Clinicopathologic features of breast cancers diagnosed in women treated with prior radiation therapy for Hodgkin lymphoma: Results from a population-based cohort

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BACKGROUND: Childhood and young adult survivors of Hodgkin lymphoma (HL) are at elevated risk of developing breast cancer, yet little data exist on the tumor characteristics that develop in this high-risk patient population. **METHODS:** The National Cancer Institute's Surveillance, Epidemiology, and End Results database was used to identify breast cancers diagnosed between 1990 and 2016 in women who had received prior radiation therapy for HL at age 30 years or younger. Clinicopathologic features of subsequent breast cancers (breast cancer after radiation therapy for HL [BC-HL]) were examined and compared with breast cancers diagnosed in women who had no prior malignancy (breast cancer with no prior malignancy [BC-NPM]). **RESULTS:** In total, 321 breast cancers were identified in 257 women who had a history of radiation therapy for HL. The median age at HL diagnosis was 22 years (interquartile range, 18-26 years), and nearly all patients in the BC-HL group (97.9%) were diagnosed ≥8 years after radiation therapy. Overall, 56 patients in the BC-HL group (21.8%) developed bilateral breast cancer. Compared with women who had BC-NPM, those who had BC-HL were younger (43 vs 60 years; $P < .001$) and were less likely to present with ductal carcinoma in situ (8.4% vs 14.9%; $P = .001$). On multivariable analysis that included adjustment for age, invasive BC-HL was associated with smaller (≤2 cm) tumor size (odds ratio, 1.64; 95% CI, 1.25-2.15) and upper outer quadrant tumors (odds ratio, 1.37; 95% CI, 1.04-1.81) compared with BC-NPM. In a subset analysis of 102 women who had HER2/*neu* status available, the distribution of biologic subtype was not significantly different between BC-HL and BC-NPM ($P = .16$). **CONCLUSIONS:** Breast cancers in women who previously received radiation therapy for HL are characterized by earlier onset disease, although most remain estrogen receptor-positive and have early stage disease at presentation. ***Cancer* 2021;0:1-8**. © *2021 American Cancer Society*.

LAY SUMMARY:

- Women who have had radiation therapy for Hodgkin lymphoma at a young age are at increased risk of developing early onset breast cancer; however, most of these breast cancers are sensitive to hormones (estrogen receptor-positive) and are diagnosed at early stages.
- Because these breast tumors are estrogen receptor-positive, medications that prevent breast cancer by blocking the effect of or lowering hormone levels (also termed *endocrine prevention*) may be useful in this group of high-risk women.

KEYWORDS: breast neoplasms, cancer epidemiology, Hodgkin lymphoma, radiation therapy.

INTRODUCTION

Childhood and young adult survivors of Hodgkin lymphoma (HL) are at an elevated risk of developing breast cancer.[1-3] This risk occurs secondary to exposure of the chest wall to radiation and corresponds to the risk levels seen in *BRCA1*/*BRCA2* carriers, with a cumulative incidence of breast cancer reaching 20% by age 40 years.[4-6] In HL survivors, the incidence of breast cancer appears to increase starting 8 years after the completion of radiation therapy. Consequently, guidelines recommend screening with bilateral breast magnetic resonance imaging (MRI) and mammography starting either at age 25 years or 8 years after radiation, whichever occurs later.[7-9]

Outside of high-risk surveillance, the optimal management approach for women with prior chest wall radiation exposure remains unclear.[10] Although early data suggest that the characteristics of breast cancers seen in young female HL survivors tend to be similar to the tumors in older women,[4] other studies suggest an increase in the proportion of bilateral[11] and estrogen receptor (ER)-negative breast cancers,[12-14] the latter of which tend to be more aggressive than their ER-positive counterparts. In a study from Elkin et al, 44% of breast cancers in HL survivors were ER-positive, whereas, in

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another study by Withrow et al, this proportion increased to 57%.[11,15]

To date, no large studies have comprehensively evaluated the biologic subtypes of breast cancer associated with a history of radiation in HL, largely because data on HER2/*neu* (HER2) status were not routinely collected before 2010.[16] Data on biologic subtype are important because they can advise whether chemotherapy may be required at the time of a breast cancer diagnosis and can help determine whether this patient population would benefit from endocrine prevention. Furthermore, although several studies have reported a reduction in breast cancer risk with prior chemotherapy exposure,[3,17] few studies have evaluated whether chemotherapy-induced ovarian insufficiency alters the biologic subtype of breast cancers that develop in women who have received radiation therapy for HL.

The objective of this study was to use a population-based cohort of HL survivors to characterize the clinicopathologic features of breast cancers diagnosed in women who received chest wall radiation before age 30 years, including an evaluation of biologic subtype in patients who had HER2 status available.

MATERIALS AND METHODS

Data Source and Cohort Selection

We used the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) treatment database, which is comprised of 18 population-based cancer registries covering a catchment area that includes 28% of the US population. The November 2019 SEER-18 submission was used for this study, which includes data on radiation treatment and chemotherapy receipt.[18] We included all female patients diagnosed between ages 10 and 30 years who had histologically confirmed HL between the years 1975 and 2012. All classic HL subtypes were included. Patients were included if they had exposure to radiation therapy, including *beam radiation*, *radiation not otherwise specified*, or *other radiation* (for historic cases). To exclude synchronous hematologic and breast malignancies, we restricted our cohort to those who had a histologically confirmed diagnosis of in situ or invasive breast cancer a minimum of 3 years after the diagnosis of HL. We subsequently excluded patients for whom histologic grade and pathologic stage of the breast cancer were not available.

Outcome of Interest

Our primary outcome of interest was the clinicopathologic features of subsequent breast cancers after radiation therapy for HL. *International Classification of Diseases for Oncology*, third edition, histologic type; histologic grade, pathologic size, and nodal status; American Joint Committee on Cancer stage; laterality; tumor location; and ER and HER2 status were obtained. For women diagnosed in January 2010 or later, biologic subtype was categorized as the following: ER-positive/HER2-negative, ER-positive/HER2-positive, ER-negative/HER2-positive, or ER-negative/HER2-negative (triple-negative breast cancer [TNBC]).

Statistical Methods

A case listing of the breast cancer after radiation therapy for HL (BC-HL) cohort was generated using the SEER*Stat 8.3.8 multiple primaries analysis function,[19] which was subsequently imported in ASCII format to SAS version 9.4 (SAS Institute, Inc) for analysis. An additional case listing of women who had a first diagnosis of breast cancer and no prior malignancy (BC-NPM) between 1990 and 2016 was obtained to serve as the control group. Demographic, clinicopathologic, and treatment-related comparisons between the 2 groups were performed using the Wilcoxon rank-sum test for continuous variables and the Pearson χ^2 test for categorical data. Multivariable analysis was then performed to identify which clinicopathologic factors were independently associated with prior radiation for HL, with age group, histologic grade, histology, tumor location, tumor size, nodal status, and ER status (ER-positive vs ER-negative) included as covariates in the model. Additional analysis was performed to determine biologic subtype in women who were diagnosed after 2010, when data on HER2 status were available. Subgroup analysis was then performed to compare the distribution of ER-positive breast cancers between patients with BC-HL who received chemotherapy for their HL versus those whose chemotherapy receipt was *none or unknown*. All statistical tests were carried out using SAS version 9.4; all statistical tests were 2-sided, and a P value of .05 was used to indicate statistical significance.

RESULTS

Cohort Characteristics

After applying the inclusion and exclusion criteria, we identified 321 breast cancers diagnosed in 257 women who had a history of radiation therapy for HL. The median age at HL diagnosis was 22 years (interquartile range, 18-26 years), and the median time to diagnosis of breast cancer was 20 years (interquartile range, 16-24 years). In the BC-HL cohort, 97.9% of breast cancers were diagnosed ≥8 years after radiation exposure. Overall, 56 patients in the BC-HL cohort (21.8%)

developed bilateral breast cancer, of whom 30 (53.6%) had bilateral invasive disease, and 26 (46.4%) had a combination of in situ and invasive disease. In total, 28 of these 56 patients (50%) presented with synchronous, bilateral breast cancer.

Table 1 details the demographic and clinical characteristics of breast cancers within the cohort. Overall, 292 breast cancers (71.3%) were invasive ductal carcinoma, 229 (10.9%) were invasive lobular carcinoma, and 27 (8.4%) were ductal carcinoma in situ. Tumors were commonly located in the upper outer quadrant of the breast (44.6%) or involved overlapping quadrants (32.4%), and most were classified as clinical T1 tumors (≤2.0 cm in size; 66.4%) and were node-negative on pathology (54.2%).

Clinicopathologic Differences of Breast Cancers in Women With Prior Radiation Therapy for HL

Compared with women who had BC-NPM, those who had BC-HL were significantly younger at the time of diagnosis (median age, 43 vs 60 years; $P < .001$) and were less likely to present with ductal carcinoma in situ (8.4% vs 14.9%; $P = .001$). On univariate analysis, relative to 998,163 invasive BC-NPM tumors, invasive BC-HL tumors (n = 292) were more likely to be high-grade (43.8% vs 32.9%; $P < .001$), ER-negative (27.7% vs 18.2%; $P < .001$), and located in the upper outer quadrant (including the axillary tail) of the breast (45.6% vs 34.8%; $P = .003$) (Table 2). Pathologic tumor size, nodal status, and disease stage in women with BC-HL were not significantly different from those in women with BC-NPM.

On multivariable analysis adjusting for age at breast cancer diagnosis, BC-HL was associated with smaller (≤2 cm) tumor size (odds ratio, 1.64; 95% CI, 1.25-2.15) and a greater likelihood of upper outer quadrant tumors (odds ratio, 1.37; 95% CI, 1.04-1.81) (Table 3). However, the association between higher histologic grade ($P = .07$) and ER-negative status ($P = .64$) in the BC-HL cohort did not persist after adjustment for age and other variables that were included in the model.

Biologic Subtype of Breast Cancers in Women With Prior Radiation Therapy for HL and Effect of Prior Chemotherapy Exposure

In 102 breast cancers diagnosed after January 2010 for which HER2 status was available, BC-HL was identified as HER2-amplified in 18.7% of patients. The dominant biologic subtype seen in women with BC-HL was ER-positive/HER2-negative (63.7%; 95% CI, 53.6%-73.0%), followed by TNBC (17.7%; 95% CI, 10.8%-26.5%), ER-positive/HER2-positive (12.8%; 95% CI, 7.0%-20.8%), and ER-negative/HER2-positive (5.9%; 95% CI, 2.2%-12.4%). Compared with 327,335 BC-NPM tumors, biologic subtype distribution was not significantly different in BC-HL tumors ($P = .16$) (Fig. 1). In a subgroup analysis of patients with BC-HL, prior chemotherapy exposure was not associated with substantial differences in the proportion of ER-positive/HER2-negative breast cancers (65.8% vs 63.5%; $P = .82$).

TABLE 1. Clinical Characteristics, n = 321

Characteristic	No. of Women (%)
Age at breast cancer diagnosis, y	
≤30	23 (7.2)
31-40	99 (30.8)
41-50	131 (40.8)
51-60	60 (18.7)
61-70	8 (2.5)
Tumor histology	
DCIS	27 (8.4)
Invasive ductal carcinoma	229 (71.3)
Invasive lobular carcinoma	35 (10.9)
Other/favorable histologies[a]	30 (9.4)
Histologic grade	
1	35 (10.9)
2	104 (32.4)
3	137 (42.7)
Unknown	45 (14.0)
Estrogen receptor status	
Positive	193 (60.1)
Negative	83 (25.9)
Unknown	45 (14.0)
Tumor location	
Upper outer quadrant	143 (44.6)
Lower outer quadrant	18 (5.6)
Inner quadrants	40 (12.5)
Central breast/nipple areola complex	16 (5.0)
Overlapping quadrants/breast NOS	104 (32.4)
Tumor size, cm	
0.0-2.0	213 (66.4)
2.1-5.0	70 (21.8)
>5.0	16 (5.0)
Unknown	22 (6.9)
Nodal status	
Negative	174 (54.2)
1-3 Nodes positive	113 (35.2)
4-9 Nodes positive	16 (5.0)
≥10 Nodes positive	10 (3.1)
Unknown	8 (2.5)
AJCC stage	
0, DCIS	27 (8.4)
I	146 (44.9)
II	86 (26.8)
III	26 (8.1)
IV	16 (5.0)
Unknown	20 (6.2)

Abbreviations: AJCC, American Joint Committee on Cancer; DCIS, ductal carcinoma in situ; NOS, not otherwise specified.
[a]Other/favorable histologies include tubular, mucinous, cribriform, papillary, apocrine, and medullary carcinomas and carcinoma of the breast NOS.

TABLE 2. Clinicopathologic Differences Between Invasive Breast Cancers Diagnosed in Women Treated With Prior Radiation for Hodgkin Lymphoma (BC-HL) or Without a History of Malignancy (BC-NPM)

Characteristic	No. of Women (%)		*P*
	BC-HL, n = 292	BC-NPM, n = 998,163	
Age at diagnosis, y			<.001
≤30	23 (7.9)	8169 (0.8)	
31-40	89 (30.5)	63,188 (6.3)	
41-50	119 (40.8)	194,988 (19.5)	
51-60	55 (18.8)	245,112 (24.6)	
61-70	6 (2.1)	233,770 (23.4)	
≥70	—	252,936 (25.3)	
Tumor histology			.06
Invasive ductal carcinoma	229 (78.4)	743,419 (74.5)	
Invasive lobular carcinoma	35 (12.0)	169,359 (17.0)	
Other/favorable histologies[a]	28 (9.6)	85,385 (8.6)	
Histologic grade			<.001
1	35 (12.0)	185,538 (18.6)	
2	92 (31.5)	381,088 (38.2)	
3	128 (43.8)	328,203 (32.9)	
Unknown	37 (12.7)	103,334 (10.4)	
Estrogen receptor status			<.001
Positive	181 (62.0)	718,159 (72.0)	
Negative	81 (27.7)	181,252 (18.2)	
Unknown	30 (10.3)	98,752 (9.8)	
Tumor location			.003
Upper outer quadrant	133 (45.6)	346,822 (34.8)	
Lower outer quadrant	16 (5.5)	68,123 (6.8)	
Upper/lower inner quadrants	33 (11.3)	159,987 (16.0)	
Central breast/nipple areola complex	14 (4.8)	58,179 (5.8)	
Overlapping quadrants/ breast NOS	96 (32.9)	365,052 (36.6)	
Tumor size, cm			.46
0.0-2.0	185 (63.4)	605,055 (60.6)	
2.1-5.0	70 (24.0)	275,650 (27.6)	
>5.0	16 (5.5)	43,788 (4.4)	
Unknown	21 (7.2)	73,670 (7.4)	
Nodal status			.97
Negative	162 (55.5)	562,242 (56.3)	
1-3 Nodes positive	97 (33.2)	321,012 (32.2)	
4-9 Nodes positive	16 (5.5)	60,538 (6.1)	
≥10 Nodes positive	10 (3.4)	29,337 (2.9)	
Unknown	7 (2.4)	25,034 (2.5)	
AJCC stage			.41
I	144 (49.3)	457,581 (45.8)	
II	86 (29.5)	313,596 (31.4)	
III	26 (8.9)	116,913 (11.7)	
IV	16 (5.5)	43,327 (4.3)	
Unknown	20 (6.9)	66,746 (6.7)	

Abbreviations: AJCC, American Joint Committee on Cancer; NOS, not otherwise specified.
[a] Other/favorable histologies include tubular, mucinous, cribriform, papillary, apocrine, and medullary carcinomas and carcinoma of the breast NOS.

TABLE 3. Multivariable Analysis of Invasive Breast Cancer Features Associated With Prior Radiation for Hodgkin Lymphoma (BC-HL) After Adjustment for Age

Characteristic	Adjusted OR for BC-HL (95% CI)	*P*
Age at diagnosis, y		<.001
≤30	1.00 (Ref)	
31-40	0.56 (0.34-0.92)	
41-50	0.24 (0.15-0.39)	
≥51	0.03 (0.02-0.05)	
Tumor histology		.50
Invasive ductal carcinoma	1.00 (Ref)	
Invasive lobular carcinoma	0.80 (0.54-1.19)	
Other/favorable histologies[a]	1.08 (0.54-1.20)	
Histologic grade		.07
1	1.00 (Ref)	
2	1.20 (0.79-1.82)	
3	1.51 (1.00-2.29)	
Estrogen receptor status		.64
Positive	1.00 (Ref)	
Negative	0.99 (0.94-1.04)	
Tumor location		.01
Overlapping quadrants	1.00 (Ref)	
Upper outer quadrant	1.37 (1.04-1.81)	
Lower outer quadrant	0.82 (0.48-1.42)	
Upper/lower inner quadrants	0.74 (0.49-1.13)	
Central breast/nipple areola complex	1.19 (0.68-2.09)	
Tumor size, cm		<.001
>2.0	1.00 (Ref)	
0.0-2.0	1.64 (1.25-2.15)	
Nodal status		.54
Negative	1.00 (Ref)	
1-3 Nodes positive	1.09 (0.84-1.42)	
4-9 Nodes positive	0.82 (0.48-1.41)	
≥10 Nodes positive	1.15 (0.58-2.28)	

Abbreviations: OR, odds ratio; Ref, reference category.
[a]Other/favorable histologies include tubular, mucinous, cribriform, papillary, apocrine, and medullary carcinomas and carcinoma of the breast not otherwise specified.

DISCUSSION

In this population-based study of women who had a history of radiation exposure for HL before age 30 years, we observed a greater likelihood of early onset breast cancers relative to women who had no history of prior malignancy. In adjusted analyses, radiation was not associated with poorer biologic features compared with breast cancers diagnosed in similarly aged women with no prior malignancy; however, higher proportions of upper outer quadrant and smaller tumors were demonstrated. Furthermore, the majority of tumors in the BC-HL cohort were hormone-sensitive (nearly two-thirds were ER-positive/HER2-negative), suggesting an opportunity for endocrine prevention in this high-risk population.

HL most commonly affects the mediastinal lymph nodes, with mantle-field or extended-field radiotherapy historically allowing radiation to penetrate the upper outer aspects of the breast and axillary tail with scatter to the medial, central, and inner quadrants of the breast.[20] Relative to women with no prior malignancy, our results indicated that tumors in the upper outer quadrant location were 38% more likely in women who received prior radiation therapy for HL. This is consistent with prior

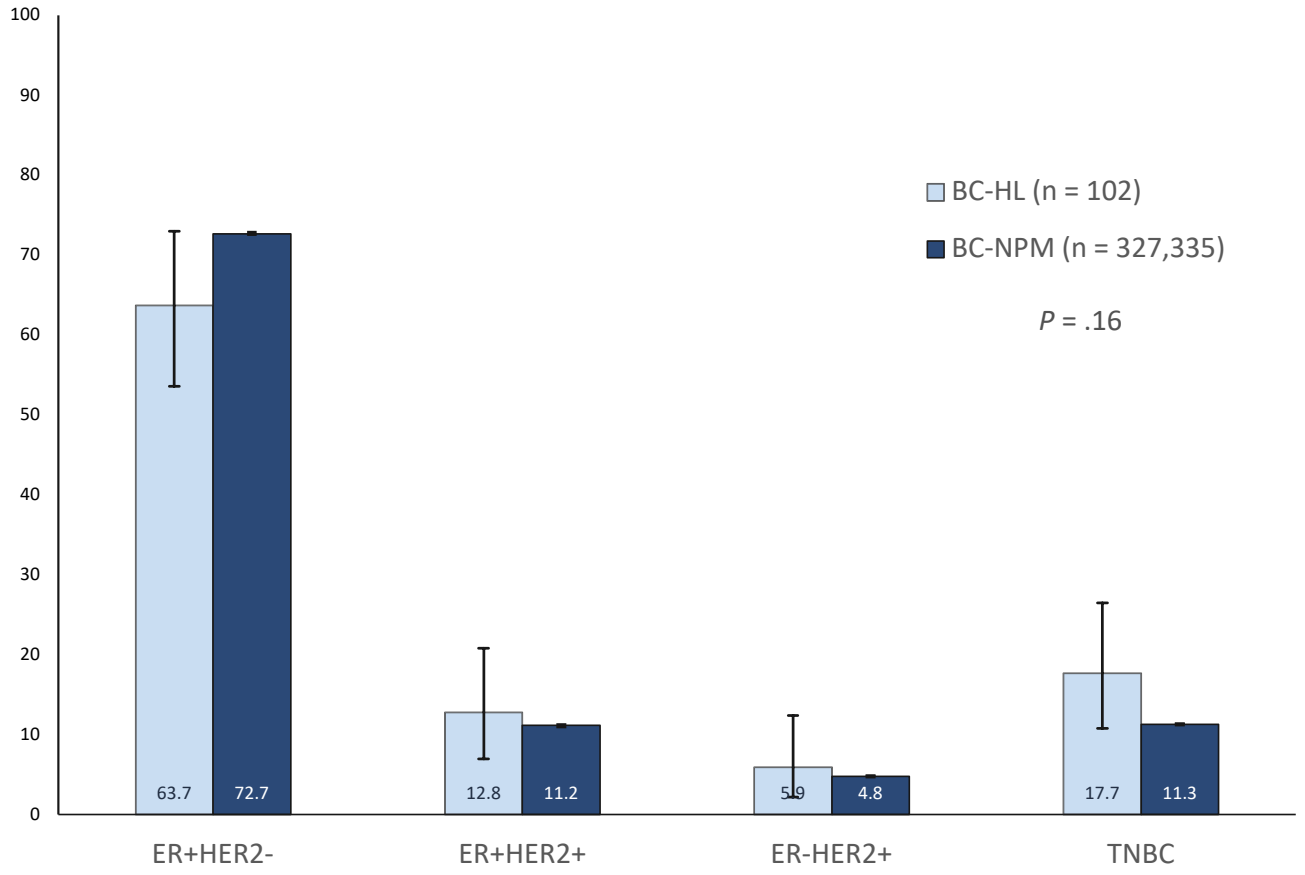

Figure 1. Distribution according to the biologic subtype of breast cancer is illustrated in women who had a history of radiation for Hodgkin lymphoma (BC-HL) and those who had no prior malignancy (BC-NPM). ER– indicates estrogen receptor-negative; ER+, estrogen receptor-positive; HER2–, HER2/*neu*-negative; TNBC, triple-negative breast cancer (negative for estrogen receptor, progesterone receptor, and HER2/*neu*).

literature, which suggests that BC-HL typically occurs in younger women within or at the margin of the radiation therapy field.[21,22] In their study of 230 breast cancers of HL survivors diagnosed between 1984 and 2010, Allen and colleagues noted that two-thirds of tumors were located in the upper outer quadrant, with a mean maximal dimension of 1.2 cm.[20] In current practice, however, the paradigm shift toward reductions in treatment volumes (involved site or nodal radiotherapy), dose reductions, and modern treatment techniques (intensity-modulated radiation treatment, deep-inspiration breath-hold technique) may significantly attenuate risk and alter the location of tumors seen in prior studies by decreased breast tissue radiation exposure.[23,24] Proton therapy also shows considerable promise in further reducing radiation dose to breasts.[25] More recent literature has reported a decrease in the risk of breast cancer after radiotherapy with less extensive supradiaphragmatic fields,[23,26] although others have reported similar risk estimates in women who were treated between 1989 and 2000 compared with those who received mantle-field irradiation in earlier decades.[17] This recent literature, however, reflects treatment in the era of involved-field radiotherapy, which does not account for the technological advances of modern radiotherapy or the further field and dose reductions used today.

The high incidence of bilateral breast cancer reported in 22% of women in the BC-HL cohort confirms prior reports that women with a history of radiation exposure have an increased propensity toward bilateral disease.[11,12] Fortunately, in our study, most patients with bilateral breast cancers had bilateral estrogen-sensitive disease (data not shown), and 88% were diagnosed in early stages with ductal carcinoma in situ and/or stage I or II breast cancer. However, in the general population, the incidence of synchronous breast cancer is only 2.9%,[27] which is significantly lower than the 11% reported herein. With this knowledge, it remains important to ensure that contralateral breast screening is performed at the time of a

unilateral breast cancer diagnosis in all women with BC-HL, particularly those considering therapeutic and prophylactic mastectomies at the time of surgery.[28]

In our cohort, the majority breast cancers were small at the time of diagnosis: two-thirds of patients were diagnosed with pathologic T1 disease. Although the SEER database lacks information on screening and mode of presentation, these characteristics are consistent with a high rate of early detection despite younger age at diagnosis. Similar findings were reported in a large, multi-institutional cohort study by Elkin et al, who demonstrated that HL survivors were more likely to have screen-detected cancers and to be diagnosed at earlier stages relative to age-matched individuals with sporadic disease.[11] Studies have shown that screening programs in HL survivors are associated with 28% to 58% uptake in invited participants.[29-31] International guidelines recommend enhanced surveillance in this patient population with the use of annual MRI and mammography starting 8 years after radiation exposure or at age 25 years, whichever occurs later.[9,32-34] Although it remains unclear whether MRI alters survival in this particular patient population, there appears to be a reduction in lead time with screening programs that initiate early onset screening.[35] This is consistent with our study, in which we observed that this approach would have sufficiently screened 98% of women during the time associated with the development of their breast cancer.

A strength of our study is that it is 1 of the largest in the currently available literature to characterize biologic subtype that includes HER2 status in women with prior radiation exposure for HL. In our subgroup analysis of 102 women who had HER2 information available, we found that 63.7% of cancers were ER-positive/HER2-negative, whereas 17.7% were TNBC, and 18.7% were HER2-amplified (either ER-positive/HER2-positive or ER-negative/HER2-positive). The subtype distribution was statistically similar to that in breast cancers among women with no prior malignancy, although higher absolute rates of TNBC were noted in our study, as previously reported. In their study of 65 invasive breast cancers diagnosed among survivors of childhood and young adult malignancies who were treated with radiation (44 after HL), Demoor-Goldschmidt et al reported a 29% rate of TNBC and a very low occurrence (3%) of HER2-amplified disease.[22] Similarly, Horst et al noted high rates of TNBC (38%) and hormone receptor-positive/HER2-negative tumors (47%) in 50 invasive breast cancers diagnosed among women who were previously irradiated for HL before age 30 years, with 15% identified as HER2-amplified.[36] A more recent study from Cutuli et al reported that HER2-amplified breast cancer was present in 5 of 41 patients (21%) who were treated after 2001 and had HER2 status available.[37] The relation between timing of radiation exposure, breast development, and biologic subtype was explored in a case-control study by Castiglioni et al, who demonstrated a significantly higher proportion of basal-like differentiation in postpubertal women who received radiation (52% of those who were exposed $\geq$4 years after menarche vs 6% of those who were exposed during breast development; $P < .0001$).[38]

In their early series of 71 breast cancers diagnosed in 65 HL survivors, Wolden et al noted similar pathologic characteristics of breast cancers relative to an age-matched cohort, with ER-positive tumors observed in 63% of their BC-HL group, and the majority (73%) presented with node-negative disease.[39] The current study extends these findings because our age-adjusted analyses demonstrate that women with BC-HL tend to have clinical features similar to those in comparably aged women with sporadic breast cancer, including a tendency toward the high-grade and ER-negative tumors seen disproportionately in younger women. Despite this, much of the cohort developed hormone-sensitive tumors (60.1% were ER-positive in the total cohort, 63.7% were ER-positive/HER2-negative in subset analysis), including women with prior chemotherapy exposure. Because chemotherapy regimens used in HL rarely result in long-term ovarian suppression, no clear protective effect against the development of breast cancer in women who have received multimodal therapy has been demonstrated. In aggregate, these findings lend support to interventions that have been effective in preventing the development of ER-positive breast cancer.

Tamoxifen is currently approved for the primary prevention of breast cancer in premenopausal, high-risk women older than 35 years; however, the 50% to 70% risk reduction noted with the medication is driven by a reduction in ER-positive disease.[40] In a recent multicentered, randomized, phase 2 trial of 72 chest-irradiated cancer survivors who were at increased risk for developing breast cancer, Bhatia et al demonstrated a significant decrease in mammographic dense area and IGF1 levels as well as an increase in IGF-BP3 among women receiving low-dose tamoxifen compared with placebo.[41] The majority of women (86%) included in that trial were HL survivors, the median age was 43.8 years, and there was no significant difference in terms of adverse events or adherence rates between the treatment and control arms (low-dose tamoxifen vs placebo, 97.5% vs 96%; $P = .9$). Although the trial was a biomarker-modulation study that was not powered to examine breast cancer incidence,

only 1 breast cancer was reported in the low-dose tamoxifen arm compared with 3 in the placebo arm at 2 years. Taken together, these findings justify the effort of a phase 3 prevention trial as well as studies exploring attitudes, perceptions, and willingness toward endocrine prevention in this high-risk patient population. Because women taking tamoxifen are advised to avoid pregnancy, defining the optimal age of initiating endocrine prevention in those with HL is necessary given fertility concerns and the impact on childbearing for women in this age group.[42] Furthermore, although well established side effects, such as hot flashes and musculoskeletal symptoms, appear to be lessened with lower dose formulations,[43] young women experience higher rates of nonadherence and discontinuation of endocrine therapy in the therapeutic setting.[44] Therefore, even if it is shown to be effective for the primary prevention of breast cancer in HL survivors, efforts to optimize tamoxifen uptake and tolerability will remain important in this patient population.

Our study has several limitations. First, we used radiation exposure as an inclusion criterion but lacked detailed information about radiation fields, target volumes, and dosages, which may affect breast cancer incidence and clinical characteristics, particularly if women who were not exposed to chest wall or supradiaphragmatic radiation were included in the cohort. Importantly, we also lacked detailed information on hormonal exposures, ovarian radiotherapy, and exposure to alkylating agents, which can affect ovarian function or lead to premature ovarian insufficiency and, in doing so, may modulate breast cancer risk. Second, information on HER2 status was only available in a subset of our population that received treatment for breast cancer during or after 2010. Third, although the SEER treatment database reports high specificity for variables associated with the receipt of radiation and chemotherapy, there is moderate sensitivity with respect to these variables. For our analysis, this lowered sensitivity may have resulted in a failure to capture all patients with HL who were exposed to radiotherapy for our initial cohort and may have resulted in an underestimation of the magnitude of the effect of chemotherapy exposure on the development of subsequent estrogen-sensitive breast cancer. Despite the stated limitations, however, our study remains one of the first population-based studies to examine biologic subtype and candidacy for endocrine prevention in this patient population. Further prospective studies are warranted to evaluate uptake and efficacy of this preventive strategy for women who have received prior chest wall radiation for childhood and young adult lymphoma.

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AUTHOR CONTRIBUTIONS

Stephanie M. Wong: Conceptualization, data curation, formal analysis, methodology, writing–original draft, and critical review and editing. **Lissa Ajjamada:** Conceptualization, methodology, and critical review and editing. **Anna C. Weiss:** Conceptualization, data curation, formal analysis, and critical review and editing. **Ipshita Prakash:** Critical review and editing. **Sonia Skamene:** Methodology and critical review and editing. **Jean Francois Boileau:** Critical review and editing. **Michael N. Pollak:** Critical review and editing. **Mark Basik:** Conceptualization, writing–original draft, and critical review and editing.

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