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Breast Cancer Risk Following Radiotherapy for Hodgkin Lymphoma: Modification by Other Risk Factors.

Running Head: Breast cancer following HL radiotherapy

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Abstract

The importance of genetic and other risk factors in the development of breast cancer after radiotherapy (RT) for Hodgkin lymphoma (HL) has not been determined. We analyzed data from a breast cancer case-control study (105 cases, 266 controls) conducted among 3,817 survivors of HL diagnosed at $\leq$ age 30 years in six population-based cancer registries. Odds ratios (OR) and excess relative risks (ERR) were calculated using conditional regression. Women who received RT exposure ($\geq$ 5 Gray (Gy) radiation dose to the breast) had a 2.7-fold increased breast cancer risk (95% confidence interval (CI) 1.4-5.2), compared with those given < 5 Gy. RT exposure ($\geq$ 5 Gy) was associated with an OR of 0.8 (95% CI, 0.2-3.4) among women with a first- or second-degree family history of breast or ovarian cancer, and 5.8 (95% CI, 2.1-16.3) among all other women (interaction p-value=.03). History of a live birth appeared to increase the breast cancer risk associated with RT among women not treated with ovarian-damaging therapies. Breast cancer risk following RT varied little according to other factors. The additional increased relative risk of breast cancer after RT for HL is unlikely to be larger among women with a family history of breast or ovarian cancer than among other women.

Introduction

Young women (age $\leq$ 30 years) treated with chest radiotherapy for Hodgkin lymphoma (HL) have among the highest breast cancer incidence rates of any population, outside familial cancer syndromes. Compared with the general population, breast cancer risks have been 4 - 56-fold elevated in treated women.[1,2] In a recent international case-control study[3], young women who received a radiation dose $\geq$ 4 gray (Gy) to the area of the breast in which cancer developed had a 2 – 8-fold increased risk, compared with women who received lower doses. Similar findings were reported in a Dutch investigation of women treated for HL at age $\leq$ 40 years,[4] nearly 80% of whom were included in the international study. Yet, many young women who receive chest radiation doses up to 60 Gy do not develop breast cancer, suggesting that endogenous or exogenous exposures mitigate risk. In other radiation-exposed populations, factors that have influenced breast cancer relative risk, for a given dose, include age at exposure and attained (current) age, with the highest relative risks for both evident at the youngest ages.[5,6] Relative risk rarely has been elevated among women exposed after age 50 years [5-8], a possible surrogate for menopause.

Women who develop de novo breast cancer before age 50 years or before menopause have a risk factor profile that differs somewhat from that of women diagnosed at older ages or after menopause.[9,10] A family history of breast cancer and a benign breast disease diagnosis are generally stronger risk factors for breast cancer in younger (< age 50 years) than in older women .[11, 12] In addition, reproductive factors such as age at first full-term pregnancy and number of live births commonly have a relatively minor effect on breast cancer risk at young ages, while they are established risk factors for older-onset cancer.[13] Compared to nulliparous women, parous women are likely to have an increased risk at young ages, possibly concentrated within 3-10 years of pregnancy, and a reduced risk at older ages.[13-16] Similarly, women in the lowest quartile of body mass index generally have an increased risk of breast cancer before age 50, compared with heavier women, but a reduced risk thereafter.[17] The consistency of such findings has led to the consideration of pre- and postmenopausal breast cancer as diseases with distinct etiologies.

In several investigations, these and other established risk factors for breast cancer have been examined as possible modifiers of risk among women exposed to radiation.[18-21] Although none emerged as strong or consistent risk modifiers, identification may have been hampered by small numbers of cases, or by inclusion primarily of women who were either post-menopausal or long-term breast cancer survivors.

In this investigation, we examined whether breast cancer risk factors might modify risk among a group of young women ($\leq$ age 30 years) who received radiation to the breast during HL treatment.

Methods

A detailed description of the study methods has been published [3].General population features are summarized in Table 1. A cohort of 3,817 female one-year survivors of Hodgkin lymphoma (HL), diagnosed at age ≤ 30 years between January 1, 1965 and December 31, 1994, was followed through September 30, 1999 in six population-based cancer registries (Iowa, Denmark, Finland, Sweden, Ontario, and four affiliated tumor registries in the Netherlands: The Netherlands Cancer Institute, the Dr. Daniel den Hoed Cancer Center, Leiden University Medical Center, Catharina Hospital Eindhoven). Record linkage methods were used to identify 105 cohort members diagnosed with primary breast cancer. At least two controls for each confirmed case were selected by stratified random sampling, matching on registry, age at HL diagnosis (± 3 years), calendar year of HL diagnosis (± 5 years), and survival after HL for at least as long as the breast cancer case, resulting in a total of 266 matched controls. The median age at HL diagnosis was 22 years (range 13-30 years) (Table 1), and the median age at breast cancer diagnosis was 41 years (range 27-57 years). The study was exempted from review by the NCI Institutional Review Board because it used only existing and anonymized data.

For all patients, detailed data regarding HL treatment were used to estimate radiation dose to the area of the breast in which cancer developed and the comparable area in controls. In our previously published findings[3], breast cancer risk increased with radiation dose, with risk elevated 8-fold among women who received a breast dose of > 40 Gy. Women treated with alkylating agent chemotherapy (35% of breast cancer cases, 50% of controls) experienced a 40% reduction in breast cancer risk, and risk was reduced 60% among women who received a radiation dose of $\geq$ 5 Gy to the ovaries (6% of cases, 15% of controls). Radiation doses < 5 Gy to the ovaries were not associated with breast cancer risk.

Breast cancer risk factors were collected primarily using a structured data collection instrument to abstract medical records, and at a few sites, self-administered interviews[4] or linkage to national cancer registries (to obtain family cancer history) were also utilized (Denmark, Finland). Each control was assigned a cutoff date, analogous to the breast cancer diagnosis date in the matched case, and only information on experiences prior to the cutoff date was included. To determine whether the results were sensitive to data collection methods, we conducted analyses in which data from each participating registry were consecutively excluded.

Conditional regression was utilized to calculate odds ratios (OR) and 95% confidence intervals (CI) for the relationship between breast cancer risk factors, radiation dose to the breast, and breast cancer risk among the matched case-control sets. Cutpoints for categorical variables were selected in part to allow calculation of statistical interactions on a multiplicative scale, using medians or quartiles of control distributions when possible. Only 1 case and 10 controls were not treated with radiotherapy. Thus, to obtain a sufficient number of unexposed women in subgroups for interaction analyses, the reference group was defined as women who had received a < 5 Gy breast dose (23 cases, 95 controls) (previous cutpoint of < 4 Gy[3] did not allow interaction analyses). In some analyses, finite estimates of relative risk on a continuous dose scale could only be obtained using a modified dose variable that set doses < 5 Gy to 0. To evaluate interaction on a multiplicative scale, we fitted the model:

$$OR = \exp\left(\Sigma_j \alpha_j x_j + \beta_1 z_1 + \beta_2 z_2 + \gamma z_1 z_2\right)$$

where $\exp(\Sigma_j \alpha_j x_j)$ is the background risk, which may be adjusted for variables x_j, z_1 is an indicator variable for the breast cancer risk factor of interest; and z_2 denotes radiation dose. Departure from the multiplicative model was evaluated by testing whether γ (the "Interaction OR") = 0 ($\exp \gamma = 1.0$). Interaction was also evaluated on an additive relative risk scale by fitting the model:

$$OR = [\exp(\Sigma_j \alpha_j x_j)]\, [1 + \beta_1 z_1 + \beta_2 z_2 + \gamma\, z_1 z_2].$$

The parameter γ is known as the "relative excess risk attributable to interaction" (RERI), or the interaction contrast ratio (ICR),[22,23] and equals the relative excess risk in those with both risk factors (RR11-1) that remains after subtracting the relative excess risk for each individual factor in the absence of the other (RR01-1) and (RR10-1). An ICR =0 indicates an exactly additive relation between the two risk factors, while an ICR > 0 suggests a greater than additive effect, and an ICR < 0 implies a less than additive joint effect. We also calculated $\gamma^* = (\beta_2 + \gamma)/ \beta_2$, which is the ratio of RT-related excess relative risks (ERR) when the risk factor is present compared with when it is absent. Although this case-control study cannot directly evaluate absolute risks, the ratio of the ERRs for those with and without the factor of interest expressed relative to a common baseline should be pertinent to this comparison. Multiplicative models were examined using SAS software version 8 (SAS Institute, Inc., Cary, NC), and additive relative risk models using the Pecan module of the software package EPICURE (HiroSoft International Corp, Seattle, WA).

Analyses regarding ever having a live birth, age at first and number of births, timing of births in relation to HL or breast cancer diagnoses, or oral contraceptive use were limited to women who did not receive HL treatment with alkylating agents (AA) and who received < 5 Gy radiation dose to the ovaries, as those treatments can alter ovarian function[24], induce menopause, influence childbearing, and also reduce breast cancer risk.[3,4,25]

Factors considered as potential confounders in the analysis included age at menarche, body mass index at HL diagnosis, age at menopause, menopausal status, ever having a live birth, age at first and number of live births, timing of live births in relation to diagnosis of HL or breast cancer, first or second degree family history of breast or ovarian cancer, and oral contraceptive use. Analyses were adjusted for HL treatment, including breast radiation dose, number of cycles of AA, and radiation dose of $\geq$ 5 Gy to the ovaries, except as noted.

Results

Women with a first- and/or second-degree family history of breast or ovarian cancer had a 2.5-fold increased breast cancer risk (95% CI, 1.2-5.3), compared to those without such history (Table 2). Differences between cases and controls with regard to other breast cancer risk factors generally resembled those identified in previous studies of premenopausal women (Table 2). Breast cancer risk was reduced among women who received AA chemotherapy or radiation $\geq$ 5 Gy to the ovaries, which may induce early menopause,[3,26] and the lower risk among exposed women who were postmenopausal at study end should be interpreted in that context. Since cancer treatment may affect fertility in HL patients, only women who did not receive AA or radiation $\geq$ 5 Gy to the ovaries (n= 68 cases, 125 controls) were included in analyses regarding reproductive factors or oral contraceptive use. These factors, however, had little influence on breast cancer excesses.

Overall, women who received a breast radiation dose of $\geq$ 5 Gy had a 2.7-fold increased breast cancer risk, relative to women who received lower doses (Table 2). For most risk factors in Table 2, there was no statistically significant interaction between the risk factor and radiation in relation to breast cancer risk, in either multiplicative or additive RR models (data not shown). However, the effect of a $\geq$ 5 Gy breast radiation dose on risk differed between women with a first- or second-degree family history of breast or ovarian cancer (OR= 0.8, 95% CI 0.2-3.4), and those without a family history (corresponding OR 5.8, 95% CI 2.1-16.3); (Interaction OR= 0.1; 95% CI 0.03-0.8; interaction p-value=.03) (Table 3). To assess whether the cutpoint at 5 Gy influenced this finding, risk modification by radiation dose also was analyzed on a continuous scale (Gy). Women who reported a first- or second-degree relative with breast or ovarian cancer also had a lower odds ratio estimate per increasing unit of breast dose (Gy) than women without such history (Interaction OR=0.93 per Gy; 95% CI 0.89-0.99; interaction p-value= .005). The lower odds ratio persisted when breast or ovarian cancer family history was confined to first-degree relatives (interaction p-value =.005), and when examined only among study sites that used cancer registry data or interviews to ascertain family history (interaction p-value= .04). The interaction did not change substantially when data from any of the six participating cancer registries were omitted.

Since the nature of the relationship between radiation, other risk factors, and breast cancer risk has not been characterized in HL patients, additive relative risk models incorporating family history were also evaluated. The joint effects of family history (first or second degree) and radiation dose were somewhat less than would be expected from adding the two risk factors, for either a dose cutpoint of $\geq$ 5 Gy or radiation dose on a continuous scale (Gy), although neither interaction was significant. However, when family history was defined to include only first-degree relatives, the ERR added with each Gy (above 5 Gy) was -.16 (95% CI, -.40 - +.23) among women with a family history, and +.17 (95% CI, .05-.51) among women without such history (ICR -.33; 95% CI, < -.33 - +.03) (additive interaction p value = .07), suggesting a joint effect that might be less than adding the two risk factors, and a possible difference in dose-response between the two groups. The ratio of these ERRs (γ*) was –0.9 (95% CI, < –0.9 - +1.2), that is, the absolute excess risk in women with a family history was estimated to be smaller and unlikely to exceed by more than a factor of 1.2 the absolute excess risk in women without such history. Thus, the additive and multiplicative RR models were generally consistent in suggesting that the relative risk associated with radiation exposure was not higher among women with a family history than among other women, and might be lower.

In addition to family history, breast cancer relative risk following radiation exposure also appeared to differ somewhat by parity status. Among women who had experienced a live birth, those who received a breast radiation dose $\geq$ 5 Gy had a 3.5-fold elevated breast cancer risk (95% CI, 1.4-8.9), compared to women who received lower doses, while among women who had not had a live birth, the corresponding OR was 1.1 (95% CI, 0.3-4.7) (Interaction OR 3.1; 95% CI, 0.6-17.2; interaction p-value= .20) (Table 4). In an analysis examining breast radiation dose on a continuous scale, women who had experienced a live birth had a greater increase in breast cancer relative risk with increasing radiation dose than women who had not (Interaction OR 1.06; 95% CI, 1.01-1.12; interaction p-value= .04). This finding is unlikely to be explained by altered ovarian function due to treatment because women who received AA or ovarian doses $\geq$ 5 Gy were excluded from these analyses. We examined whether ovarian doses < 5 Gy could have altered ovarian function among included women, possibly accounting for the findings. Breast cancer risk was not reduced among women who received ovarian doses of 0.2-0.92 Gy or 0.93-4.99 Gy (tertiles) compared with those who received ovarian doses < 0.2 Gy. In addition, the interaction between a live birth and breast radiation dose (Gy) persisted even among women who received ovarian radiation doses < 1 Gy (63% of cases, 65% of controls) (data not shown). The interaction was not altered when data were excluded from any contributing cancer registry except the Netherlands (largest contributor): among remaining registries the statistical power was lower, and the relationship was similar in direction and magnitude, but no longer significant. In additive RR models, the effect on risk of a breast radiation dose $\geq$ 5 Gy or per Gy (continuous dose variable) did not differ among women who had a live birth vs. those who had not (additive interaction p-value = .31, .20, respectively).

Among women who had a live birth before HL diagnosis, breast cancer risk was not influenced by the relative timing of most recent birth in relation to HL diagnosis (Table 5). Women whose most recent live birth after HL diagnosis was within 60 months (control median) had a 2.6-fold elevated breast cancer risk, relative to those whose most recent birth occurred at a longer interval (who thus were also fertile after HL treatment). The timing of live births in relation to breast cancer diagnosis/study cutoff date had no appreciable influence on breast cancer risk.

Discussion

No previous study to date has examined the influence of breast cancer risk factors and radiation dose in relation to breast cancer risk among young women treated for HL. Extensive efforts were made to estimate radiation dose to the area where the breast tumor occurred, and that received by the ovaries, and to collect details regarding cytotoxic drug treatment. Information regarding factors that might modify breast cancer risk in young women is important, as the cumulative incidence may approach 20% by age 45 years among women treated before age 17 years.[2]

Our data suggest that among women with a first or second-degree family history of breast or ovarian cancer, the additional increase in relative risk of breast cancer with increasing radiation dose probably does not exceed that of women without such history, and it may be lower. The combined effect of family history and breast radiation dose (on a categorical ($\geq$ 5 Gy) or continuous (Gy) scale) was less than that expected from multiplying the two risk factors, thus we were able to reject a multiplicative model in favor of a sub-multiplicative model. In additive RR models, the combined effects were in the direction of less than additive. While information regarding breast or ovarian cancer family history may have been more completely ascertained among breast cancer cases than controls, misclassification that differs by case-control status, when assessing an interaction, usually biases the interaction risk estimate towards the null (OR =1.0),[27] and is unlikely to account for the observations. Our findings also are supported by the persistence of altered breast cancer risk among women from sites that collected information from cancer registries or questionnaires, and among women with a first-degree family history only.

Some evidence supports the possibility that women with a family history of breast or ovarian cancer may have an altered response to radiation. Family history frequently reflects the effect of rare, highly penetrant alterations in genes such as BRCA1, BRCA2, tp53, and PTEN.[28] After 1-10 Gy radiation, cell lines deficient in BRCA1 or BRCA2 have demonstrated widespread cell death and a reduced capacity to repair DNA damage,[29,30] suggesting that in mutation carriers, unrepaired damaged cells might undergo cell death rather than serve as cancer-initiating cells. In our study, the area of the breast where the tumor occurred received a median dose of 24.8 Gy (median 20.2 Gy to comparable area in controls), a dose likely to induce cell death in a substantial proportion of radiosensitive cells. The prevalence of BRCA1 or BRCA2 mutation carriers,[31, 32] however, is too low to account entirely for our findings. BRCA1, BRCA2 and the putative breast cancer susceptibility gene mutated in ataxia telangiectasia (ATM) interact in the cellular response to radiation-induced DNA damage.[33, 34] Individuals diagnosed with AT,[35] and heterozygous carriers of ATM missense variants [36, 37] may have an increased HL risk, and may be over-represented in our population. In one study, HL survivors who carried ATM missense alterations were less likely to develop breast cancer following RT than noncarriers,[36] suggesting a possible differential effect of treatment, while ATM truncating mutations have not been identified among HL survivors who developed breast cancer.[38,39]

Our data also suggest that the dose-response relationship between breast radiation exposure and subsequent cancer risk may be stronger, on a multiplicative but not an additive RR scale, among young women who ever had a live birth. Women who received therapies associated with ovarian damage were excluded from this analysis, and we did not find indirect evidence of diminished fertility among included women. In animal experiments, mammary tumor incidence has been considerably higher among rats irradiated with 2.6 Gy while pregnant (92%) or lactating (90-96%) than among virgin animals (26-33%).[40-42] Increased production of prolactin during pregnancy and lactation has been implicated as one factor promoting mammary carcinogenesis: in another investigation, the incidence of mammary tumors in rats was 2% after low-dose irradiation alone, 41.6% if a prolactin-secreting pituitary transplant was given shortly afterwards, and 24% if the prolactin-secreting transplant was given 12 months after irradiation.[43] In some[13-16] but not all[44, 45] epidemiologic studies, premenopausal breast cancer risk has been increased among parous women or specifically among women who gave birth within the previous 3-10 years, consistent with the possible growth-promoting effects of elevated gestational hormones. In the Nurses' Health Study, the increased risk among parous women seems to persist for at least 20-30 years following a first pregnancy.[13] In our study, parous women who delivered infants within 60 months after HL had a further increased risk relative to other parous women. Although a critical post-exposure period has not been identified, the hormonal milieu in the years following radiation exposure appears to act as a primary breast cancer determinant: women exposed after age 40-49 years do not have an increased risk[5,7-8], and younger women who also receive therapies that decrease ovarian function or induce menopause have a reduced risk.[25,26]

Our results should be considered in light of the study strengths and limitations. Breast cancer risk factor information was collected primarily from medical records, thus case data were missing less often than control data, although any misclassification should bias the interaction OR estimate towards the null (1.0).[27] Even though these analyses were conducted within the largest study to date of breast cancer following HL, sample sizes in various subgroups were small, limiting statistical power to detect differences in stratum-specific odds ratios. Given the unknown nature of the interaction between therapeutic doses of radiation and breast cancer risk factors, we tested for joint effects on more than one statistical scale, which may increase the probability of false positive findings.[46] In addition, doses much lower than 5 Gy have been associated with increased breast cancer risk, [6,47,48] and interaction estimates should be attenuated with inclusion of such exposure in the reference group, thus interaction also was examined with RT dose on a continuous scale.

Women included in our study received very high radiation doses to the breast, thus our results, if verified in similar populations, may not be generalizable to those who receive lower doses. Smaller radiotherapy fields and doses are used in current HL treatment protocols, and some AAs (i.e., mechlorethamine) that affect fertility are now administered infrequently, and the effects of these newer treatment strategies have not been evaluated. Our results suggest that the additional increase in breast cancer relative risk after radiotherapy for HL is unlikely to be larger among women with a family history of breast or ovarian cancer than among other women. Consideration of breast cancer risk factors may offer insights regarding the increased breast cancer risk following radiotherapy for HL, and perhaps holds promise for identification of subgroups with altered susceptibility, and subsequent application of risk-adapted therapy.

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Table 1. Characteristics of women diagnosed with Hodgkin Lymphoma (HL) at age 30 years or younger who developed breast cancer, and matched controls.

	Cases (n = 105)		Matched Controls (n = 266)	
	No.	%	No.	%
Cancer registry				
Denmark	15	14.3	29	10.9
Finland	10	9.5	19	7.1
Iowa	4	3.8	8	3.0
Netherlands	40	38.1	138	51.9
Ontario	20	19.1	40	15.0
Sweden	16	15.2	32	12.0
Age at diagnosis of HL (yrs)				
13 - 21	50	47.6	120	45.2
22 - 30	55	52.4	146	54.8
Year of diagnosis of HL				
<1970	34	32.4	68	25.6
1970 - 79	61	58.1	165	62.0
1980 - 94	10	9.5	33	12.4

Table 1. Characteristics of women diagnosed with Hodgkin Lymphoma (HL) at age 30 years or younger who developed breast cancer, and matched controls (continued).

	Cases (n = 105)		Matched Controls (n = 266)	
	No.	%	No.	%
Age at diagnosis of breast cancer/ cutoff date in controls (years)				
27 - 41	58	55.2	139	52.3
42 - 57	47	44.8	127	47.7
Treatment for HL				
Radiation dose to specific breast location (Gy)				
0 – 4.9	23	21.9	95	35.7
5.0 – 23.0	23	21.9	47	17.7
23.1 – 37.1	29	27.6	63	23.7
37.2 – 61.3	30	28.6	61	22.9
Alkylating agent chemotherapy:				
No	68	64.8	132	49.6
Yes	37	35.2	134	50.4
Radiation dose to ovaries:				
< 5 Gy	98	93.3	226	85.0
$\geq$5 Gy	7	6.7	40	15.0

Table 1. Characteristics of women diagnosed with Hodgkin Lymphoma (HL) at age 30 years or younger who developed breast cancer, and matched controls (continued).

	Cases (n = 105)		Matched Controls (n = 266)	
	No.	%	No.	%
Interval to breast cancer (years)				NA
1 – 4	0	-		
5 – 14	31	29.6		
15 – 24	60	57.1		
≥25	14	13.3		

Abbreviations: HL, Hodgkin lymphoma; Gy, gray; NA, not applicable.

Table 2. Risk of breast cancer among women diagnosed with Hodgkin Lymphoma (HL) at age 30 years or younger according to treatment for HL and breast cancer risk factors

	Cases		Matched Controls		Odds ratio	
	No.	%	No.	%	(adjusted[1])	95% CI
Among all women: cases (n = 105) and matched controls (n = 266)						
Age at menarche (yrs)						
>12	43	41.0	106	39.8	1.0	
≤12	28	26.7	51	19.2	1.2	(0.7 to 2.3)
Unknown	34	32.3	109	41.0		
Body Mass Index (kg/m^2) at HL diagnosis[‡]						
<19.45	30	28.6	53	20.0	1.0	
19.5 – 21.1	14	13.3	52	19.5	0.5	(0.2 to 1.2)
21.2 – 23.3	17	16.2	51	19.2	0.5	(0.2 to 1.1)
≥ 23.4	14	13.3	52	19.5	0.4	(0.2 to 0.9)
Unknown	30	28.6	58	21.8		

Table 2. Risk of breast cancer among women diagnosed with Hodgkin Lymphoma (HL) at age 30 years or younger according to treatment for HL and breast cancer risk factors

	Cases		Matched Controls		Odds ratio	
	No.	%	No.	%	(adjusted[†])	95% CI
Among all women: cases (n = 105) and matched controls (n = 266)						
1st or 2nd degree relative with breast or ovarian cancer						
No	46	43.8	129	48.5	1.0	
Yes	28	26.7	28	10.5	2.5	(1.2 to 5.3)
Unknown	31	29.5	109	41.0	--	

Table 2. Risk of breast cancer among women diagnosed with Hodgkin Lymphoma (HL) at age 30 years or younger according to treatment for HL and breast cancer risk factors (continued)

	Cases		Matched Controls		Odds ratio	
	No.	%	No.	%	(adjusted†)	95% CI
Menopausal status at breast cancer diagnosis (cases) or study cutoff date (controls) §						
Pre/perimenopausal:						
No AA & radiation to ovaries < 5 Gy	51	72.9	86	64.7	1.0	(reference)
AA or radiation to ovaries ≥ 5 Gy	20	27.1	47	35.3	0.7	(0.3 to 1.5)
Postmenopausal:§						
No AA & radiation to ovaries < 5 Gy	11	52.0	13	15.3	1.0	(reference)
AA or radiation to ovaries ≥5 Gy	12	48.0	72	84.7	0.2	(0.1 to 1.3)
Unknown	11		48			

Table 2. Risk of breast cancer among women diagnosed with Hodgkin Lymphoma (HL) at age 30 years or younger according to treatment for HL and breast cancer risk factors (continued)

	Cases		Matched Controls		Odds ratio	
	No.	%	No.	%	(adjusted†)	95% CI
Among women who did not receive AA and who received RT to ovaries <5 Gy: cases (n = 68) and matched controls (n = 125)						
Ever live birth‡:						
No	17	25.0	29	23.2	1.0	
Yes	51	75.0	94	75.2	0.9	(0.4 to 1.9)
Unknown	0	0.0	2	1.6	--	
Age at first live birth‡ ¶ (yrs)						
≤22	15	22.1	27	21.6	1.0	
23-26	19	27.9	29	23.2	1.0	(0.5 to 2.2)
≥27	16	23.5	32	25.6	0.9	(0.4 to 2.2)
Unknown	1	1.5	8	6.4	--	
Nulliparous or no live births	17	25.0	29	23.2	--	

Table 2. Risk of breast cancer among women diagnosed with Hodgkin Lymphoma (HL) at age 30 years or younger according to treatment for HL and breast cancer risk factors (continued)

	Cases		Matched Controls		Odds ratio	
	No.	%	No.	%	(adjusted[†])	95% CI
Among women who did not receive AA and who received RT to ovaries <5 Gy: cases (n = 68) and matched controls (n = 125)						
No. of live births[‡ ¶ ^]						
1	14	20.6	20	16.0	1.0	
2	19	27.9	44	35.2	0.8	(0.3 to 2.4)
≥3	18	26.5	30	24.0	0.9	(0.3 to 2.5)
Unknown	0	0.0	2	1.6	--	
Nulliparous or no live births	17	25.0	29	23.2	--	
Timing of live births[‡^]						
All live births before HL	14	20.6	20	16.0	1.0	
All live births after HL	27	39.7	51	40.8	0.8	(0.3 to 2.1)
Live births before and after HL	10	14.7	18	14.4	0.7	(0.3 to 2.1)
Unknown	0	0.0	7	5.6	--	

Table 2. Risk of breast cancer among women diagnosed with Hodgkin Lymphoma (HL) at age 30 years or younger according to treatment for HL and breast cancer risk factors (continued).

	Cases		Matched Controls		Odds ratio	
	No.	%	No.	%	(adjusted†)	95% CI
Among women who did not receive AA and who received RT to ovaries <5 Gy: cases (n = 68) and matched controls (n = 125)						
Timing of live births‡^ (cont)						
Nulliparous or no live births	17	25.0	29	23.2	--	
Oral contraceptive use‡						
Never	20	29.4	29	23.2	1.0	
Ever	37	54.4	77	61.6	1.0	(0.5 to 2.2)
1-6 years	9	13.2	29	23.2	0.9	(0.3 to 2.4)
≥ 7 years	20	29.4	28	22.4	1.9	(0.7 to 5.0)
Duration unknown	8	11.8	20	16.0		
Unknown	11	16.2	19	15.2		

Table 2. Risk of breast cancer among women diagnosed with Hodgkin Lymphoma (HL) at age 30 years or younger according to treatment for HL and breast cancer risk factors (continued).

	Cases		Matched Controls		Odds ratio	
	No.	%	No.	%	(adjusted†)	95% CI
Treatment for HL among all women: cases (n = 105) and matched controls (n = 266)						
Radiation dose to specific breast location (Gy)						
0 – 4.9	23	21.9	95	35.7	1.0	
5.0 – 61.3	82	78.1	171	64.3	2.7	(1.4 to 5.2)
Risk per Gy					*1.04*	*(1.0 to 1.07)*

Abbreviations: HL, Hodgkin lymphoma; CI, confidence interval, AA, alkylating agents, RT, radiotherapy; Gy, gray

† All risk factor analyses were adjusted for breast radiation dose, ovarian radiation dose, and number of cycles of AA chemotherapy. Women who had an unknown radiation dose to the breast (1 case, 7 controls) or an unknown radiation dose to the ovaries (4 controls) were assigned the median dose in controls, 23.0 Gy or 0.44 Gy, respectively.

‡ Pre-and postmenopausal women did not differ in breast cancer risk according to body mass index (measured at the time of HL diagnosis), thus only combined results are presented. p=.02 for trend in risk by quartile of body mass index; p = .01 for trend in risk by body mass index on a continuous scale.

§ Adjusted for breast radiation dose only. Treatment with AA chemotherapy or receiving a dose to the ovary $\geq$ 5 Gy can induce menopause; odds ratios presented separately for those that received such treatment to illustrate the need to exclude these women from selected analyses. When adjusted only for breast radiation dose, all postmenopausal women combined had a reduced breast cancer risk (OR 0.3; 95% CI 0.2-0.7), relative to pre/perimenopausal women.

‡ As treatment with AA chemotherapy or receiving a dose to the ovary $\geq$ 5 Gy could potentially influence the timing and number of children by reducing fertility, women who received these treatments (n =37 cases, 141 controls) were considered unexposed in these analyses and placed in a separate category by an indicator variable.

¶ Among women who had experienced a live birth only.

^ Analyses regarding age at first live birth were adjusted for number of live births (1, 2, $\geq$3) and analyses regarding number of live births and timing of live births were adjusted for age at first live birth ($\leq$ 22, 23-26, $\geq$ 27).

Table 3. Risk of breast cancer among women diagnosed with Hodgkin Lymphoma (HL) at age 30 years or younger according to radiotherapy and family history of breast/ovarian cancer in 1st or 2nd degree relatives.

Characteristic	Exposure	Cases		Controls		Adjusted		Effect ≥5 Gy			
		No.	%	No.	%	OR[†]	95% CI	OR	95% CI	OR	95% CI
All women: cases (n=105) and matched controls (n=266): [‡]											
FH[*]	RT >5 Gy							No FH*:		Positive FH*:	
No	No	8	7.6	53	19.9	1.0	(reference)	1.0	(reference)		
No	Yes	38	36.2	76	28.6	5.8	(2.1 to 16.3)	5.8	(2.1 to 16.3)		
Yes	No	8	7.6	7	2.6	11.5	(2.5 to 52.6)			1.0	(reference)
Yes	Yes	20	19.0	21	7.9	9.5	(3.0 to 30.1) [§]			0.8	(0.2 to 3.4)
Unknown		31	29.5	109	41.0						

Abbreviations: HL, Hodgkin lymphoma; FH, family history; OR, odds ratio; CI, confidence interval; AA, alkylating agents; RT, radiotherapy; Gy, gray.

* History of breast and/or ovarian cancer in a first or second degree relative.

† Analyses were adjusted for ovarian radiation dose, and number of cycles of AA chemotherapy.

‡ Women who had an unknown breast radiation dose (n=1 case; 7 controls) or an unknown ovarian dose (n=4 controls) were assigned the median dose in controls (2300 cGy, 44.5 cGy, respectively) in these analyses.

§ Interaction OR (multiplicative scale):

Interaction OR (multiplicative scale):	OR (95% CI)
Interaction OR: breast dose of 5 Gy or more and 1st or 2nd degree family history:	0.14 (0.03 to 0.81)
Interaction OR: breast dose on a continuous scale (Gy) and 1st or 2nd degree family history:	0.93 (0.89 to 0.99)
Interaction OR: breast dose on a continuous scale (Gy) and 1st degree family history (14 cases, 15 controls):	0.91 (0.85 to 0.98)

Interaction Contrast Ratio (ICR)): (additive RR scale)	ICR (95% CI)
ICR: breast dose of 5 Gy or more and 1st or 2nd degree family history:	-6.8 (-52.4 to +7.8)
ICR: modified breast dose on a continuous scale (Gy) and 1st or 2nd degree family history:	-0.22 (-1.1 to +0.27)
ICR: modified breast dose on a continuous scale (Gy) and 1st degree family history	-0.33 (* to + .03)

* not estimated

Table 4. Risk of breast cancer among women diagnosed with Hodgkin Lymphoma (HL) at age 30 years or younger according to radiotherapy and history of a live birth.

Characteristic	Exposure	Cases		Controls		Adjusted		Effect ≥5 Gy			
		No.	%	No.	%	OR	95% CI	OR	95% CI	OR	95% CI
Among women who did not receive AA and who received RT to ovaries <5 Gy[‡ §]: cases (n=68) and matched controls (n=125):											
Live birth[¶]	RT >5 Gy							No live births:		Live births:	
No	No	5	7.4	7	5.6	1.0	(reference)	1.0	(reference)		
No	Yes	12	17.6	22	17.6	1.1	(0.3 to 4.7)	1.1	(0.3 to 4.7)		
Yes	No	10	14.7	39	31.2	0.4	(0.1 to 1.6)			1.0	(reference)
Yes	Yes	41	60.3	55	44.0	1.4	(0.4 to 4.8)^			3.5	(1.4 to 8.9)
Unknown		0		2	1.6						

Abbreviations: HL, Hodgkin lymphoma; OR, odds ratio; CI, confidence interval, AA, alkylating agents, RT, radiotherapy; Gy, gray

‡ Women who had an unknown breast radiation dose (n=1 case; 7 controls) or an unknown ovarian dose (n=4 controls) were assigned the median dose in controls (2300 cGy, 44.5 cGy, respectively) in these analyses.

§ As these treatments can induce menopause and influence the probability of having a live birth, exposed women were excluded from this analysis.

¶ Information regarding stillbirths, which are included in the definition of parity, was not collected for some women, thus only live births are included.

^ Interaction OR (multiplicative scale):	OR (95% CI)
Interaction OR: breast dose of 5 Gy or more and ever live birth :	3.1 (95% CI 0.6-17.2).
Interaction OR: breast dose on a continuous scale (Gy) and ever live birth:	1.06 (95% CI 1.01-1.12)

Interaction Contrast Ratio (ICR)): (additive RR scale)	ICR (95% CI)
ICR: breast dose of 5 Gy or more and ever live birth:	0.93 (-1.8 - +3.36)
ICR: breast dose on a continuous scale (Gy) and ever live birth:	0.05 (-.20 - +.22)

Table 5. Risk of breast cancer among women diagnosed with Hodgkin Lymphoma (HL) at age 30 years or younger who had a live birth, according to timing of live births.

	Cases		Matched controls		Odds ratio	
	No.	%	No.	%	(adjusted[†])	95% CI
Among women who did not receive AA or RT to ovaries ≥5 Gy, and also had ≥1 live birth: cases (n = 50) and matched controls (n = 96)[‡]						
Most recent live birth *preceding* HL: [‡]						
Live birth ≥16 mos.	13	54.2	16	43.2	1.0	
Live birth < 16 mos.	10	41.7	16	43.2	1.2	(0.4 to 3.4)
Unknown	1	4.1	5	13.6		

Table 5. Risk of breast cancer among women diagnosed with Hodgkin Lymphoma (HL) at age 30 years or younger who had a live birth, according to timing of live births (continued).

Characteristics	Cases No.	Cases %	Matched controls No.	Matched controls %	Odds ratio (adjusted†)	95% CI
Among women who did not receive AA and who received <5 Gy RT to ovaries, and also had ≥1 live birth: Cases (n = 50) and matched controls (n = 96)						
Most recent live birth *following* HL: ‡						
Live birth > 60 mos	10	27.0	33	44.6	1.0	
Live birth ≤ 60 mos	25	67.6	33	44.6	2.6	(1.0 to 6.7)
Unknown	2	5.4	8	10.8		

Table 5. Risk of breast cancer among women diagnosed with Hodgkin Lymphoma (HL) at age 30 years or younger according to timing of live births (continued)

Characteristics	Cases No.	Cases %	Matched controls No.	Matched controls %	Odds ratio (adjusted[†])	95% CI
Among women who did not receive AA and who received <5 Gy RT to ovaries, and had ≥ 1 live birth: Cases (n = 50) and matched controls (n = 96).						
Years elapsed between most recent live birth and breast cancer diagnosis /control cutoff date:						
≥20 yrs	11	22.0	20	20.8	1.0	
15-19 yrs	16	32.0	23	24.0	1.0	(0.3-3.6)
10-14 yrs	8	16.0	18	18.8	0.5	(0.1-2.8)
5-9 yrs	8	16.0	10	10.4	0.9	(0.2-4.4)
<5 yrs	6	12.0	13	13.5	0.6	(0.1-7.4)
Unknown parity or timing of most recent birth	1	2.0	12	12.5		

Abbreviations: HL, Hodgkins lymphoma; OR, odds ratio; CI, confidence interval, AA, alkylating agents, RT, radiotherapy.

† Analyses were adjusted for age at first live birth (: ≤22, 23-26, ≥ 27).

‡ Columns do not add to 50 cases and 96 controls because some women had a live birth both before and after HL, and are counted in both analyses, while others are counted only once.