



Surgical Management and Contralateral Breast Cancer Risk in Women with History of Radiation Therapy for Hodgkin Lymphoma: Results from a Population-Based Cohort

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ABSTRACT

Background. Women with history of chest irradiation for Hodgkin lymphoma are at increased risk of developing bilateral breast cancer, although contralateral breast cancer risk estimates in this population remain undefined.

Methods. We queried the SEER database for women treated with radiation therapy for Hodgkin lymphoma prior to age 30 years and were diagnosed with a subsequent breast cancer between 1990–2016. Trends in surgical management and the 5- and 10-year cumulative incidence of contralateral breast cancer were evaluated.

Results. The cohort included 295 women with a median age of 22 years (range 8–30 years) at Hodgkin lymphoma diagnosis, and 42 years (range 22–65 years) at breast cancer diagnosis. Overall, 263 (89.2%) presented with unilateral breast cancer, while 32 (10.8%) presented with synchronous bilateral breast cancer. Breast-conserving

surgery was performed in 17.3% of patients, while mastectomy was performed in 82.7%. In 263 patients presenting with unilateral breast cancer, 50 (19.0%) underwent breast-conserving surgery and 213 (81.0%) underwent mastectomy. Subgroup analysis of mastectomy patients demonstrated a 40.5% bilateral mastectomy rate. The 5-year incidence of contralateral breast cancer in women who underwent unilateral surgery was 9.4% [95% confidence interval (CI), 5.6–15.4%], increasing to 20.2% (95% CI, 13.7–29.2%) at 10-year and 29.9% (95% CI, 20.8–41.9%) at 15-year follow-up.

Conclusions. Women with a history of prior chest radiation for Hodgkin lymphoma with a diagnosis of breast cancer have a 10-year contralateral breast cancer risk of 20%. These findings support consideration of contralateral prophylactic mastectomy during surgical decision-making for management of this high-risk patient population.

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Women with history of mantle radiation for Hodgkin lymphoma in adolescence or young adulthood are at an elevated risk of developing breast cancer later in life.^{1,2} The estimated actuarial cumulative probability of breast cancer in women exposed to radiation prior to age 30 years is 35% by 40–50 years of age.^{3,4} This increased risk is initially detected 8–15 years after radiation treatment and lasts up to 20 years after radiation exposure.^{5,6} Women who were exposed to lower doses of radiation or those exposed after age 30 years are at a lower risk for

developing breast cancer than women exposed to higher doses of radiation or those who were exposed earlier on in their lifetimes.^{1,7,8} In contrast, women treated with chest wall radiation for Hodgkin lymphoma beyond the age of 40–50 years do not appear to be at dramatically increased risk.^{8,9}

Historically, the recommended management for breast cancer in patients with prior radiation for Hodgkin lymphoma was mastectomy, as normal tissue tolerance was expected to preclude an additional full course of radiotherapy.^{10–12} However, there is evolving evidence suggesting that breast-conserving surgery followed by radiation could be an effective treatment in select patients, with low rates of recurrence and high rates of survival.^{9, 13–15} In patients who undergo mastectomy, contralateral prophylactic mastectomy should be considered owing to the elevated risk of bilateral breast cancer.^{16,17} However, the optimal surgical management remains undefined and little is known regarding the current use of contralateral prophylactic mastectomy and breast reconstruction in these patients. An additional unknown is the risk of developing contralateral breast cancer after unilateral surgery is performed in these patients.

The overall aim of this study is to evaluate the current management trends in breast cancer patients previously treated with radiation therapy for Hodgkin lymphoma, assessing the use of contralateral prophylactic mastectomy and breast reconstruction in these patients. Additionally, this study seeks to determine the cumulative incidence of contralateral breast cancer in individuals treated with unilateral breast-conserving surgery and mastectomy.

PATIENTS AND METHODS

Data Source and Cohort Selection

We queried the Surveillance, Epidemiology, and End Results (SEER) database, which includes demographic, clinical, and treatment-related data from cancer registries across the USA whose catchment area includes 34% of the US population.¹⁸ We used the November 2018 SEER-18 submission, containing data from 1990–2016. Our cohort included women who were diagnosed with Hodgkin lymphoma prior to 30 years of age ($n = 21,310$), were treated with radiation therapy ($n = 9623$), and developed breast cancer more than 6 months following their diagnosis of Hodgkin lymphoma ($n = 336$) (Appendix). We excluded patients who were diagnosed with breast cancer before 1990 ($n = 10$), patients diagnosed with stage IV breast cancer ($n = 20$), and patients who did not undergo surgery or whose surgical details were unknown ($n = 11$). Our final analytic cohort included 295 patients with breast cancer

treated with prior radiation therapy for Hodgkin Lymphoma in childhood or young adulthood. Because the study used publicly available, deidentified data, it was considered exempt from the Jewish General Hospital institutional review board.

Outcomes of Interest

Our primary outcome of interest was type of breast surgery. We categorized surgical management into breast-conserving surgery or mastectomy. Women who underwent the following surgical procedures were categorized as having undergone breast-conserving surgery: partial mastectomy, partial mastectomy with nipple resection, lumpectomy, excisional biopsy, re-excision of biopsy site, quadrantectomy, and segmental mastectomy. We defined mastectomy as women undergoing subcutaneous mastectomy, total simple mastectomy, and modified radical mastectomy. For women with unilateral breast cancer, we evaluated the rates of contralateral prophylactic mastectomy, defined as unilateral therapeutic mastectomy “with removal of the uninvolved contralateral breast.” Patients receiving unilateral mastectomy or contralateral prophylactic mastectomy were deemed to have undergone additional reconstruction if surgery codes for reconstruction with tissue, implant, combined (tissue and implant), or “reconstruction not otherwise specified” were used. Our secondary outcome of interest included the cumulative incidence of contralateral invasive breast cancer in those undergoing unilateral surgery. Patients with bilateral breast cancer or those who underwent bilateral surgery for a unilateral breast cancer were excluded from the analysis.

Independent Variables of Interest

Our independent variables consisted of demographic characteristics such as age at diagnosis of Hodgkin lymphoma, age at diagnosis of breast cancer, and race. Clinical and pathologic variables, including breast tumor histology, tumor laterality (bilateral or unilateral), histologic grade, invasive tumor size, nodal status, and hormone-receptor status were also evaluated. Hormone-receptor status was defined as positive if estrogen receptor (ER) or progesterone receptor (PR) was positive, negative if both ER and PR negative or ER negative and PR positive, or unknown/not reported. Human epidermal growth factor receptor-2 (HER2) status was only available for select cases diagnosed after 2010 and was therefore excluded from the analysis.

Statistical Analysis

Baseline patient and tumor characteristics were compared using Pearson's chi-squared test for categorical variables and the Wilcoxon rank-sum test for continuous variables. Subgroup analysis was performed in mastectomy patients to evaluate the association between receipt of breast reconstruction and surgical laterality (unilateral mastectomy versus contralateral prophylactic mastectomy). The Kaplan–Meier method was used to display the cumulative incidence of subsequent breast cancers in women undergoing unilateral breast surgery, following exclusion of women with synchronous bilateral breast cancer. The analyses were then stratified by type of surgery and hormone-receptor status of the index tumor. All *P*-values were two-sided, with a threshold of 0.05 used to indicate statistical significance. All statistical analyses were performed using SAS version 9.4 (Cary, NC).

RESULTS

Patient Characteristics

The patient demographics and characteristics of the final analytic cohort ($n = 295$) are presented in Table 1. The median age of patients at Hodgkin lymphoma diagnosis was 22 years (range 8–30 years), and the median age of patients at breast cancer diagnosis was 42 years (range 22–65 years). The majority of patients presented with unilateral breast cancer (89.2%, $n = 263$), although 10.8% ($n = 32$) presented with synchronous bilateral breast cancer. Eighty percent of patients had invasive ductal carcinoma ($n = 236$) and most were intermediate–high histologic grade (grade II, 32.5%; grade III 46.2%). Despite this, most patients presented with early-stage disease; 63% were T1 ($n = 181$) and 62.9% were node negative ($n = 180$). Hormone-receptor-positive breast cancer accounted for 64.0% of the total cohort ($n = 183$).

Surgical Management

Overall, 17.3% ($n = 51$) of patients underwent breast-conserving surgery and 82.7% ($n = 244$) underwent mastectomy. In the 263 patients presenting with unilateral breast cancer, 50 (19.0%) underwent breast-conserving surgery and 213 (81.0%) underwent mastectomy. Subgroup analysis of 185 mastectomy patients with surgical laterality information available yielded a 40.5% bilateral mastectomy rate. From the patients that underwent unilateral and bilateral mastectomy for unilateral breast cancer, 33.3% and 60% had reconstruction, respectively (Table 2). Most unilateral breast cancer patients did not receive adjuvant radiation (87.1%, $n = 229$).

Of the 32 patients that presented with synchronous bilateral breast cancer, nearly all underwent bilateral mastectomy (96.9%, $n = 31$). Among the patients who underwent bilateral mastectomies, 61.3% had reconstruction ($n = 19$). A minority of synchronous bilateral breast cancer patients (9.4%) received adjuvant radiation (Table 2).

Incidence and Characteristics of Contralateral Breast Cancers

In the 188 women undergoing unilateral surgery for unilateral breast cancer, the 5-year incidence rate of contralateral breast cancer was 9.4% (95% CI, 5.6–15.4%). The cumulative incidence increased to 20.2% (95% CI, 13.7–29.2%) at 10 years, and 29.9% (95% CI, 20.8–41.9%) at 15 years of follow-up (Fig. 1A).

The incidence of contralateral breast cancer was then stratified by index breast surgery and hormone receptor status. Of the 138 women who underwent unilateral mastectomy for unilateral breast cancer, 23 developed a contralateral breast cancer after a median 6.5 years (range 0.5–15 years). The 10-year cumulative incidence rate of contralateral breast cancer was 20.6% (95% CI, 13.2–31.4%) (Fig. 1B). Of the 50 women who underwent breast-conserving surgery for unilateral breast cancer, 4 developed second ipsilateral breast cancers and 6 developed contralateral breast cancers during a median follow up of 6.0 years (range 1.0–26 years). The 10-year cumulative incidence rate of contralateral breast cancer was 19.1% (95% CI, 8.8–38.6%) (Fig. 1B). There was no difference in contralateral breast cancer risk on the basis of type of breast surgery of the index breast cancer (log rank $p = 0.48$).

The hormone-receptor status of the index breast cancer was also not associated with significant differences in time to contralateral breast cancer (log rank $p = 0.13$, Fig 2). In patients with hormone-receptor positive disease, the 10-year rate of contralateral breast cancer was 23.0% (95% CI, 14.5–35.4%), compared with 18.1% (95% CI, 8.3–36.6%) in those with hormone-receptor negative breast cancer. Overall, the majority (58.6%) of contralateral breast cancers were invasive, with the remaining 41.4% diagnosed as ductal carcinoma in situ. Of the invasive contralateral breast cancers, 70.6% were hormone-receptor positive, 47.0% were histologic grade III, and 76.5% were early stage (I–II) at diagnosis.

TABLE 1 Cohort characteristics (*n* = 295)

Characteristic		
Median (range) age of Hodgkin lymphoma diagnosis (years)	22	(8–30)
Median (range) age of breast cancer diagnosis (years)	42	(22–65)
Race/ethnicity, <i>n</i> (%)		
White (including Hispanic)	264	(89.5)
Black	23	(7.8)
Asian/Pacific Islander	8	(2.7)
Laterality at initial breast cancer diagnosis, <i>n</i> (row %)		
Unilateral	263	(89.2)
Bilateral (synchronous)	32	(10.8)
Tumor histology, <i>n</i> (%)		
Ductal carcinoma in situ	9	(3.1)
Invasive ductal carcinoma	236	(80.0)
Invasive lobular carcinoma	29	(9.8)
Other histologies	21	(7.1)
Histologic grade*, <i>n</i> (%)		
Grade I	33	(11.5)
Grade II	93	(32.5)
Grade III	132	(46.2)
Unknown	28	(9.8)
Invasive tumor size*, <i>n</i> (%)		
Microscopic focus	9	(3.2)
0.1–1.0 cm	65	(22.7)
1.1–2.0 cm	107	(37.4)
2.1–5.0 cm	68	(23.8)
5+ cm	18	(6.3)
Unknown/not recorded	19	(6.6)
Nodal status*, <i>n</i> (%)		
Negative	180	(62.9)
1–3 nodes positive	74	(25.9)
4–9 nodes positive	20	(7.0)
5+ nodes positive	9	(3.2)
Unknown/not recorded	3	(1.1)
Hormone receptor status*, <i>n</i> (%)		
Hormone receptor positive	183	(64.0)
Hormone receptor negative	86	(30.1)
Unknown/not recorded	17	(5.9)

*Excluding in situ malignancies

DISCUSSION

In this population-based cohort of breast cancer patients with history of radiation for Hodgkin lymphoma prior to age 30 years, we found that over 80% of women underwent surgical management with mastectomy, while only 17% underwent breast-conserving surgery. In the subgroup of women with unilateral breast cancer and contralateral surgery information available, we noted 40.5% elected for bilateral mastectomy. In those who chose to undergo unilateral surgery for unilateral breast cancer, the 10-year risk

of developing contralateral breast cancer was 20%, increasing to 30% after 15 years with no evidence of plateau at longer follow-up.

Our findings are concordant with standard treatment recommendations that endorse the use of mastectomy in circumstances where prior chest irradiation remains a relative contraindication to breast-conserving therapy. However, recent studies suggest that breast-conserving surgery and radiation can be performed safely, despite the concerns for breast, lung, and cardiac radiation tolerance.^{9,13,14} Radiotherapy techniques to treat the breast in

TABLE 2 Local management by laterality at initial breast cancer diagnosis (*n* = 295)

	Unilateral breast cancer (<i>n</i> = 263)	Synchronous bilateral breast cancer (<i>n</i> = 32)
Surgical management, <i>n</i> (%)		
Breast-conserving surgery	50 (19.0)	1 (3.1)
Unilateral mastectomy	138 (52.5)	0 (0)
Bilateral mastectomy	75 (28.5)	31 (96.9)
Reconstruction, <i>n</i> (% mastectomy)		
Unilateral mastectomy	46 (33.3)	0 (0)
Bilateral mastectomy	45 (60.0)	19 (61.3)
Adjuvant radiation, <i>n</i> (%)		
Yes	34 (12.9)	3 (9.4)
No/unknown if received radiation	229 (87.1)	29 (90.6)

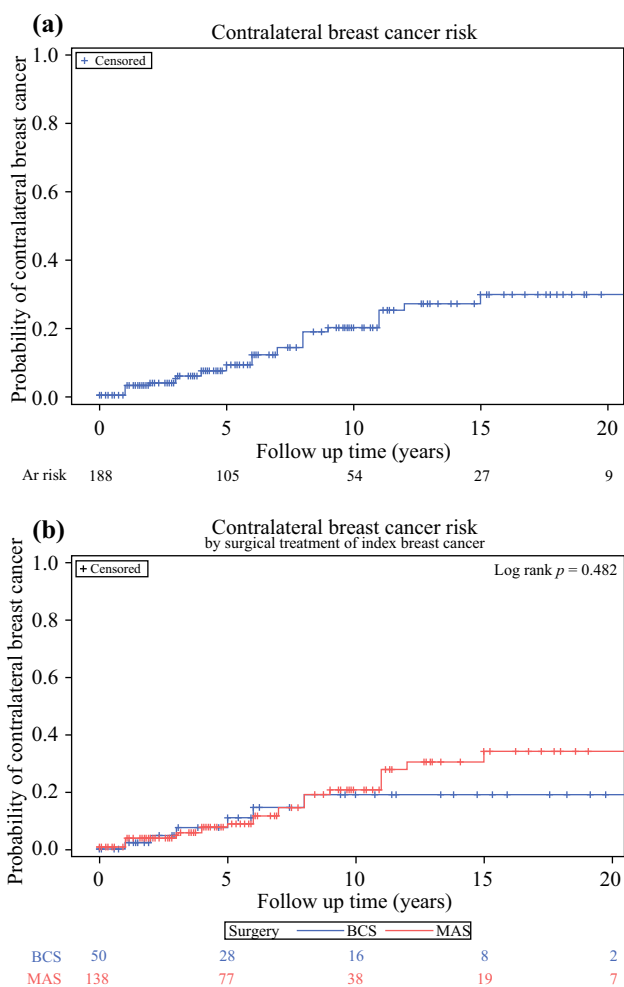


FIG. 1. Cumulative incidence curves of contralateral breast cancers in women with history of radiation therapy for Hodgkin lymphoma undergoing (A) unilateral surgery or (B) breast-conserving surgery or unilateral mastectomy for unilateral breast cancer

the re-irradiation setting often differ compared with classical 3D conformal breast irradiation using tangential fields

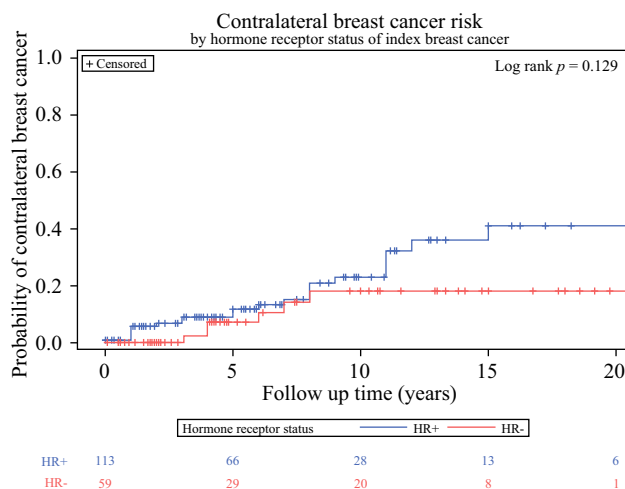


FIG. 2. Cumulative incidence of contralateral breast cancers in women with history of radiation therapy for Hodgkin lymphoma with history of unilateral surgery for unilateral breast cancer, by hormone receptor status of the index breast cancer

with the aim of decreasing toxicity. In a series of 72 Hodgkin lymphoma patients with breast cancer treated at Institut Curie, Haberer et al. reported successful whole breast irradiation in 30 women who underwent initial lumpectomy.¹³ Another study by Intra et al. at the University of Milan assessed 43 breast cancer patients with prior radiation treated with breast-conserving surgery and intraoperative radiotherapy with electrons (ELIOT), a form of partial breast irradiation given only to the tumor bed.⁹ They found that breast-conserving surgery and intraoperative radiotherapy was well-tolerated in these patients, with low rates of acute toxicity and recurrence. Several additional radiotherapy techniques, including partial breast irradiation,¹⁹ treatment in the prone position,²⁰ intensity-modulated radiation therapy,²¹ active breathing control with deep inspiration breath hold,²² and even proton

therapy²³ can all significantly reduce radiation exposure to underlying tissues. Patients who elect for breast-conserving therapy should, however, be counseled regarding the risk of a future breast cancer in both the ipsilateral and contralateral breast.

Prior research indicates that women with history of radiation therapy for Hodgkin lymphoma in adolescence or young adulthood are at a high risk of developing bilateral breast cancer.^{24,25} The incidence of bilateral breast cancer in this population ranges from 10–29.4%.^{10,11,26} In a study by Cutuli et al., 11% of the breast cancers in women with a history of Hodgkin lymphoma were bilateral.²⁶ In contrast, the rate of bilateral malignancy in women with an average risk presenting with breast cancer falls between 0.3% and 3%.²⁶ Consistent with the published literature, 11% of the patients in our cohort presented with synchronous bilateral breast cancer and nearly all of them underwent bilateral mastectomies. This finding supports the continued use of preoperative MRI in this patient population to exclude the presence of contralateral disease and to plan axillary management at the time of prophylactic surgery.

In Hodgkin lymphoma patients with a diagnosis of breast cancer, the precise risk of developing contralateral breast cancer with unilateral surgery is an important preoperative consideration for patients. Data from our cohort suggest that contralateral breast cancer risk is 20% at 10 years, similar to that of *BRCA1/2* carriers,²⁷ and is significantly higher than the risk seen in breast cancer patients of average risk, where the 10-year incidence of contralateral breast cancer is 2.5–4%.^{28,29} Our results extend prior work by Basu et al. and Henderson et al., demonstrating a high rate of metachronous bilateral breast cancer in women treated with prior radiation for Hodgkin lymphoma.^{24,25} Population-based studies have also demonstrated an increased likelihood of developing additional breast cancers; in their study of 316 Hodgkin lymphoma patients of all ages treated both with and without radiation therapy who later developed breast cancer, Veit-Rubin et al. reported a 5-year cumulative risk of a second breast cancer of 5.75% (laterality not specified).⁸ Taken together, our findings, and those previously reported, support current guidelines that recommend consideration of contralateral prophylactic mastectomy in Hodgkin lymphoma patients undergoing therapeutic mastectomy for unilateral breast cancer, provided there is a history of chest wall radiation prior to 30 years of age. They also support careful consideration of bilateral prophylactic mastectomy in Hodgkin lymphoma patients with the above risk factors who wish to avoid future breast cancer diagnoses.

In our study, the unexpected finding that patients with hormone-receptor-positive breast cancer did not experience a lower contralateral breast cancer risk relative to hormone-receptor-negative patients warrants further evaluation.

Guidelines recommend patients with hormone-receptor-positive disease be treated with a minimum of 5 years of adjuvant endocrine therapy, which is associated with a well-established 30–60% reduction in contralateral breast cancer risk.²⁹ In women with an average risk, this protective effect is driven largely by a lower incidence of hormone-receptor-positive breast cancers. Recent phase II biomarker modulator studies provide support for endocrine prevention, specifically in patients with supradiaphragmatic radiation exposure at a young age. Possible explanations for the discrepant results reported herein include reduced compliance to endocrine therapy in the study population, attenuated effect of endocrine therapy in this high risk patient population, or a lack of statistical power to detect small differences owing to the small number of events in this study. Thus, until additional large studies validate our findings, these results should be interpreted with caution.

Although the risk of bilateral breast cancer is well established, the risk of complications following mastectomy and reconstruction in patients with a history of radiation for Hodgkin Lymphoma remains less well documented. In our study, we found that two-thirds of patients underwent reconstruction after bilateral mastectomies. Freniere et al. evaluated immediate reconstruction outcomes after unilateral and bilateral mastectomies for 52 patients that previously underwent mantle radiation for Hodgkin lymphoma.³⁰ They found post-mastectomy reconstruction to be safe and successful with low complication rates using both implant-based and autologous reconstructive approaches. A 3.7% rate of explantation was noted in the implant-based group, while no flap losses were seen in the autologous group, although the need for unplanned revisions was sixfold higher in the latter.³⁰

Our study has several limitations, including its population-based and retrospective nature, and should therefore be interpreted within the context of the data. The results may have been subject to coding and/or misclassification errors, and the small sample size necessitated a long inclusion period of study, which would have been subject to heterogeneous and evolving treatment strategies for both Hodgkin lymphoma and breast cancer. Additionally, individual-level risk factors are lacking, including important treatment variables such as specific location of radiation treatment (mediastinal or non-mediastinal), extent of radiation fields (extended field, involved field, or involved site), radiation dose and fractionation, and receipt of adjuvant endocrine therapy, as they were not available in SEER. These are important variables as they directly influence breast cancer risk and prognoses.^{1,5,6} Finally, for the analysis of contralateral breast cancer risk, we lacked knowledge around the incidence of prophylactic

mastectomy outside of active treatment for breast cancer, which would have increased the number of censored patients and may have led to an underestimation of estimates.

Despite the stated limitations, to our knowledge, this study is one of the largest in the literature evaluating breast cancer surgical management in patients with prior radiation for Hodgkin lymphoma and is one of the first to report 5- and 10-year contralateral breast cancer risk estimates specifically. This information can be used to inform patients around the likelihood of developing contralateral breast cancer with unilateral surgery, to aid decision-making around contralateral prophylactic mastectomy. Further research is needed to compare the survival and patient-reported outcomes across different surgical treatments to characterize the optimal management strategy for this subgroup of patients, as beyond risk reduction contralateral prophylactic mastectomy may not alter breast cancer specific mortality. Additionally, further research is warranted to determine if breast-conserving surgery and radiation are oncologically and cosmetically acceptable for Hodgkin lymphoma patients with prior radiation exposure, as the data continue to evolve around these treatment options.

APPENDIX: STEPWISE COHORT ASCERTAINMENT

	Remaining	Removed (% cohort)
All female patients with Hodgkin lymphoma	58,238	
Include those diagnosed prior to 30 years of age	21,310	36,928 (63.4%)
Include those treated with radiation therapy	9623	11,687 (54.8%)
Include those with a documented subsequent breast cancer > 6 months following their diagnosis of Hodgkin Lymphoma	336	9287 (96.5%)
Exclude those with breast cancers diagnosed before 1990	326	10 (3.0%)
Exclude patients diagnosed with stage IV breast cancer	306	20 (6.1%)
Exclude patients who did not undergo surgery/surgical details unknown	295	11 (3.6%)
Final cohort	295	

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