Roles of Radiation Dose, Chemotherapy, and Hormonal Factors in Breast Cancer Following Hodgkin's Disease

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Background: **Female survivors of Hodgkin's disease (HD) have a strongly elevated risk of breast cancer, but factors responsible for the increased risk are not well known.** ***Methods:*** **We investigated the effects of radiation dose, chemotherapy (CT), and reproductive factors on breast cancer risk in a nested case–control study in The Netherlands in a cohort of 770 female patients who had been diagnosed with HD before age 41. Detailed treatment information and data on reproductive factors were collected for 48 case patients who developed breast cancer 5 or more years after diagnosis of HD and 175 matched control subjects. The radiation dose was estimated to the area of the breast where the case patient's tumor had developed and to a comparable location in matched control subjects. Relative risks (RRs) of breast cancer were calculated by conditional logistic regression. Statistical tests were two-sided.** ***Results:*** **The risk of breast cancer increased statistically significantly with radiation dose (P_{trend} = .01); patients who received 38.5 Gy or more had an RR of 4.5 (95% confidence interval [CI] = 1.3 to 16) times that of patients who received less than 4 Gy. Patients who received both CT and radiotherapy (RT) had a statistically significantly lower risk than those treated with RT alone (RR = 0.45, 95% CI = 0.22 to 0.91). Breast cancer risk increased with increasing radiation dose among patients who received RT only (RR = 12.7, 95% CI = 1.8 to 86, for patients receiving ⩾38.5 Gy) but not among patients treated with CT and RT. Sixty-nine percent of control subjects treated with RT and more than six cycles of CT, but only 9% of those who received RT alone, reached menopause before age 41. Reaching menopause before age 36 was associated with a strongly reduced risk of breast cancer (RR = 0.06, 95% CI = 0.01 to 0.45).** ***Conclusion:*** **Breast cancer risk increases with increasing radiation dose up to at least 40 Gy. The substantial risk reduction associated with CT may reflect its effect on menopausal age, suggesting that ovarian hormones promote tumorigenesis after radiation has produced an initiating event. [J Natl Cancer Inst 2003;95:971–80]**

Modern radiotherapy (RT) and combination chemotherapy (CT) have dramatically improved the prognosis of patients with Hodgkin's disease (HD). However, the increased cure rates are offset by increasing awareness that survivors experience an increased risk of second malignancy. In particular, the strongly elevated risk of breast cancer after RT for HD has become a major concern for female survivors *(1–12).* In most studies, increased risks are observed beginning 10–15 years after irradiation for HD, and the excess risk persists for at least 20 years *(6,7,11,13,14).* Furthermore, the relative risk (RR) of breast cancer increases steeply with younger age at first irradiation *(6,11,13,14),* with RRs ranging from 17 to 458 (compared with general population rates) for those treated before age 16 *(2,5–11,14,15).* No statistically significant increase in breast cancer risk has been reported for HD patients treated after age 40 *(13,14).*

The elevated risk of breast cancer following irradiation for HD is not surprising in view of the reported excess risks of breast cancer after other radiation exposures (e.g., from multiple chest fluoroscopies, radiation treatment for benign disease, and the atomic bombings in Japan) *(16–21).* In the low-dose range (⩽5 Gy), breast cancer risk increases linearly with radiation dose *(16,17,19,22–24).* When addressing the possibility of dose reductions in mantle RT for HD, an important unanswered question is whether the linear dose response extends to the higher dose ranges (i.e., 24–44 Gy) that are used therapeutically. Although one study found that a higher radiation dose to the mantle region (⩾20 Gy versus <20 Gy) was associated with a higher risk of breast cancer *(2),* and some studies reported that most breast tumors arise in or at the margin of the radiation field *(2,5,9,25,26),* no studies have, to our knowledge, examined the association between individually estimated radiation doses at the precise site of subsequent breast tumor development and breast cancer risk.

Most HD patients are currently treated with a combination of CT and RT. It is not known, however, whether CT-induced premature menopause, associated use of hormone replacement therapy (HRT), or reproductive risk factors affect radiation-associated breast cancer risk in women treated for HD. To investigate these issues, we undertook a case–control study in The Netherlands in which we collected detailed information on all relevant risk factors.

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Subjects and Methods

Study Population

A nested case–control study was conducted in a joint cohort of 2637 patients with HD who were admitted to The Netherlands Cancer Institute in Amsterdam (n = 921), the Dr. Daniel den Hoed Cancer Center in Rotterdam (n = 1016), the Leiden University Medical Center (n = 530), or the Catharina Hospital Eindhoven (n = 170) between 1965 and 1988. Methods used to identify the cohorts in the four centers and to assess second cancer risk have been described extensively elsewhere *(11,27–29).* Twenty-nine percent of the members of the combined cohort (n = 770) consisted of female patients diagnosed with HD at age 40 or younger, and 650 of those patients survived 5 or more years. Follow-up as to the recent medical status of the patients was estimated to be complete for 91% of the cohort members *(11).*

Case patients were defined as female cohort members who developed histologically confirmed breast cancer at least 5 years after having been diagnosed with HD at 40 years of age or younger. Patients who developed breast cancer within 5 years of HD diagnosis or after an HD diagnosis at 41 years of age or older were not eligible for the case–control study because no statistically significant excess risk of breast cancer has been reported for such patients *(11,15).* For the purpose of this study, ductal carcinoma *in situ* of the breast, which was diagnosed in one woman, was considered as breast cancer. Patients who had received RT or CT before the diagnosis of HD were excluded. Forty-eight breast cancer patients in the cohort were eligible for study. For all of these patients, the breast cancer diagnosis was confirmed by review of pathology reports.

For each case patient, at least four matched control subjects were sought from the cohort of HD patients. Control subjects were matched to each case patient on age at diagnosis of HD (within 3 years) and date of diagnosis of HD (within 5 years). They also had to have survived without a second cancer for at least as long as the interval between the diagnoses of HD and breast cancer in the case patient. Four or more control subjects were identified for each of 27 case patients, three control subjects were identified for each of 14 case patients, two control subjects were identified for each of four case patients, and one control subject was identified for each of three case patients.

In three centers, case patients and control subjects who were alive in 1998 (n = 154) also were asked to participate in a related study that examined whether ATM heterozygosity increases the risk of radiation-associated breast cancer *(30).* These patients were also asked to complete a questionnaire on reproductive history and other breast cancer risk factors. The questionnaire was returned by 129 patients (31 case patients and 98 control subjects, response rate = 84%).

Data Collection

For all subjects, full medical records were obtained for detailed data abstraction of all treatments received. When part of the treatment had been given outside the four participating centers, the data abstractors went to the other treating hospitals to collect the relevant data. Information was collected on characteristics of HD (morphology and stage), all CT and RT given for HD, splenectomy, weight, height, reproductive factors (number of full-term pregnancies before and after HD diagnosis, cessation of menstruation after CT, and age at menopause), use of HRT, and family history of cancer. For each course or cycle of CT, the details abstracted included the name and total dose of each drug used, the dates of administration, and whether it was given in combination with other cytostatic drugs. For RT, we abstracted from the radiation chart the dose and location of the fields irradiated. In addition, all radiation treatment charts were photocopied for later use in estimating dose to the area of breast tumor development. For breast cancer case patients, we also collected data on laterality, location of breast tumor, stage, morphology and treatment of breast cancer, and occurrence of contralateral breast cancer.

The questionnaire given to the patients in the ATM study asked about age at menarche, age at first and subsequent births, duration of each pregnancy, number of miscarriages, changes in menstrual cycle characteristics after CT and pelvic RT, age at menopause, use of exogenous hormones (brand name and duration of all oral contraceptives and hormone replacement drugs ever used), and family history of cancer.

Complete data on menopausal status, age at menopause, and parity before and after HD were eventually available for 99% of the patients included in our case–control study. Complete data on age at menarche and age at each subsequent pregnancy were available for 79% of the study population.

Radiation Treatments and Dosimetry

Of the 220 patients who received RT (all of the case patients and 172 of the 175 control subjects), all but two had treatment with mantle, supraclavicular, mediastinal, axillary, or splenic fields, the fields that give the highest dose to the breast. Most of the patients (78%) were treated with high-energy photons, usually 8 MeV; the remainder were treated with orthovoltage x-rays, cobalt-60, or electrons. The average tumor doses for mantle RT were 38.5 Gy (median = 40 Gy) for case patients and 37.6 Gy (median = 39.8 Gy) for control subjects.

The aim of the dosimetry study was to estimate the actual absorbed dose to the site of the breast cancer and the ovaries. For each subject in a case–control set, the radiation dose was estimated as the dose to the site of breast tumor development in the case patient and the dose to a comparable location in the control subjects. Absorbed radiation doses to unblocked fields were based on experimental measurements in a water phantom to 60 cm outside the field *(31,32).* The dose to blocked fields was estimated as a percentage of the in-beam full dose (using beam data from the machine type used for a particular patient). Correction factors were applied with the use of the Pinnacle-3 treatment Planning system (ADAC Laboratories, Milpitas, CA), based on tumor distance from block edge. Dosimetry was based on details of RT abstracted from the radiation charts, simulation films of all radiation treatments, and copies of the mammograms (or other diagnostic test results) that indicated the precise location of the breast tumor. Each patient's record was reviewed by a radiation oncologist, a physicist, and a dosimetrist for position of the breast tumor site relative to the treatment fields. Tumor sites were determined to be either in a radiation beam (blocked or unblocked), on the edge of a beam or a block, or outside of a beam. The dose estimates included contributions from all fields. Attenuation by the lung blocks was included in the breast doses from treatments in the chest. Ovaries were assumed to be in normal position unless the record indicated that the patient had had an oophoropexy.

Statistical Analysis

The odds ratio of breast cancer associated with specific exposures (e.g., radiation dose or CT) was estimated by comparing the case patients' exposure histories with those of their matched controls, using conditional logistic regression methods *(33).* Odds ratios were used as valid risk estimates of RRs and are therefore referred to as such. RR estimates, *P* values, and 95% confidence intervals (CIs) for the RR estimates were calculated with the microcomputer program EGRET *(34),* and comparisons between exposure categories were based on likelihood ratio tests. All tests of statistical significance were two-sided. Because all subjects had received RT, CT, or both, it was not possible to estimate the RR of specific treatments as compared with a reference category of subjects never exposed to possible carcinogenic agents. Furthermore, only three patients (all control subjects) had received CT alone, making it impossible to directly compare the risks associated with RT alone with those associated with CT alone. Therefore, in our crude treatment analyses, the RR for patients treated with RT and CT was estimated relative to those treated with RT alone.

For each case patient, we considered only the therapies and reproductive events in the period between the diagnoses of HD and breast cancer; for the corresponding control patient(s), the analysis took into account only the therapy abstracted from a period of equal length, starting with the diagnosis of HD. Throughout the manuscript, for all patients, the end of the coding period is denoted as the cutoff date.

In evaluating the association between breast cancer risk and RT, we used, for each case–control set, the radiation dose to the area of the breast where the breast cancer of the case patient had developed. For the seven patients who were diagnosed with contralateral breast cancer, the radiation dose to the site of the first breast cancer was used in all analyses. Risk of breast cancer was either estimated with breast radiation dose treated as a continuous variable or grouped according to quartiles. Radiation dose to the ovaries was dichotomized on the basis of mean dose ($\geq$5 Gy versus <5 Gy). If the ovaries had received different doses, we used the lower dose in the analysis. The number of CT cycles with alkylating agents (i.e., mechlorethamine and procarbazine) was also treated as a continuous variable or was categorized into fewer than six or six or more cycles.

Multivariable analyses were done to account for potential confounding effects of pregnancies before and after HD, total number of children, age at birth of first and last child, menopausal status, age at menopause, family history of breast cancer, HRT, use of oral contraceptives, and body mass index (BMI; weight in kilograms divided by height in meters squared). When examining the association between CT and breast cancer risk, we initially adjusted for radiation dose only and not for menopausal status and age, because these variables can be considered intermediate factors in the causal pathway between CT and breast cancer risk. Subsequently, to examine whether CT has an effect on breast cancer risk independent of its effect on ovarian function, we also adjusted for menopausal status and age.

We examined whether number of years with intact ovarian function after irradiation for HD affected breast cancer risk. (Because we matched on age at diagnosis of HD there was too little variation in number of years with intact ovarian function before HD to examine this variable.) In women who were postmenopausal at the cutoff date, the time period with intact ovarian function after HD was calculated by subtracting the patient's age at first irradiation from her age at menopause, taking into account possible episodes (>1 year) without menstrual cycles immediately after treatment for HD. For women who were premenopausal at the cutoff date, we subtracted age at first irradiation from age at cutoff date.

Interactions between radiation dose to the relevant breast area and CT (or menopausal status or number of years with intact ovarian function after HD treatment) were examined in various models, with radiation dose and CT (or menopausal variables) being treated as either continuous or categorical variables.

RESULTS

General characteristics of the case patients and control subjects are shown in Table 1. The median age at diagnosis of HD was 25 years for the breast cancer patients (range = 15–40 years) and 24 years for the control subjects (range = 13–40 years). Approximately 50% of the case patients and control subjects were diagnosed with HD before 1974, and 25% were diagnosed after 1978. Overall, 97% of the control subjects were matched within 3 years of the case patient's age at diagnosis of HD, and 93% of the control subjects were matched within 3 calendar years of the case patient's year of diagnosis of HD. The median interval between the diagnoses of HD and breast cancer was 18.7 years, and the median age at diagnosis of breast cancer was 44 years. Approximately 13% of all breast cancers occurred before age 35. Slightly more breast cancers occurred in the left breast than in the right one. Tumors arose most often in the upper outer quadrant (42%). Fifty-four percent of the breast tumors were first noted by the women themselves, 21% were detected by clinical breast examination and/or mammography as part of a surveillance program for survivors of HD, and 8% were found by the national breast cancer screening program. Eighty-three percent of the case patients were diagnosed with early-stage breast cancer. After a mean follow-up of 3.4 years, nine of the 48 case patients had died of breast cancer.

We first compared breast cancer risk among broad treatment groups. All 48 breast cancer patients had received RT for HD, as had 98% of the control women (Table 1). Patients treated with both CT and RT had a statistically significantly lower risk of breast cancer than patients treated with RT alone (RR = 0.39, $P = .005$) (Table 2). Adjustment for radiation dose to breast and ovaries did not materially change this result (RR = 0.45). The difference between the risks associated with RT alone and with RT and CT was not due to different radiation doses, because patients treated with CT and RT and those treated with RT alone received similar radiation doses to the site of breast cancer occurrence (median doses to control subjects were 24.6 Gy and 23.6 Gy, respectively).

We next analyzed the effect of radiation dose on breast cancer risk. In the breast cancer patients, the mean radiation dose to the area of the breast where the tumor had developed was 25.2 Gy, compared with 22.1 Gy among irradiated control women ($P = .22$). The risk of breast cancer increased statistically significantly over quartiles of radiation dose ($P_{trend} = .01$), with patients who received 38.5 Gy or more (highest quartile) having a crude RR of 4.47 (95% CI = 1.25 to 16.0) times that of patients who received less than 4 Gy (lowest quartile) (Table 2). After adjustment for menopausal age and status, the risk was even higher (RR = 8.18, 95% CI = 1.64 to 40.8). The effect of radiation dose to the breast area as a continuous variable was best fitted by a linear term ($P = .015$, adjusted for menopausal

Table 1. Characteristics of case patients with breast cancer and their matched controls*

	Case patients (n = 48)	Controls (n = 175)
	No. (%)	No. (%)
Calendar year of diagnosis of Hodgkin's disease		
<1970	16 (33.3)	38 (21.7)
1970–1973	8 (16.7)	46 (26.3)
1974–1978	11 (22.9)	48 (27.4)
⩾1979	13 (27.1)	43 (24.6)
Age at diagnosis of Hodgkin's disease, y		
<20	14 (29.2)	55 (31.4)
20–24	9 (18.8)	47 (26.9)
25–29	17 (35.4)	36 (20.6)
⩾30	8 (16.7)	37 (21.1)
Stage of Hodgkin's disease		
I	14 (29.2)	41 (23.4)
II	33 (68.8)	98 (56.0)
III or IV	1 (2.1)	36 (20.6)
Treatment		
Radiotherapy only	30 (62.5)	68 (38.9)
Radiotherapy and chemotherapy	18 (37.5)	104 (59.4)
Chemotherapy only	0 (0)	3 (1.7)
Interval (y) between diagnoses of Hodgkin's disease and breast cancer		
5–14	11 (22.9)	n.a.
15–19	16 (33.3)	n.a.
20–24	14 (29.2)	n.a.
⩾25	7 (14.6)	n.a.
Age at diagnosis of breast cancer, y		
<35	6 (12.5)	n.a.
35–39	8 (16.7)	n.a.
40–44	11 (22.9)	n.a.
45–49	15 (31.3)	n.a.
⩾50	8 (16.7)	n.a.
Breast cancer detection		
Patient or spouse	26 (54.2)	n.a.
Physical examination/mammography†	10 (20.8)	n.a.
National screening program	4 (8.3)	n.a.
Other/not specified	8 (16.7)	n.a.
Laterality of breast cancer		
Right	21 (43.8)	n.a.
Left	27 (56.3)	n.a.
Quadrant of breast cancer		
Upper inner	8 (16.7)	n.a.
Lower inner	1 (2.1)	n.a.
Upper outer	20 (41.7)	n.a.
Lower outer	7 (14.6)	n.a.
Nipple/central portion	9 (18.8)	n.a.
Overlapping quadrants	3 (6.3)	n.a.
Stage of breast cancer		
DCIS	1 (2.1)	n.a.
I	16 (33.3)	n.a.
II	23 (47.9)	n.a.
III or IV	7 (14.6)	n.a.
Unknown	1 (2.1)	n.a.

*n.a. = not applicable; DCIS = ductal carcinoma *in situ*.

†As part of a surveillance program for survivors of Hodgkin's disease.

variables). The excess RR per Gy (ERR/Gy) was estimated to be 0.03 (95% CI = 0.002 to 0.06). Seven of the 48 case patients were diagnosed with contralateral breast cancer. Three of these patients had synchronous tumors, and the four others were all diagnosed with the second breast cancer within 15 months of the first one. The median radiation doses to the areas of the breast where the first and second tumors developed were 39.6 Gy and 33.3 Gy, respectively, which is not statistically significantly different from the median radiation dose to the area of breast tumor development in case patients with only one breast tumor (25.2 Gy) ($P = .90$, two-sample test for difference in median).

A greater number of cycles with alkylating CT was associated with a statistically significantly decreased risk of breast cancer. Patients who had six or more cycles of CT had an adjusted RR of 0.33 (95% CI = 0.13 to 0.86) compared with patients who had received RT alone (Table 2). A radiation dose to the ovaries of 5 Gy or more was also associated with a decreased risk of breast cancer (RR = 0.13, 95% CI = 0.02 to 1.08). The modifying effect of CT on the risk associated with RT was evaluated by fitting radiation dose–response slopes simultaneously for subjects who had and who had not received CT (Table 3). For patients who received RT alone, the risk of breast cancer increased strongly with increasing radiation dose ($P_{trend} = .003$); patients who received a dose of 38.5 Gy or more had an RR of 12.7 (95% CI = 1.8 to 86). No such trend was observed among patients who were treated with CT plus RT. The difference in dose–response trends between the two treatment categories was statistically significant ($P = .008$). For patients treated with RT alone, the ERR/Gy was 0.06 (95% CI = 0.01 to 0.13).

We next examined whether the modifying effect of CT on radiation-associated breast cancer risk could be explained by the induction of premature menopause by CT. Indeed, our data clearly indicate that CT was associated with a high prevalence of subsequent premature menopause. The percentages of control women who were postmenopausal at the cutoff date were 16% (11/68) for those who received RT alone and 54% (56/103) for those treated with RT and CT. Furthermore, only 9% (6/68) of control women who received RT alone reached menopause before age 41, versus 44% (45/103) of control women treated with RT and any type of CT and 69% (18/26) of the subset of control women who had been treated with RT and more than six cycles of CT ($P<.001$ for difference between first and last group). The median age at menopause in both of the latter two groups was 32 years. Furthermore, all five control subjects who had RT alone and received a radiation dose to the ovaries of 5 Gy or more reached menopause before age 41, at a median age of 33 years, whereas only 2% (1/63) of control women who received lower doses to the ovaries reached menopause at such a young age. The risk of breast cancer was 70% lower in women who were postmenopausal at the cutoff date than in women who were premenopausal (Table 4). Reaching menopause before age 31 after having been treated for HD was associated with a strongly reduced risk of breast cancer as compared with remaining premenopausal (RR = 0.09, 95% CI = 0.01 to 0.81) (Table 4). Entering menopause before age 36, as compared with remaining premenopausal or entering menopause after age 45, was also associated with a substantially decreased risk of breast cancer (RR = 0.06, 95% CI = 0.01 to 0.45). Furthermore, the risk of breast cancer increased strongly with longer time from HD treatment to menopause; RRs were 0.15, 0.24, and 0.91 for less than 5, 5–14, and 15 or more years spent in premenopause, respectively ($P_{trend}<.001$) (Table 4). Statistical models confirmed that the risk reduction associated with CT could be explained by a strong effect of CT on age at menopause (data not shown).

As shown in Table 5, women who had less than 15 premenopausal years after RT for HD had a lower risk of breast cancer at both radiation dose levels than those who had spent more years in premenopause. In addition, the RR for the higher radiation dose category (⩾24 Gy) versus lower doses was much higher for women with 15 or more years between RT for HD and menopause than for those who had less than 15 years, although the difference in RRs was not statistically significant.

Table 2. Relative risk of breast cancer after Hodgkin's disease treatment according to treatment category*

Treatment parameter	Cases	Controls	Crude analysis RR (95% CI)	Crude analysis *P* value	Adjusted analysis† RR (95% CI)	Adjusted analysis† *P* value	Adjusted analysis‡ RR (95% CI)	Adjusted analysis‡ *P* value
Treatment								
RT alone	30	68	1.0 (referent)		1.0 (referent)		1.0 (referent)	
RT + CT§	18	107	0.39 (0.20 to 0.75)	.005	0.45 (0.22 to 0.91)	.03	0.60 (0.29 to 1.26)‖	.18
Radiation dose to affected breast area (Gy) by quartile								
0.26–3.9 (median = 3.6)	9	47	1.0 (referent)		1.0 (referent)		1.0 (referent)‖	
4–23.2 (median = 15.5)	10	39	1.05 (0.32 to 3.51)	.94	1.11 (0.32 to 3.85)	.87	1.20 (0.35 to 4.19)	.77
24–38.2 (median = 30.2)	14	44	3.23 (0.90 to 11.6)	.07	4.20 (0.99 to 17.8)	.05	4.91 (1.06 to 22.8)	.04
38.5–56 (median = 40.7)	15	45	4.47 (1.25 to 16.0)	.02	5.16 (1.27 to 21.0)	.02	8.18 (1.64 to 40.8)	.01
Radiation dose to ovary, Gy¶								
<5 (median = 0.37)§	47	151	1.0 (referent)		1.0 (referent)		n.a.	n.a.
⩾5 (median = 34.8)	1	24	0.12 (0.02 to 0.93)	.04	0.13 (0.02 to 1.08)	.06	n.a.	n.a.
No. of cycles with CT#								
No CT	30	68	1.0 (referent)		1.0 (referent)		1.0 (referent)	
Nonalkylating single agents	6	15	0.97 (0.34 to 2.80)	.96	1.26 (0.42 to 3.82)	.68	1.32 (0.43 to 4.07)	.63
<6 cycles (or alkylating single agents)	4	30	0.33 (0.11 to 1.03)	.06	0.31 (0.09 to 1.05)	.06	0.39 (0.12 to 1.29)	.12
⩾6 cycles	8	62	0.28 (0.11 to 0.66)	.004	0.33 (0.13 to 0.86)	.02	0.47 (0.16 to 1.34)‖	.16
Mechlorethamine dose								
No mechlorethamine	37	101	1.0 (referent)		1.0 (referent)		1.0 (referent)	
<85 mg	4	38	0.51 (0.13 to 1.98)	.33	0.55 (0.13 to 2.31)	.41	0.54 (0.12 to 2.35)	.41
⩾85 mg	7	36	0.93 (0.26 to 3.35)	.92	0.91 (0.24 to 3.46)	.89	1.01 (0.24 to 4.29)‖	.99
Procarbazine dose								
No procarbazine	38	92	1.0 (referent)		1.0 (referent)		1.0 (referent)	
<9.5 g	5	42	0.36 (0.10 to 1.29)	.12	0.30 (0.08 to 1.19)	.09	0.34 (0.08 to 1.35)‖	.12
⩾9.5 g	5	41	0.33 (0.09 to 1.22)	.10	0.20 (0.04 to 0.91)	.04	0.32 (0.07 to 1.58)	.16

*RR = relative risk; CI = confidence interval; RT = radiotherapy; CT = chemotherapy; n.a. = not applicable.

†Treatment adjusted for breast radiation dose and ovary radiation dose; breast radiation dose adjusted for ovary radiation dose and CT (yes/no); ovary radiation dose adjusted for breast radiation dose and CT (yes/no); number of cycles adjusted for breast radiation dose and ovary radiation dose; mechlorethamine and procarbazine dose adjusted for breast radiation dose, ovary radiation dose, and CT (yes/no).

‡Treatment adjusted for breast radiation dose, menopausal status, and menopausal age; radiation dose adjusted for menopausal status and menopausal age; number of cycles adjusted for breast radiation dose, menopausal status, and menopausal age; mechlorethamine and procarbazine dose adjusted for breast radiation dose, menopausal status, menopausal age, and CT (yes/no).

§Includes three controls subjects who had CT only, and whose ovary radiation dose was therefore set to zero.

‖Excludes one control subject with missing menopausal data.

¶Radiation dose was dichotomized at the mean.

#Cycles are combinations of cytostatic agents with at least one alkylating agent.

Table 3. Relative risk (RR) of breast cancer after Hodgkin's disease treatment, according to quartiles of radiation dose to affected breast area and chemotherapy (yes/no)*

Treatment	Matched RR (95% CI) by quartiles of radiation dose received (cases/controls) 0.26–3.9 Gy	4–23.2 Gy	24–38.2 Gy	38.5–56 Gy
RT only (P_{trend} = .003)	1.0 (referent) (4/16)	0.48 (0.07 to 3.2) (3/18)	6.07 (1.0 to 37)† (10/16)	12.7 (1.8 to 86)‡ (13/18)
RT + CT§	0.80 (0.18 to 3.5) (5/31)	1.17 (0.25 to 5.5) (7/21)	1.83 (0.28 to 12) (4/28)	0.89 (0.12 to 6.8) (2/27)

*RR = relative risk from conditional logistic regression; CI = confidence interval; RT = radiotherapy; CT = chemotherapy.

†*P* for comparison with the reference group (RR = 1.0) = .05.

‡*P* for comparison with the reference group (RR = 1.0) = .009.

§Includes three control subjects who had CT only.

We also evaluated whether CT type and dose affected breast cancer risk after its effect on ovarian function had been accounted for (i.e., by adjustment for menopausal status and age; rightmost column of Table 2). The most commonly used form of CT was the mechlorethamine–procarbazine type. Overall, 56% (10/18) of CT-treated breast cancer case patients (versus 68% [73/107] of CT-treated control subjects) had been given mechlorethamine–procarbazine combinations. Neither total number of cycles with alkylating CT (Table 2), number of cycles with mechlorethamine–procarbazine combinations (data not shown), cumulative dose of mechlorethamine or procarbazine (data not shown), nor dose category according to median dose (Table 2) was statistically significantly related to the risk of breast cancer in models that included menopausal status and age at menopause (Table 2).

We next evaluated associations with reproductive risk factors known to affect breast cancer risk in the population at large. Women who had given birth before they were treated for HD had a slightly reduced risk of breast cancer, whereas women with successful pregnancies after HD had a slightly elevated risk (Table 6); neither change, however, was statistically significant. The use of HRT was uncommon in The Netherlands in the era

Table 4. Relative risk (RR) of breast cancer after Hodgkin's disease (HD) treatment, according to menopausal status and age at menopause

	Case patients (n = 48)	Control subjects (n = 175)	
	No. (%)	No. (%)	RR† (95% CI)
Menopausal status at cutoff date‡§			
Pre- or perimenopausal	36 (75)	105 (60)	1.0 (referent)
Postmenopausal	12 (25)	69 (40)	0.30 (0.12 to 0.75)
Age at menopause‡			
Pre- or perimenopausal at cutoff date	36 (75)	105 (60)	1.0 (referent)
19–30 y	1 (2)	20 (12)	0.09 (0.01 to 0.81)
31–40 y	3 (6)	33 (19)	0.25 (0.07 to 0.92)
⩾41 y	8 (17)	16 (9)	0.84 (0.23 to 3.05)
Age at menopause‡			
No premature menopause‖	41 (85)	113 (65)	1.0 (referent)
19–35 y	1 (2)	39 (22)	0.06 (0.01 to 0.45)
36–45 y	6 (13)	22 (13)	0.80 (0.26 to 2.40)
Age at menopause (continuous per year)‡			1.12 (1.02 to 1.23)
Time from HD treatment to menopause‡			
Premenopausal	36 (75)	105 (60)	1.0 (referent)
⩾15 y	6 (13)	10 (6)	0.91 (0.26 to 3.18)
5–14 y	3 (6)	22 (13)	0.24 (0.06 to 0.96)
<5 y	3 (6)	37 (21)	0.15 (0.03 to 0.60)
No. of years spent in premenopause after HD (continuous)‡			1.11 (1.00 to 1.22)

*CI = confidence interval.

†The variables menopausal status, age at menopause, time from HD treatment to menopause, and no. of years spent in premenopause after HD were adjusted for radiation dose to breast area.

‡Unknown for one control subject.

§Menopausal status at cutoff date according to treatment category was as follows: Among 30 case patients and 68 control subjects treated with radiotherapy (RT) alone, five and 11 women, respectively, were postmenopausal at cutoff date; among 18 case patients and 104 control subjects treated with RT plus chemotherapy (CT), seven and 56, respectively, were postmenopausal at cutoff date (for one control subject in this treatment group, menopausal status was unknown). Two of the three control women treated with CT only were postmenopausal at cutoff date.

‖No premature menopause was defined as pre- or perimenopausal at cutoff date or age at menopause >45 y.

Table 5. Relative risk (RR) of breast cancer after Hodgkin's disease (HD), according to radiation dose and number of premenopausal years

	Matched RR (95% CI) by radiation dose (cases/controls)*	
	<24 Gy	⩾24 Gy
No. of years menstruating after HD†		
⩾15	1.0 (referent) (15/49)	13.0 (1.42 to 120) (18/37)
<15	0.16 (0.03 to 1.02) (4/36)	0.70 (0.14 to 3.57) (11/52)

*CI = confidence interval. Cut points for radiation dose and no. of years menstruating after treatment for HD are defined by the medians in control subjects.

†Unknown for one control subject.

during which most of the patients in our study entered menopause. Only three case patients and 38 control women had used HRT for a median duration of 3 years (Table 6). HRT use (versus no use) and use for 3 years or more (versus use for <3 years) were not associated with a statistically significant increase in breast cancer risk. We also examined the effect of BMI among women who were postmenopausal at the cutoff date. Postmenopausal women with a BMI above the median of 21.2 kg/m^2 did not have a statistically significantly higher risk of breast cancer than women with a lower BMI (RR = 3.95, 95% CI = 0.69 to 22.8; $P = .12$). Age at first birth, age at menarche, and oral contraceptive use did not appear to be related to the risk of breast cancer, but numbers in subcategories were small.

The effects of the matching variables (age at diagnosis of HD and time since HD diagnosis) on the risk estimates were examined in a stratified analysis (data not shown). The RRs of breast cancer associated with radiation dose were higher in patients diagnosed with HD before the median age of 25 years than among patients diagnosed at an older age. In addition, the risk of radiation-associated breast cancer was similar for patients with a follow-up interval of less than or more than the median of 19 years. However, none of these differences reached statistical significance, possibly because of the small numbers available for subgroup analyses.

DISCUSSION

To our knowledge, this study is the first to reliably examine radiation dose response for breast cancer in the high dose ranges used therapeutically. The effects of CT and reproductive factors, including menopausal age, on radiation-associated risk of breast cancer in survivors of HD have also not been assessed before. Based on individually estimated radiation doses to affected breast areas, we found that breast cancer risk rose with increasing radiation dose, even at doses above 38 Gy. CT modified the radiation dose response, such that the risk of breast cancer increased strongly with increasing radiation dose among patients who received RT only, whereas no clear trend was observed among patients treated with CT and RT. We believe that the risk reduction associated with the use of CT is due to an effect of CT on ovarian function. A larger number of premenopausal years following RT for HD was strongly associated with increased risk of breast cancer. Together, these observations suggest that ovarian hormones play a critical role in promoting tumorigenesis

Table 6. Reproductive and other risk factors of Hodgkin's disease (HD) patients in relation to subsequent breast cancer risk*

	Case patients (n = 48)	Control subjects (n = 175)	
	No. (%)	No. (%)	RR† (95% CI)
Parity‡			
Nulliparous	11 (23)	49 (29)	1.0 (referent)
Parous before diagnosis of HD, no completed pregnancies after HD	11 (23)	54 (31)	0.50 (0.13 to 1.91)
Parous only after HD diagnosis	20 (42)	54 (31)	1.19 (0.48 to 2.99)
Completed pregnancies before and after HD	6 (13)	15 (9)	0.76 (0.21 to 2.66)
Total No. of children‡			
Nulliparous	11 (23)	49 (28)	1.0 (referent)
1–2	22 (46)	95 (55)	0.87 (0.37 to 2.03)
⩾3	15 (31)	28 (16)	1.34 (0.43 to 4.11)
Age at first birth, y§			
Nulliparous	11 (23)	51 (30)	1.0 (referent)
<25	17 (35)	55 (33)	0.82 (0.29 to 2.28)
25–29	13 (27)	45 (27)	1.03 (0.40 to 2.64)
⩾30	7 (15)	18 (11)	1.16 (0.34 to 3.94)
Age at menarche, y			
⩽12	15 (31)	54 (31)	1.0 (referent)
13–14	25 (52)	98 (56)	0.83 (0.34 to 2.02)
⩾15	8 (17)	23 (13)	1.44 (0.40 to 5.13)
BMI in postmenopausal women, kg/m^2‖			
⩽21.2 (median of controls)	4 (33)	35 (51)	1.0 (referent)
>21.2	8 (67)	34 (49)	3.95 (0.69 to 22.8)
Use of hormone replacement therapy¶			
No	45 (94)	137 (78)	1.0 (referent)
Yes, <3 y	0 (0)	17 (10)	
Yes, ⩾3 y	3 (6)	21 (12)	2.16 (0.36 to 12.9)
Oral contraceptive use			
No	15 (31)	64 (37)	1.0 (referent)
Yes, <7.7 y (median of cases and controls)	15 (31)	57 (33)	1.11 (0.47 to 2.62)
Yes, ⩾7.7 y	18 (38)	54 (31)	1.50 (0.61 to 3.65)
Family history of breast cancer			
No	38 (79)	154 (88)	1.0 (referent)
Yes	10 (21)	21 (12)	1.63 (0.64 to 4.16)

*RR = relative risk; CI = confidence interval; BMI = body mass index.

†The variable body mass index was adjusted for radiation dose only; all other variables were adjusted for radiation dose (continuous variable) and menopausal age and status.

‡Unknown for three control subjects.

§Unknown for six control subjects.

‖Unknown for one control subject.

¶Includes oral contraceptive use after menopause.

after radiation has produced an initiating event. Such a model may explain why women exposed to radiation when very young experience a much greater increase in breast cancer risk *(6,11, 13,35)* than women exposed in their 30s or 40s, who have few years of endogenous estrogen exposure remaining. Extensive information on the doses of all cytostatic agents received was available in our study, and no association between breast cancer risk and any type of CT was found after adjusting for menopausal variables. This result indicates that CT does not appear to have a stimulating effect on breast cancer development independent of its damaging effect on ovarian function.

Despite a large number of experimental and epidemiologic studies, the effect of radiation dose on tumor induction is not yet fully understood. The incidence of radiation-induced tumors is well known to rise in the low-dose range *(16,17,19,22–24),* and it has been speculated that the risk declines with increasing radiation dose as radiation cell kill becomes the predominant effect. For leukemia, a downturn of the risk at a bone marrow dose of several Gy has been shown, although the data are not entirely consistent *(23).* For breast cancer and other solid tumors, there is convincing evidence for a strongly linear radiation dose response in the lower dose ranges (up to ≈5 Gy) *(16,17,19,22,24,36,37),* but very few data are available with regard to shape of the dose–response curve in the (therapeutic) high-dose range (24–44 Gy). Mantle field irradiation exposes the medial and lateral portions of the breast to direct radiation, and the remaining blocked areas receive from 3% to 15% of the dose delivered, depending on the size of the breasts and the position of the patient *(38–41).* Hence, typical mantle treatment with a midline dose of 40 Gy results in a large dose gradient across the breast (3–42 Gy). Our data show increasing risk of breast cancer over this entire dose range, with no evidence of a decline in risk at the highest doses. However, the slope of the radiation dose–response curve appears to be less steep than observed in epidemiologic studies covering the lower dose ranges (0–5 Gy) *(16–18,21,24).* Therefore, it is possible that the linear dose–response function consistently observed for the low dose ranges attenuates at the high doses used in cancer treatment. In this regard, it is of interest that a recent study of lung cancer risk following RT for HD also reported an upward trend in lung cancer risk with increasing radiation dose up to 40 Gy or more *(42).*

Only a few studies have examined the effect of CT on the risk of breast cancer following radiation for HD. In three studies, CT was associated with reduced breast cancer risk *(11,13,43),* although Hancock et al. *(5)* reported that the addition of mechlorethamine, vincristine, procarbazine, and prednisone (MOPP)-

containing combination CT to RT increased breast cancer risk. CT can cause premature menopause, which is known to decrease breast cancer risk considerably in the population at large *(44)*. Indeed, shortly after the introduction of combination CT in HD treatment, it became clear that female patients often experience temporary or permanent ovarian failure after intensive CT *(45–48)*. However, few studies have examined menopausal age in women whose ovarian function was retained or recovered after CT during adolescence or young adulthood *(49)*. Our data show that a high percentage (44%) of control women treated with RT and any type of CT reached menopause at age 40 or before; more than half of these women experienced permanent ovarian failure shortly after treatment, but, strikingly, approximately 40% did not experience premature menopause until 5 or more years after CT, likely as a result of CT-induced depletion of the follicle pool in the ovaries. The reduced risk of RT-associated breast cancer in HD patients also treated with CT was most likely due to CT-induced premature menopause. We also found that pelvic irradiation resulting in an ovarian dose of 5 Gy or more was associated with reduced breast cancer risk, presumably through its effect on ovarian function.

In our study, women with a very premature menopause (before age 36) had a 94% lower risk of breast cancer than women who did not have a premature menopause, and women exposed to endogenous ovarian hormones for less than 5 years following RT experienced a risk reduction of 85%. Although our estimate for the risk reduction associated with a very premature menopause (before age 36) was imprecise because it was based on only one case patient and 39 control women, the extent of the risk reduction appears to be even greater than is seen in nonirradiated populations *(44)*.

Because the long-term use of HRT for menopausal symptoms has been shown to increase breast cancer risk *(50),* it seems possible that HRT use might diminish the risk reduction associated with premature menopause. In the hospitals involved in this study, however, HRT for treatment of CT-induced menopause was prescribed only rarely for women with HD treated before the 1980s. Only 10% of the women in our study used HRT for 3 years or more. This was an advantage in that it allowed us to assess the effect of loss of ovarian function without the confounding effects of subsequent hormone supplementation; however, it was a disadvantage in that our estimates for the reduction of breast cancer risk associated with CT-induced premature menopause do not reflect current treatment policy. Long-term HRT is now commonly prescribed for HD patients to address the adverse consequences of early menopause on bone density and quality of life.

Very few studies have evaluated interactions between radiation dose and other risk factors for breast cancer, such as reproductive factors *(36,51,52)*. However, such studies are important for identifying population subgroups that are at increased risk for the development of radiation-induced breast cancer. Furthermore, we may learn from interaction effects why radiation dose is much more effective in causing breast cancer when exposure occurs at an early age *(51)*. Land et al. *(51)* found that, in Japanese atomic bomb survivors, radiation dose and nulliparity (as well as late age at first birth) act multiplicatively in the causation of breast cancer. This would imply that the absolute excess risk of developing radiation-induced breast cancer is much lower in parous women than nulliparous women, as well as in women who are younger at first birth than women who are older. In tuberculosis patients exposed to several chest fluoroscopies, superadditive departures from additivity (in the direction of a multiplicative effect) were found for radiation dose and nulliparity *(36)*. However, no significant departure from additivity was found for the joint effects of reproductive variables and radiation dose in a postpartum mastitis cohort *(52)*. The age- and dose-specific absolute excess rates of breast cancer have been found to be remarkably similar across studies in the Japanese atomic bomb survivors and in medically irradiated populations in the United States, implying interaction at the additive level between radiation dose and the risk factors underlying the much greater breast cancer risk in American women than Japanese women *(37)*. In our study, which evaluated much higher radiation doses than the above-mentioned reports, we found some evidence for interaction at the multiplicative level between radiation dose and CT (Table 3), or (CT-induced) premature ovarian failure (Table 5). That is, among patients who had radiation alone, most of whom were still premenopausal at the end of follow-up, the increase in breast cancer risk with radiation dose was greater than it was among patients who had additional CT, more than half of whom became postmenopausal during follow-up and therefore had less than 15 years exposure to endogenous ovarian hormones. This observation implies that risks associated with exposure to endogenous estrogens appeared to at least multiply risks associated with radiation.

When evaluating the results of our study, several strengths and weaknesses should be considered. A unique feature of our study is that we estimated radiation dose to the precise location where the breast cancer had developed. However, although we were able to use simulation films of the original HD radiation treatment and mammograms indicating tumor location for nearly all patients, some inaccuracies in breast dosimetry were inevitable, depending on the size and the position of the breast. Inaccuracies were particularly likely for tumors located near the edge of the radiation fields and for those in large breasts, especially if the size of the breast increased in the years after RT. Another strength of our study is that, through a questionnaire addressed to the women themselves, we obtained nearly complete data on hormonal risk factors. However, a limitation of our study is the relatively small number of breast cancer patients. As a result, the study did not have sufficient power to examine the role of risk factors that are less strongly associated with breast cancer than radiation dose and early menopausal age, such as pregnancies before and after treatment for HD. The effects of radiation dose in more detailed categories will be examined in a larger international case–control study of breast cancer following HD coordinated by the National Cancer Institute of the United States *(53)*.

Our results have several clinical implications. First, the strong radiation dose–response relationship up to at least 40 Gy emphasizes the importance of minimizing radiation doses and fields without compromising the excellent cure rates *(54)* that have been achieved for HD. Our results suggest that the lower radiation doses and reduced fields applied in current HD trials may already be expected to attenuate the increased breast cancer risk in more recently treated patients. Until there is evidence of substantially reduced risk with newer treatments, however, the follow-up of women treated with mantle field irradiation before age 30 should include at least yearly clinical breast examination and annual mammography beginning 8 years after irradiation *(3,55,56)*. The importance of regular breast examinations over

an extended period should be explained to young women with HD, and they should be taught breast self-examination. Because the efficacy of screening methods for this special patient group is unknown, a study examining the efficacy of various imaging modalities (including magnetic resonance imaging) would be worthwhile *(3)*.

Finally, our finding that breast cancer risk following RT is strongly reduced in women who have experienced CT-induced premature menopause has implications for potential chemopreventive strategies. In other high-risk populations, such as BRCA1 and BRCA2 mutation carriers, several breast cancer chemoprevention trials are in progress worldwide. Because the risk of developing breast cancer at a young age is about equally high in women irradiated for HD as adolescents or young adults, chemoprevention studies aiming to reduce exposure to ovarian steroids in this population are an important next step.

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