specific location in the breast where the cancer was diagnosed and to the corresponding region in the control patients. The reference group consists of patients who did not meet exposure criteria. Analyses of radiation dose delivered to the breast were adjusted for number of cycles of alkylating agents and radiation dose delivered to the ovaries; analyses of number of cycles of alkylating agents were adjusted for radiation dose delivered to the breast and radiation dose to the ovaries; analyses of radiation dose delivered to the ovaries were adjusted for radiation dose to the breast and number of cycles of alkylating agents.

†Excludes 1 case patient and 7 control patients whose radiation dose to the breast could not be estimated and an additional 2 case patients and 2 control patients whose matched sets contained only case patients (or only control patients) after the exclusions. Specific location refers to the area of the breast in which cancer developed (cases) and a comparable anatomical site in matched controls with Hodgkin disease and no personal history of breast cancer.

Table 3. Risk of Breast Cancer Following Hodgkin Disease, by Number of Cycles of Alkylating Agents and Radiation Dose Delivered to the Ovaries

	<5 Gy Radiation Delivered to Ovaries				≥5 Gy Radiation Delivered to Ovaries			
	No. (%)				No. (%)			
Alkylating Agent Chemotherapy	Cases (n = 98)	Matched Controls (n = 227)	RR (95% CI)*	*P* Value	Cases (n = 7)	Matched Controls (n = 39)	RR (95% CI)*	*P* Value
No. of cycles								
0	68 (69.4)	125 (55.1)	Reference		0	7 (17.9)	0.0 (0-0.5)	.01
1-8	26 (26.5)	67 (29.5)	0.7 (0.3-1.2)	.18	4 (57.1)	18 (46.2)	0.2 (0.05-0.7)	.01
≥9	4 (4.1)	35 (15.4)	0.2 (0.05-0.5)	<.001	3 (42.9)	14 (35.9)	0.3 (0.1-1.1)	.08

Abbreviations: CI, confidence interval; RR, relative risk.
*Adjusted for radiation dose delivered to breast. For this analysis, alkylating agents given in a noncyclic pattern (6 case patients, 30 control patients) were converted to a cyclic equivalent based on cumulative dose and duration of administration. Breast cancer deficits shown in this table roughly paralleled the percentage of women who became menopausal after treatment. Among women who received doses ≥5 Gy delivered to the ovaries, more than 90% were menopausal after treatment, independent of the number of alkylating agent cycles. Of women who received doses <5 Gy, the percentage of menopausal women increased with increasing number of alkylating agent cycles from 15% to 28% to 75% for those given 0, 1-8, and 9 cycles, respectively.

Table 4. Risk of Breast Cancer Following Hodgkin Disease Among Women Receiving Alkylating Agent Chemotherapy, by Type of Agent and Cumulative Dose of Mechlorethamine and Procarbazine

	No. (%)*			
	Cases (n = 105)	Matched Controls (n = 266)	RR (95% CI)†	*P* Value
Alkylating Agent‡				
No alkylating agent	68 (64.8)	132 (49.6)	Reference	
Mechlorethamine	31 (29.5)	107 (40.2)	0.5 (0.3-0.9)	.02
MOPP	23 (21.9)	72 (27.1)	0.6 (0.3-1.0)	.07
MOPP + other alkylating agents§	8 (7.6)	35 (13.1)	0.4 (0.1-1.0)	.04
Other alkylating agents (no mechlorethamine)	6 (5.7)	27 (10.2)	0.3 (0.1-0.9)	.02
Cyclophosphamide and procarbazine	3 (2.9)	14 (5.3)	0.3 (0.1-0.9)	.04
Other‖	3 (2.9)	13 (4.9)	0.4 (0.1-1.5)	.20
Cumulative Dose of Alkylating Agent				
Mechlorethamine, mg/m^2				
None	74 (70.4)	159 (59.8)	Reference	
<37	11 (10.5)	28 (10.5)	0.7 (0.3-1.6)	.42
37-54	11 (10.5)	27 (10.2)	0.9 (0.4-2.1)	.80
55-70	3 (2.9)	25 (9.4)	0.2 (0.1-0.8)	.02
≥71	6 (5.8)	27 (10.2)	0.4 (0.1-0.9)	.03
Procarbazine, mg/m^2				
None	70 (66.7)	137 (51.5)	Reference	
<4200	11 (10.5)	34 (12.8)	0.5 (0.2-1.2)	.11
4200-5799	10 (9.5)	33 (12.4)	0.7 (0.3-1.5)	.34
5800-7799	4 (3.8)	30 (11.3)	0.2 (0.05-0.5)	.001
≥7800	10 (9.5)	32 (12.0)	0.5 (0.2-1.3)	.16

Abbreviations: CI, confidence interval; MOPP, mechlorethamine, vincristine, procarbazine, and prednisone; RR, relative risk.
*Percentages may not sum to 100 due to rounding.
†Adjusted for radiation dose delivered to the breast and dose delivered to the ovaries. Analyses in "Cumulative Dose of Alkylating Agent" section were also adjusted for the number of cycles of alkylating agents among patients not receiving the indicated cytotoxic drug.
‡Treatment categories are mutually exclusive. Alkylating drugs were usually given in combination with other drugs, as indicated.
§Alkylating agents include carmustine, chlorambucil, cyclophosphamide, dacarbazine, lomustine, and procarbazine.
‖Alkylating agents include carmustine, chlorambucil, cisplatin, cyclophosphamide, dacarbazine, ifosfamide, lomustine, and procarbazine.

whom risk continued to increase with increasing radiation dose ($P=.03$ for trend). Increased risks of breast cancer associated with radiation were observed in all latency intervals after 5 years, including 25 years or more (RR, 2.3; 95% CI, 0.5-16.5), with no evidence of diminution with time ($P>.50$ for heterogeneity). Among patients who were followed for 25 or more years, a test for trend with radiation dose was statistically significant ($P=.03$). Risk of breast cancer was significantly increased (RR, 3.5; 95% CI, 1.6-8.3) among premenopausal and perimenopausal women, but radiation-related risk was not statistically distinguishable from the lower risk among postmenopausal women ($P>.50$ for difference). Radiation-related risk of breast cancer also did not differ significantly by parity ($P=.59$), stage of HD ($P=.45$), or staging splenectomy ($P=.65$).

The risk of breast cancer according to age (≤21 years and 22-30 years) at radiotherapy and categories (tertiles) of radiation dose delivered to the breast are shown in the upper half of TABLE 6. For each age group, risk of breast cancer increased with increasing radiation dose ($P=.007$ and $P=.02$ for trend, respectively). The lower half of Table 6 shows risks by categories of radiation dose delivered to the breast and by whether or not patients were treated with alkylating agents or radiation doses of 5 Gy or more delivered to the ovaries. The estimated excess RR per gray for women who received such treatment was 0.049 (95% CI, 0.004-0.34) ($P=.09$ for trend with dose), whereas the excess RR per gray following chest radiotherapy only was 0.15 (95% CI, 0.04-0.73) ($P<.001$ for trend with

dose). A test for the difference in the excess RRs ($P = .06$) suggested that the radiation-related risk was attenuated by treatment with alkylating agents or radiation doses of 5 Gy or more delivered to the ovaries.

The relation between radiation dose delivered to the breast and risk of breast cancer did not differ significantly between European and North American registries ($P > .50$ for difference). However, the risk of breast cancer following 6 cycles of alkylating agent treatment was 0.33 (95% CI, 0.15-0.65) for European sites and 0.97 (95% CI, 0.41-2.0) for North American registries ($P = .048$ for difference). Within Europe, significant reductions in risk were observed for the Netherlands (for 6 cycles: RR, 0.24; 95% CI, 0.06-0.70; $P = .005$ for trend) and the remaining European registries (RR for 6 cycles, 0.41; 95% CI, 0.15-0.95; $P = .04$ for trend); risk patterns for cumulative dose of mechlorethamine or procarbazine were similar.

COMMENT

This is the largest study to date of breast cancer among women treated for HD at age 30 years or younger to simultaneously include quantitative estimates of radiation dose delivered to the precise location where the breast tumor was diagnosed, radiation dose delivered to the ovary, and cumulative amount of alkylating agent chemotherapy received. Radiation dose delivered to the breast was related to increased risk of cancer, albeit at a lower

Table 5. Risk of Radiation-Associated Breast Cancer According to Age at Radiotherapy for Hodgkin Disease, Age at Breast Cancer Diagnosis, Time Since Radiotherapy, and Other Variables

	No. (%)					
	Radiation Dose <4 Gy (Reference)*		Radiation Dose ≥4 Gy			
Variable	Cases (n = 15)	Matched Controls (n = 76)	Cases (n = 90)	Matched Controls (n = 190)	RR (95% CI)†	*P* Value
Age at radiotherapy, y						
13-17	3 (20.0)	19 (25.0)	17 (18.9)	34 (17.9)	4.2 (1.1-21.8)	.04
18-21	4 (26.7)	20 (26.3)	26 (28.9)	57 (30.0)	2.1 (0.7-8.3)	.22
22-25	2 (13.3)	9 (11.8)	17 (18.9)	39 (20.5)	2.0 (0.3-17.2)	.46
26-30	6 (40.0)	28 (36.9)	30 (33.3)	60 (31.6)	2.9 (1.0-10.5)	.05
Age at breast cancer, y						
<35	3 (20.0)	17 (22.4)	18 (20.0)	36 (18.9)	2.6 (0.7-12.2)	.15
35-39	2 (13.3)	15 (19.7)	21 (23.3)	44 (23.2)	5.0 (1.0-40.2)	.05
40-44	3 (20.0)	18 (23.7)	26 (28.9)	59 (31.1)	2.7 (0.8-13.1)	.13
45-49	5 (33.4)	20 (26.3)	17 (18.9)	37 (19.4)	2.2 (0.6-9.0)	.21
≥50	2 (13.3)	6 (7.9)	8 (8.9)	14 (7.4)	2.4 (0.3-48.9)	.43
Time since radiotherapy, y						
5-9	0	6 (7.9)	5 (5.6)	6 (3.2)	Undefined (1.1-undefined)	.04
10-14	4 (26.7)	15 (19.7)	22 (24.4)	48 (25.3)	1.6 (0.5-6.1)	.47
15-19	2 (13.3)	20 (26.3)	32 (35.6)	72 (37.8)	5.8 (1.5-38.9)	.01
20-24	6 (40.0)	23 (30.3)	21 (23.3)	48 (25.3)	2.1 (0.6-8.2)	.24
≥25	3 (20.0)	12 (15.8)	10 (11.1)	16 (8.4)	2.3 (0.5-16.5)	.30
Menopausal status at study end						
Premenopusal and perimenopausal	10 (66.7)	46 (60.5)	61 (67.8)	87 (45.8)	3.5 (1.6-8.3)	.002
Postmenopausal	3 (20.0)	18 (23.7)	20 (22.2)	67 (35.3)	1.9 (0.5-12.9)	.38
Unknown	2 (13.3)	12 (15.8)	9 (10.0)	36 (18.9)	1.6 (0.3-12.4)	.59
Pregnancy status at diagnosis of Hodgkin disease‡						
Nulliparous	10 (76.9)	50 (69.4)	59 (66.3)	111 (63.1)	2.9 (1.3-6.9)	.006
Parous	3 (23.1)	22 (30.6)	30 (33.7)	65 (36.9)	4.5 (1.2-24.3)	.02
Stage of Hodgkin disease						
I or II	13 (86.7)	66 (86.8)	81 (90.0)	148 (77.9)	3.0 (1.5-6.6)	.002
III or IV	2 (13.3)	10 (13.2)	9 (10.0)	42 (22.1)	1.4 (0.3-11.0)	.71
Staging splenectomy§						
No	11 (78.6)	57 (76.0)	57 (66.3)	103 (55.7)	3.1 (1.5-7.2)	.003
Yes	3 (21.4)	18 (24.0)	29 (33.7)	82 (44.3)	2.2 (0.6-10.3)	.24

Abbreviations: CI, confidence interval; RR, relative risk.
*Reference group.
†Except for analyses of menopausal status, analyses were adjusted for number of cycles of alkylating agents and radiation dose delivered to the ovaries. Models for analyses in the last 4 sections included categorical main effects for the variable of interest.
‡Three case patients and 18 control patients for whom data on parity were not available were excluded from the analysis.
§Five case patients and 6 control patients for whom data on staging splenectomy were not available were excluded from the analysis.

level than that observed in other studies,[30] and ovarian damage by either radiation or chemotherapy was related to a decreased risk of cancer.

In view of the high rate of cure associated with HD, our major objective was to quantify the relation between radiation dose delivered to the breast and the long-term risk of breast cancer, taking into consideration other patient and treatment parameters. It is not yet known whether recently introduced radiotherapy regimens that incorporate lower doses and smaller fields for HD will result in decreases in the long-term risk of radiation-associated second cancers.[16] This question is especially pertinent for radiation-related breast cancer, since the shape of the dose-response curve is uncertain, especially at high therapeutic doses, where it has been postulated that a cell-killing effect may actually result in decreases in risk of cancer.[13,32] In contrast, our data showed a strong relation between increasing radiation doses of up to 40.5 to 61.3 Gy and statistically significant excesses of breast cancer, based on individual dosimetry that accounted for tumor location. The up to 8-fold increased risks underscore the importance of continuing to minimize therapeutic doses of radiotherapy to treat HD without sacrificing efficacy.

It is noteworthy, however, that the increased risks of breast cancer in our study occurred throughout a range of high doses. Mantle radiotherapy results in a more than 10-fold spectrum of radiation dose delivered across the breast (3 to 42 Gy for tumor doses of 40 Gy),[33] with lower doses delivered to tissue beneath the lung block and the largest doses delivered to the unshielded upper outer quadrant.[34] Portions of the breast beneath the lung block receive approximately 10% of the tumor dose, and 24% of the breast cancers in our series occurred in the blocked treatment field. Decreases in the tumor doses used in mantle radiotherapy would commensurately reduce the magnitude of the overall dose gradient across the breast, which includes scattered dose that likely plays a role in carcinogenesis, as postulated by Prosnitz.[35] Although our results suggest that reduction of mantle dose will result in a diminution in risks of breast cancer, long-term follow-up will be required to ascertain the extent to which risks can be lowered, in view of the well-established sensitivity of the breast of young women to ionizing radiation.[36]

Despite current reductions in the dose and volume of mantle radiotherapy, a considerable population of women treated for HD with previously used, more aggressive regimens remain at increased risk for breast cancer.[9,37] Our study shows that a significant relation between radiation dose and risk of breast cancer exists for more than 25 years after treatment. Breast cancer excesses have persisted for life in several other populations of women exposed to ionizing radiation.[13] Our findings should heighten the awareness of health care professionals and survivors of HD with regard to the high risk of breast cancer among women treated with chest radiotherapy at a young age, underscore the importance of screening, and prompt consideration of primary prevention strategies. Although no consensus recommendations exist with regard to breast cancer screening for young women

Table 6. Risk of Secondary Breast Cancer, by Radiation Dose Delivered to Site of Breast Cancer, Age at Radiotherapy for Hodgkin Disease, Radiation Dose Delivered to Ovaries, and Alkylating Agent Therapy

Radiation Dose Delivered to Site of Secondary Breast Cancer, Gy	No. (%)				No. (%)			
	Cases	Matched Controls	RR (95% CI)*	*P* Value	Cases	Matched Controls	RR (95% CI)*	*P* Value
	Age at Radiotherapy, y							
	≤21				22-30			
Total	48	123			54	134		
<4	7 (14.6)	39 (31.7)	Reference		8 (14.8)	37 (27.6)	Reference	
4.0-23.0	14 (29.2)	31 (25.2)	2.2 (0.8-6.7)	.13	15 (27.8)	29 (21.7)	2.9 (0.98-9.8)	.05
23.1-37.1	15 (31.2)	26 (21.1)	3.3 (1.0-11.7)	.046	14 (25.9)	35 (26.1)	3.3 (0.98-13.3)	.05
37.2-61.3	12 (25.0)	27 (22.0)	5.2 (1.3-23.7)	.02	17 (31.5)	33 (24.6)	4.5 (1.2-20.1)	.03
	Treatment							
	No Alkylating Agents; Radiotherapy <5 Gy Delivered to Ovaries				Any Alkylating Agents, or Radiotherapy ≥5 Gy Delivered to Ovaries			
Total	67	122			35	135		
<4	9 (13.4)	38 (31.1)	Reference		6 (17.1)	38 (28.1)	0.6 (0.2-2.0)	.45
4.0-23.0	13 (19.4)	26 (21.3)	2.1 (0.8-6.2)	.15	16 (45.8)	34 (25.2)	1.7 (0.6-4.9)	.31
23.1-37.1	22 (32.8)	27 (22.1)	5.0 (1.7-16.4)	.004	7 (20.0)	34 (25.2)	1.2 (0.3-4.3)	.80
37.2-61.3	23 (34.4)	31 (25.5)	7.2 (2.2-26.5)	<.001	6 (17.1)	29 (21.5)	1.5 (0.4-5.7)	.55

Abbreviations: CI, confidence interval; RR, relative risk.
*Relative risks by "age at radiotherapy" were adjusted for number of cycles of alkylating agents and radiation dose delivered to ovaries. Relative risks by "treatment" were not adjusted for these variables. All analyses exclude 1 case patient and 7 control patients for whom radiation dose delivered to the breast could not be estimated, and an additional 2 case patients and 2 control patients whose matched sets contained only case patients (or only control patients) after the exclusions. The overall RR (95% CI) of breast cancer for patients receiving radiation doses of 4.0-23.0 Gy, 23.1-37.1 Gy, and 37.2-61.3 Gy was 2.5 (1.2-5.7), 3.3 (1.4-8.3), and 4.7 (1.8-13.1), respectively.

treated for HD using radiotherapy,[17,22,38-42] many investigators advocate a baseline mammogram 5 to 8 years following initial treatment.[17,22,38-40,42] It is unsettling that a recent report of women treated for HD prior to age 30 years found that 40% did not perceive themselves to be at increased risk of breast cancer,[22] suggesting the continued need for patient education and programs of public awareness.

A 40% to 60% reduction in risk of breast cancer has been described following premature surgical menopause, with the greatest decreases evident for women before the ages of 35 years to 50 years.[43-45] Both a radiation dose of 5 Gy or more delivered to the ovary and the use of alkylating agents decreased the risk of breast cancer following chest radiotherapy for HD in our study, most likely by causing ovarian dysfunction, including the induction of premature menopause. The effect of radiation dose delivered to the ovary during subdiaphragmatic radiotherapy for HD on the subsequent risk of breast cancer has not been addressed in large studies, although the importance of oophoropexy to preserve ovarian function in premenopausal women with HD was recognized more than 30 years ago,[46] and surgical approaches continue to be refined.[47] Pelvic radiotherapy for women with menorrhagia (mean age, 45 years) using a dose of 5 Gy or more delivered to the ovary was associated with a significant 64% reduction in risk of breast cancer,[48] and women treated with radiation for cervical cancer (mean age, 52 years; mean ovarian dose, 32 Gy) experienced a 34% deficit.[49] The damaging effects on ovarian function of alkylating agent chemotherapy for HD have been described,[50,51] including a possible dose response with procarbazine,[51] but antimetabolites and plant alkaloids do not appear to result in ovarian failure.[52] The reduction in risk of breast cancer among women in Europe, but not North America, who received alkylating agent treatment for HD is unexplained. It is possible that the known higher prevalence and potency of hormone therapy in North America compared with Europe[53-55] is associated with an increased risk of breast cancer[56,57] that counteracts the protective effect of chemotherapy; unfortunately, our data on hormonal therapy were inadequate to address this issue.

Our results should be viewed within the various strengths and weaknesses of our international investigation. The large study base of more than 3800 young women with HD treated as early as the mid-1960s allowed us to quantify the radiation effect over a range of doses delivered to the breast. An inherent limitation of investigations of second cancers following HD, however, is the lack of a nonexposed comparison group, since treatment requires radiotherapy, chemotherapy, or both. Most of our analyses, however, focused on exposure-response relationships either by using continuous variables or by estimating risks by several ordered groups of exposure levels. The inclusion of women with low exposures in the comparison group is unlikely to result in overestimates of risk, although it could attenuate them.

Intensive efforts were made to reconstruct radiation dose delivered to the breast during treatment for HD, which included a careful review of detailed radiotherapy records and other clinical materials as well as information regarding location of the breast cancer; however, variation in the position of the breast tissue in patients treated in the prone position with mantle radiotherapy, and any changes in the size and shape of the breasts over time, also could have influenced our dose estimates. Any such variability should be nondifferential with respect to radiation dose delivered to the site of second breast cancer, and the true dose-response relationship would likely be stronger than we report.

Sample sizes were small for several subgroup analyses (eg, Table 5), limiting the ability to detect differences between groups. Although risk estimates could be derived, the 95% confidence limits were frequently wide. Thus, while the statistical power to discern effects of radiotherapy and chemotherapy is high overall, there can be much uncertainty for subgroup analyses when numbers are small. Although our findings may be relevant to the use of chest radiotherapy in other cancers (including pediatric malignancies such as Wilm tumor, for which significantly increased 12-fold risks of breast cancer have been reported[58]) the immune deficiency associated with HD[59] may limit the generalizability of our findings.

Given the overall reduction in risk of breast cancer in our study associated with use of alkylating agents or with radiation doses of 5 Gy or more delivered to the ovary, it would be interesting to evaluate the hormone-receptor status of the resultant tumors. There is a general paucity of data on the hormone receptor status of breast cancer occurring after HD, with even the largest series[17] to date lacking information for almost 60% of patients. Similarly, we were unable to assess the influence of hormone-receptor status or number of years of menses. Future studies addressing the risk of breast cancer after HD should make a concerted effort to include data on these and other hormonal factors, as well as detailed information on treatment.

Since studies of late effects are by necessity retrospective, our investigation may not reflect more recent approaches to treatment for HD. Our study also has limited applicability for predicting risks of breast cancer at low, nontherapeutic doses of radiation, since few, if any, patients received doses below about 1 Gy directed to the breast. The estimated excess RR of breast cancer per unit dose of radiation among women who received chest radiotherapy alone was smaller than in other studies of women exposed at a young age,[13,30] reflecting, perhaps, a complex interplay of induction by radiation, cell killing at high doses, and a compromised immune system. Nonetheless, our data provide important information with regard to risk of breast cancer following a broad spectrum of radiation doses used in therapeutic protocols and are directly applicable to patients with HD.

In summary, young women with HD may receive treatments that both increase their risk of breast cancer (ie, radiation dose delivered to the breast) and treatments that decrease their risk of breast cancer (ie, selected alkylating-agent chemotherapy; radiation dose delivered to the ovary). The overall increase in risk may be due in part to the result of mutational changes that, after prolonged hormonal stimulation, develop into breast cancer. The decrease in risk is likely due to a reduction or cessation of ovarian function and accompanying diminution in hormonal stimulation of breast tissue. The risks of breast cancer observed for patients in our series treated with chest radiotherapy alone are most relevant to current practice, given the current use of chemotherapy regimens such as ABVD (doxorubicin, bleomycin, vinblastine, dacarbazine), which do not seem to result in ovarian damage.[60,61] Among 1000 women treated for HD at age 30 years or younger with mantle radiotherapy alone using a dose of 40 Gy delivered to the breast and followed up for 25 years, an excess of 83 breast cancers in tissue exposed to this dose might be expected on the basis of our data. Radiation doses of 20 Gy and 10 Gy delivered to tissues might result in an excess of 42 and 21 breast cancers per 1000 women, respectively.

Despite our quantification of this serious late effect, it is clear that the major gains and successes in the treatment of HD greatly outweigh the treatment-related risks of breast cancer and other late sequelae. Given current modifications in approaches to radiotherapy,[14,15] in the future late effects should have less impact on the lives of women with HD. In the interim, for current survivors of HD, the high risk of radiation-associated breast cancer, which in our study did not diminish at the highest doses or in the longest follow-up, suggests the need for programs of clinician and patient awareness, lifetime surveillance, and possible prevention strategies.

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Once in his life a man ought to concentrate his mind upon the remembered earth, I believe. He ought to give himself up to a particular landscape in his experience, to look at it from as many angles as he can, to wonder about it, to dwell upon it. He ought to imagine that he touches it with his hands at every season and listens to the sounds that are made upon it. He ought to imagine the creatures there and all the faintest motions of the wind. He ought to recollect the glare of noon and all the colors of the dawn and dusk.

—N. Scott Momaday (1934-)