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UNILATERAL AND BILATERAL BREAST CANCER IN WOMEN SURVIVING PEDIATRIC HODGKIN'S DISEASE

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Abstract

Purpose—To define demographic and therapeutic associations with the risk of breast cancer in children treated for Hodgkin's disease (HD), particularly the frequency and interval to the development of contralateral breast cancer.

Methods and Materials—All 398 female patients (<19 years) treated for HD in five institutions during the accrual period were evaluated. Mean follow-up was 16.9 years. The standardized incidence ratio (SIR) was calculated as the ratio of the observed number of cases to the expected number of cases, estimated using age-matched controls from the Surveillance, Epidemiology, and End Results database.

Results—A total of 29 women developed breast cancer (25 invasive, 4 ductal carcinoma *in situ*; SIR, 37.25; 95% confidence interval, 24.96–53.64). Time to diagnosis was 9.4 to 36.1 years. Cumulative incidence was 24% at 30 years. Ten patients (34%) had bilateral disease (9 metachronous, 1 synchronous). The interval to contralateral breast cancer was 12 to 34 months. On univariate analysis, significant variables included stage of HD, mantle radiation dose, pelvic radiation (protective), and follow-up time. On multivariate analysis, early stage and older age at diagnosis of HD (<12 vs. >12 years) were significant predictors of secondary breast cancer.

Conclusions—Women surviving pediatric HD were found to have a 37-fold increase in the risk of breast cancer and a high likelihood of rapidly developing bilateral disease. Early-stage HD and age greater than 12 years at diagnosis of HD were independent risk factors. Higher radiation doses may augment risk, and pelvic radiation may be protective. Breast cancer screening methodology and frequency, plus the role of prophylaxis in patients with unilateral disease, require definition.

INTRODUCTION

Breast cancer is the most common secondary solid tumor after pediatric Hodgkin's disease (HD) and is associated with therapy for the primary malignancy (1–7). Identification of patient characteristics and risk factors that predispose these women to develop breast cancer is necessary to modify current therapy for HD, as well as to formulate screening strategies.

Adolescent age at the time of diagnosis of HD, and high radiation doses and volumes that include breast tissue, have been implicated as risk factors; and some patients rapidly develop bilateral disease (7–13). Recent literature has also linked pelvic radiation and the use of alkylators with a decreased risk of breast cancer (14–17).

The study of secondary breast cancer is rendered difficult by the long latency period and the small patient numbers encountered at any single institution. We report the incidence of breast cancer in 398 women treated for pediatric HD at five institutions and comprehensively review patient characteristics to identify factors that predispose children treated for HD to develop breast cancer. We also seek to review characteristics of secondary breast cancer including time to diagnosis of breast cancer, age at the time of diagnosis, and frequency of bilateral disease.

METHODS AND MATERIALS

Patient cohort

Five institutions participated in the study, including the University of Rochester Medical Center, the Boston Children's Hospital and the Dana Farber Cancer Institute, St. Jude Children's Research Hospital, University of Florida Medical Center, and the Sidney Kimmel Cancer Center at Johns Hopkins. Accrual began in 1960 and ended in 1990. All female patients with HD who had received their primary treatment in the accrual period in the pediatric oncology service of each of the five institutions and were less than 19 years of age at the time of diagnosis were included in the study. Patients with a history of cancer before the diagnosis were excluded from study. At each institution, medical records were reviewed to obtain information regarding demographics, characteristics of HD and its treatment, subsequent malignant neoplasms, and breast cancer characteristics. For the entire population of male and female patients treated at these institutions, contact was documented for 89% within the previous 5 years, and for 59% within the previous 2 years. This study was approved by the institutional review boards of all centers.

Treatment characteristics

Because the treatment protocols used in the study subjects varied with time and across institutions, a technique was devised to compare chemotherapy regimens. The dosage range of each agent was tabulated to obtain quartile values. The total dose of an agent used in any individual patient (primary therapy and relapse) was then assigned a score from 1 to 4, depending on its quartile. The sum of scores of all prescribed agents belonging to the alkylator class was considered to be the alkylator score for that patient. The anthracycline score was calculated similarly. The radiation dose used for statistical analysis was that administered to the mantle.

Statistical analysis

A secondary breast cancer was defined as breast cancer that occurred at any time after the diagnosis of HD. For each subject, the follow-up interval was defined as the interval between the date of diagnosis of HD to the earliest occurrence of breast cancer, death, or last available contact time. The standardized incidence ratios (SIRs) were calculated as the ratio of observed cases to expected cases. The expected number was calculated by applying age-, and sex-specific incidence rates from the registry of the Surveillance, Epidemiology, and End Results (SEER) Program of the National Cancer Institute (1992–1996) to the respective person-years of follow-up in each group using a standard time period (18). This conservative approach introduces minimal error. Confidence intervals (CIs) for the incidence ratios were determined by Poisson distribution. Absolute excess risk was calculated as the difference between the observed and the expected incidence of breast cancer divided by the total number of person-years of follow-up. This number was multiplied by 10,000 to obtain the absolute excess risk of breast cancer per 10,000 person-years.

Univariate analyses were performed using the Chi-square test, Student's *t* test, and Mantel-Haenszel test of trend for categorical, continuous, and ordinal variables, respectively. Survival curves were calculated using the Kaplan-Meier method. The Cox proportional hazards model was used for multivariate analysis. For all analyses, a two-sided α level of 0.05 was used to determine statistical significance.

RESULTS

The patient population consisted of 398 female patients, with 6,323 person-years of follow-up. The mean age at diagnosis of HD was 14.5 years, and the mean follow-up was 16.9 years. Early-stage (Stages I and II) disease was present in 253 patients (63.6%), and advanced stage (Stages III and IV) disease was noted in 145 (36.4%). Most patients in the study (67.6%) had undergone splenectomy. In all, 88 patients (22.1%) experienced relapse. Of the patients, 44% were treated with radiation therapy alone, only 9% with chemotherapy alone, and 47% with a combination of radiation and chemotherapy. Most patients (86.6%) received mantle radiation, and 62.3% of all patients received a mantle radiation dose of at least 35 Gy. A total of 98 patients (24.6%) also received pelvic radiation. The mean anthracycline score was 2.2 and the alkylator score was 5.7 among patients who received these agents.

Incidence of breast cancer and demographics

Breast cancer was diagnosed in 29 women (7%) (Table 1) and accounted for 40% of all second malignancies among female patients. A total of 25 patients had invasive breast cancer and 4 patients had ductal carcinoma *in situ*. The standardized relative risk was 37.25 (95% confidence interval [CI], 24.96–53.64) and the absolute excess risk was 18.62 per 10,000 person-years. The racial/ethnic composition and mean age at diagnosis of HD were similar among patients with and without breast cancer. The mean follow-up time among patients who developed breast cancer (23.7 years) was significantly higher than that among subjects who did not develop breast cancer (16.3 years; $p < 0.01$).

Association of breast cancer with characteristics and treatment of Hodgkin's disease

The histological distribution of HD, rates of splenectomy and relapse, modality of treatment used for HD, and chemotherapy scores were similar among patients with breast cancer and those without. However subjects with breast cancer were found to be significantly more likely to have received higher doses of mantle radiation than subjects who did not develop breast cancer (Table 1). Complicating this observation is that patients treated with higher radiation doses have had longer follow-up. Using analysis of variance to examine FU time

across the three categories of mantle radiation (<25 Gy, 25–<35 Gy, 35 Gy), mean follow-up intervals were 168, 183, and 212 months, respectively ($p = 0.0007$). Finally, pelvic radiation was found to be associated with a significantly lower rate of breast cancer in the overall study population ($p = 0.0032$).

Association of breast cancer with stage of Hodgkin's disease

Of the 29 patients with breast cancer, 28 had been diagnosed with early-stage HD. This association of stage of HD with subsequent development of breast cancer was statistically significant ($p < 0.0001$). To further define the independent or confounding effect of stage of HD, characteristics of subjects with early-stage HD were examined in comparison to subjects with advanced stage HD (Table 2).

Subjects with early and advanced stage HD contributed 4,125 and 2,198 person-years of follow-up, respectively. The age at diagnosis of HD, follow-up time, and rate of relapse were similar in patients with early and advanced stage disease. However there were significant differences in the treatment modality used ($p < 0.0001$). Specifically, subjects with early-stage HD were more likely to have been treated with radiation alone (59.3% vs. 16.6%), and slightly more likely to have received radiation to the mantle field (89.7% vs. 81.4%). Patients with early-stage HD were also significantly more likely to have received higher doses of mantle radiation (36.4 Gy vs. 30.2 Gy for advanced-stage patients), though in absolute terms this dose difference is small (Table 2) ($p < 0.0001$). Although 38 of the 253 patients (15%) with Stage I and II HD underwent irradiation to the pelvis, vs. 60 of 145 patients (41%) with Stage III and IV disease, this would not account for the substantial difference in the likelihood of breast cancer in the two groups.

Multivariate analysis

On multivariate analysis, a proportional-hazards model that included age at diagnosis, stage of HD, chemotherapy score, mantle radiation dose (none, <30 Gy, 30 Gy) and radiation volume demonstrated that stage of disease ($p = 0.004$) and age (>12 years vs. 12 years) ($p = 0.033$) were found to be statistically significant predictors of breast cancer after accounting for the other variables in the model.

Breast cancer characteristics

The median age at the time of diagnosis of breast cancer was 31.4 years (range, 26.50–54.5 years). The time to develop breast cancer ranged from 9.4 to 36.1 years. The cumulative incidence for the development of breast cancer was 24% by 30 years of follow-up (Fig. 1). Both breasts were equally at risk. Bilateral disease was present in 10 patients (34%), in 1 patient synchronous and in 9 metachronous. The mean time from the diagnosis of HD to the development of breast cancer was 18.7 years. The interval to developing contralateral breast cancer ranged from 12 to 34 months, with a mean of 23 months (in 5 patients with metachronous tumors for whom data were available). The lateral or central aspects of the breast were more likely to be involved (in 15 of 17 patients for whom data were available). The most common histology of breast cancer was invasive ductal carcinoma. One patient was found to have an inflammatory carcinoma. Specific information regarding estrogen/progesterone receptor, HER2, BRCA1 or BRCA2 status of the tumors was not known. Tumor size was reported in 17 patients: six patients had tumors greater than 2 cm, including one that was greater than 5 cm.

Survival

Of the patients with breast cancer, 3 patients died. In 2 cases death was caused by breast cancer complications; in the third case information on the cause of death was not available.

Among patients without breast cancer, 79 (21.4%) died. Patients with breast cancer had a significantly better survival rate than patients who did not develop breast cancer (Fig. 2).

DISCUSSION

In this study, women treated for pediatric HD had a 37-fold increased risk for the development of breast cancer compared with women in the general population. The Late Effects Study Group followed 1,380 children treated for HD and reported that breast cancer was the most common solid tumor (SIR 75.3, 95% CI, 44.9–118.4) with an estimated actuarial incidence approaching 35% in women (95% CI, 17.4–52.6) by 40 years of age (6). An updated report from the same group reported an SIR of 55.5 (95% CI, 39.5–75.9) (31). Two other studies (8, 34) of survivors of childhood HD have reported relative risk estimates of 16.9 and 26.2. The risk estimate from our study is consistent with this range of risk estimates obtained in other studies.

Association with HD stage at diagnosis

We found a strong association between stage of HD at diagnosis and development of breast cancer, possibly related to the difference in radiation dose for patients with early vs. advanced stage disease. Patients with early-stage HD were significantly more likely to have been treated with radiation alone and to have received a higher mantle dose than patients with advanced stage HD. However, the difference in mean mantle radiation dose (36.4 Gy for early-stage vs. 30.2 Gy for advanced-stage disease) was slight, which would suggest an unexpectedly steep dose–response relationship between radiation dose and the occurrence of breast cancer. Too few patients received either no or low-dose radiation to enable us to investigate the independent or confounding effect of radiation and stage of disease. Alternate explanations for the difference in risk according to stage relate to a protective effect of chemotherapy in the advanced-stage cancer patients or to biologic predispositions linked with stage.

Association with radiation dose

Our study suggests an association of radiation dose with breast cancer, though this is qualified by the longer follow-up of patients treated with higher radiation doses. An increased risk of breast cancer associated with radiation has been reported in other studies, including radiation from atom bomb detonation, multiple X-rays, and radiation exposure for benign causes (19–23). A recent cancer registry-based study of breast cancer among females treated for HD during adolescence or young adulthood reported that the cumulative absolute risk of breast cancer increased with radiation dose among patients who had received alkylator therapy as well as those who had not received alkylators (42). In contrast, a recent study of breast cancers after radiation therapy for all childhood cancers did not find a significant association between radiation dose and subsequent breast cancer, suggesting that the increased risk of breast cancer after HD may indicate a specific susceptibility for developing breast cancer, or a particular susceptibility to radiation and/or chemotherapy, or both (24). Interestingly, our multivariate analysis revealed an independent effect of stage on risk even after adjustment for mantle radiation dose. Numerous genetic risk factors such as BRCA 1 and 2 have been identified to distinguish individuals genetically predisposed to develop breast cancer (25). Further investigation is necessary to determine whether patients with early-stage disease are biologically different from the general population and those with advanced-stage HD. A cancer susceptibility gene may render them at a greater risk for subsequent malignancy or may potentiate the mutagenic effects of radiation and/or chemotherapy used to cure the primary malignancy. Limited studies of predominantly adult cohorts with secondary breast cancer have not disclosed a relationship with previously

identified breast cancer–predisposing genetic mutations such as TP-53, BRCA1, BRCA2, and ATM (26–28).

Association with age at treatment

Age greater than 12 years at the time of diagnosis was also an independent predictor of increased risk of breast cancer. It has been hypothesized that proliferating breast tissue at adolescence is more susceptible to malignant transformation from exposure to radiation. Several studies have reported an increased risk of subsequent breast cancer among women treated for HD during adolescence or young adulthood and among survivors of atom bomb exposure (6, 9, 22, 23, 29, 30); however other studies have reached differing conclusions (7, 31).

Association with pelvic irradiation and alkylator chemotherapy

Of note in this study, radiation to the pelvis conferred a protective effect against breast cancer. Several studies of patients treated for HD have reported that chemotherapy, radiation to the ovaries (>5 Gy), and/or premature menopause are factors associated with a reduction in risk of breast cancer (14, 16, 43). In recent years, many risk factors for breast cancer in the general population have been discovered pertaining to exposure to estrogen, such as younger age at menarche, older age at menopause, nulliparity, older age at first live birth, and postmenopausal hormone replacement therapy. The finding that pelvic radiation has a protective effect against breast cancer suggests that the influence of estrogen on the risk of breast cancer in this population may be similar to that seen in the general population.

Similarly, in some recent studies, alkylators have been shown to confer a protective effect on the risk of breast cancer, presumably also by affecting ovarian function (16). In contrast, alkylators were not found to have a protective effect on the risk of breast cancer in the Childhood Cancer Survivor Study (CCSS) cohort (32). We found no significant association between alkylator dose and subsequent breast cancer. This may be because the doses of alkylators used in the study population were not large enough to cause ovarian damage, and children may be more resistant than adults to such effects. Alternately, the range of alkylator doses may have been too narrow to show a difference in risk of breast cancer.

Interval to development of breast cancer

In this study, the mean time to the development of breast cancer was 18.7 years. The mean follow-up time was shorter at 16.9 years. It is likely that additional patients would be diagnosed with breast cancer with continued follow-up. The cumulative incidence of breast cancer continued to rise beyond 20 years in this study. This is consistent with findings from other studies. A large international cancer registry-based study also reported that the elevated risk of breast cancer persisted for more than 25 years after the diagnosis of HD (1). The Late Effects Study Group reported that the cumulative incidence of breast cancer was 16.9% at 30 years of follow-up with a relative risk of 24.5 (95% CI, 4.9–71.6) among women followed for over 29 years. Travis *et al.* reported that, for a woman treated at the age of 25 years with radiation and without alkylators, the cumulative incidence estimates of breast cancer by age 35, 45, and 55 years were 1.4% (0.9–2.1%), 11.1 (7.4–16.3%), and 29% (20.2–40.1%) respectively(42).

Screening for breast cancer

The minimal interval to secondary breast cancer in our study was 9 years after the diagnosis of HD. The median age of patients at the time of diagnosis of breast cancer was 31.4 years, indicating that breast cancer occurs at a younger age in women treated for HD than in the general population. Therefore, screening for breast cancer in women treated for HD should

be initiated at an earlier age than in the general population. As the shortest time to diagnosis of breast cancer was 9 years after the diagnosis of HD in this study, we recommend the initiation of screening programs by this interval after the diagnosis of HD. In addition to physical examination and mammography, patients should be encouraged to perform breast self-examination at an early age. Recently MRI has been reported as a more sensitive screening test than mammography in women with a familial or genetic predisposition for breast cancer (33, 40), and it may be beneficial particularly in young women with dense breast tissue. Evaluation of alternative imaging techniques in women with HD also may prove beneficial. The approach to prevention, including the role of preventive drugs such as tamoxifen, as well as surgical options such as prophylactic mastectomy, needs to be further defined. Data regarding the use of these approaches in this population of high-risk patients are currently not available.

Development of bilateral breast cancer

Of the women in our cohort who developed breast cancer, 10 women (34%) developed bilateral breast cancer. Various studies have reported rates of bilateral breast cancer ranging from 9% to 29% among patients treated for HD (6, 34, 35). In the general population, the incidence of simultaneous bilateral breast cancer is reportedly 3% (36), whereas the risk of contralateral breast cancer is <1% per year in women (37). Women with a family history of breast cancer are reported to have a 35% risk of contralateral breast cancer by age 16 years (38). In women who are BRCA1 and BRCA2 carriers, the contralateral breast cancer risk is 20% to 31%, and 12% at 5 years, respectively (15, 39, 41). Thus, similar to women with other predisposing factors for breast cancer, survivors of pediatric HD have a high risk of developing bilateral disease. They are also likely to develop bilateral disease in a shorter time than the general population.

CONCLUSION

Current treatment protocols for HD use lower doses and smaller fields of radiation as compared with the treatment received by the women in this study. Follow-up studies on these recently treated patients are awaited to determine whether the reduction in exposure to radiation has led to the decrease in the incidence of secondary breast cancer, and also whether there has been a concomitant increase in the incidence of other adverse effects related to therapy such as secondary leukemias. Given the long latency period of these complications, it may take several years before a definitive conclusion can be reached.

In summary, women who are survivors of pediatric HD have a significantly increased risk of subsequent breast cancer compared with the general population and are at a high risk of developing bilateral disease within a short interval. We report the association of early-stage HD, high radiation dose, and age >12 years at diagnosis of HD with this risk. Combined modality treatment using lower doses of radiation than those used previously, and tailoring radiotherapy to eliminate as much breast tissue as possible from the radiation field may reduce this risk. Screening programs to detect breast cancer should be initiated within 9 years after HD. Known predisposing factors such as estrogen therapy or hormone replacement should be avoided. The role of chemoprevention (before the development of breast cancer or after the diagnosis of unilateral disease) to decrease the risk of contralateral tumor merits further investigation. Additional studies are also necessary to determine whether patients with early-stage HD are biologically different and therefore predisposed to develop breast cancer.

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Fig. 1. Cumulative incidence of breast cancer among patients treated for pediatric Hodgkin's disease. The cumulative incidence of breast cancer was 25% by 30 years after diagnosis of Hodgkin's disease.

Fig. 2. Survival curves of women in the cohort who developed breast cancer compared with the overall female cohort.

Table 1

Characteristics of the study population

Characteristic	Developed breast cancer		Did not develop breast cancer		p-Value
	n	%	n	%	
No. of patients	29	7.3	369	92.7	
Stage of HD					
I	7	24.1	43	11.7	<0.0001
II	21	72.4	182	49.3	
III	1	3.5	98	26.6	
IV	0	0.0	46	12.5	
Splenectomy					
Yes	21	72.4	248	67.4	NS
No	8	27.6	120	32.6	
Relapse					
Yes	8	27.6	80	21.7	NS
No	21	72.4	289	78.3	
Treatment for HD					
RT alone	18	62.1	156	42.3	NS
CT alone	3	10.3	34	9.2	
RT + CT	8	27.6	179	48.5	
Mantle RT					
Yes	28	96.6	317	85.9	NS
No	1	3.4	52	14.1	
Mantle RT dose					
35 Gy	25	86.2	223	60.6	0.0073
25-35 Gy	1	3.5	22	6.0	MH trend
<25 Gy	2	6.8	71	19.3	
None	1	3.5	52	14.1	
Pelvic radiation					
Yes	1	3.4	97	26.3	0.0032
No	28	96.6	272	73.7	
Mean age (y)					

Characteristic	Developed breast cancer		Did not develop breast cancer		p-Value
	n	%	n	%	
At HD diagnosis	15.0		14.5		NS
Range		8.9–18.4		1.3–18.9	
Mean follow-up (y)		23.7		16.3	<0.01
Range		14.9–36.2		0.7–37.4	

Abbreviations: CT = chemotherapy; HD = Hodgkin's disease; NS = not significant; RT = radiation therapy.

Table 2

Patient characteristics by stage of Hodgkin's disease

Variable	Stages I and II		Stages III and IV		p Value
	n	%	n	%	
No. of patients	253	63.6	145	36.4	
Treatment for HD					
RT alone	150	59.3	24	16.6	<0.0001
CT alone	13	5.1	24	16.6	
RT + CT	90	35.6	97	66.9	
Mantle RT					
Yes	227	89.7	118	81.4	0.0216
No	26	10.3	27	18.6	
Mantle RT dose *					
35 Gy	186	73.5	62	43.1	<0.0001
25-35 Gy	18	7.1	5	3.5	MH trend
<25 Gy	23	9.1	50	34.7	
None	26	10.3	27	18.7	

Abbreviations: CT = chemotherapy; HD = Hodgkin's disease; RT = radiation therapy.

* Stages I and II: mean dose, 36.4 Gy; Stages III and IV: mean dose, 30.2 Gy.