Published OnlineFirst October 26, 2010; DOI: 10.1158/1055-9965.EPI-09-1245

Cancer Epidemiology, Biomarkers & Prevention

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Cancer Epidemiol Biomarkers Prev 2010;19:2734-2746. Published OnlineFirst October 26, 2010.

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Research Article
See commentary p. 2715

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Risk Factors for Lymphedema after Breast Cancer Treatment

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Abstract

Background: As cancer treatments evolve, it is important to reevaluate their effect on lymphedema risk in breast cancer survivors.

Methods: A population-based random sample of 631 women from metropolitan Philadelphia, Pennsylvania, diagnosed with incident breast cancer in 1999 to 2001, was followed for 5 years. Risk factor information was obtained by questionnaire and medical record review. Lymphedema was assessed with a validated questionnaire. Using Cox proportional hazards models, we estimated the relative incidence rates [hazard ratios (HR)] of lymphedema with standard adjusted multivariable analyses ignoring interactions, followed by models including clinically plausible treatment interactions.

Results: Compared with no lymph node surgery, adjusted HRs for lymphedema were increased following axillary lymph node dissection [ALND; HR, 2.61; 95% confidence interval (95% CI), 1.77-3.84] but not sentinel lymph node biopsy (SLNB; HR, 1.04; 95% CI, 0.58-1.88). Risk was not increased following irradiation [breast/chest wall only: HR, 1.18 (95% CI, 0.80-1.73); breast/chest wall plus supraclavicular field (+/− full axilla): HR, 0.86 (95% CI, 0.48-1.54)]. Eighty-one percent of chemotherapy was anthracycline based. The HR for anthracycline chemotherapy versus no chemotherapy was 1.46 (95% CI, 1.04-2.04), persisting after stratifying on stage at diagnosis or number of positive nodes. Treatment combinations involving ALND or chemotherapy resulted in approximately 4- to 5-fold increases in HRs for lymphedema [e.g., HR of 4.16 (95% CI, 1.32-12.45) for SLNB/chemotherapy/no radiation] compared with no treatment.

Conclusion: With standard multivariable analyses, ALND and chemotherapy increased lymphedema risk whereas radiation therapy and SLNB did not. However, risk varied by combinations of exposures.

Impact: Treatment patterns should be considered when counseling and monitoring patients for lymphedema.

Cancer Epidemiol Biomarkers Prev; 19(11); 2734–46. ©2010 AACR.

Introduction

Lymphedema is a common and debilitating condition experienced by breast cancer survivors (1-6). Mechanisms and risk factors remain unclear. Axillary lymph node dissection (ALND) and axillary radiation therapy have been cited as the most important risk factors for lymphedema (7-15). However, approaches to breast cancer diagnosis and treatment have evolved, and the effect of these changes on risk of lymphedema is not known. For example, using sentinel lymph node biopsy (SLNB) as a first-line approach to evaluating the axilla is becoming commonplace (16), but as recently reviewed (17) and reported by others (18-20), whether ALND should follow a positive SLNB (completion ALND) is being actively investigated. Although algorithms have been developed to assist decision making (17, 21), there is no consensus (17). To minimize recurrence, completion ALND is commonly used, and in certain circumstances, axillary radiation therapy or systemic chemotherapy is recommended in place of completion ALND (17).

Clearly, preventing cancer recurrence is the primary concern of treatment. However, given the multiple cancer treatment options, the potential for such morbidities as lymphedema associated with axillary evaluation and accompanying treatment should be considered. One such concern is whether the lower risk of lymphedema following SLNB persists after nodal irradiation or after adjuvant chemotherapy. Older studies of axillary nodal irradiation following ALND might not be pertinent to decisions about lymphedema risk when axillary radiation follows SLNB. Second, current practice, with greater reliance on computerized tomography for radiation treatment planning, can improve radiation dose homogeneity, decrease toxicity, and avoid irradiating lymph

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doi: 10.1158/1055-9965.EPI-09-1245

Published OnlineFirst October 26, 2010; DOI: 10.1158/1055-9965.EPI-09-1245

node structures when not indicated (22-26). Moreover, unlike older studies, multiagent chemotherapy, especially anthracycline-based chemotherapy with or without taxane, is common (27). According to recent reviews (7-14, 28), studies rarely include sufficient information on treatment and patient characteristics to assess the independent and joint contributions of each. Thus, examining currently used treatments, as well as the entire sequence of treatments, with respect to lymphedema is crucial to current oncology practice.

We conducted a population-based prospective study of lymphedema to examine, first, the association of lymphedema with breast cancer treatments individually or in combination with other treatments over time, and second, patient characteristics identifiable at cancer diagnosis associated with increased risk of lymphedema, regardless of subsequent cancer treatment, which could prompt additional counseling and monitoring for lymphedema.

Materials and Methods

Study design and study population

Methods for this study have been described previously (29). Briefly, eligible patients were female residents of Philadelphia and Delaware Counties in Pennsylvania first diagnosed with histologically confirmed breast cancer between May 1, 1999 and September 30, 2001. After obtaining Institutional Review Board approvals, potential participants were identified from 30 hospitals, which diagnosed or treated approximately 95% of all newly diagnosed primary breast cancer patients residing in these two counties during the study years (30).

We selected an age-stratified random sample of 33% of patients ages 50 to 79 years and up to 100% of women ages either <50 or ≥80 years. Physician permission was obtained before patient contact; all participants provided written informed consent. Women identified in this sample who were enrolled were followed prospectively for up to 5 years.

Data collection

Trained interviewers administered a structured questionnaire on demographics, lifestyle, access to care, medical conditions, presence and timing of cancer treatments, and presence and degree of lymphedema. The first interview was in-person, followed by telephone interviews approximately 7 to 9 months apart. Except for some questions about sociodemographic and preexisting conditions at cancer diagnosis, all questions were repeated at each follow-up interview. Medical record reviews provided supplementary data on staging and specifics of cancer treatments.

Variable definitions

Lymphedema. Historically, differences in the circumference or volume of the limbs have been most commonly used to assess the presence and degree of lymphedema (31, 32), despite the lack of consistent measurement-based criteria for diagnosis (3, 8, 14, 28, 31-34). However, arm measurements at each follow-up were not feasible for this study, given the large cohort and the expense of making multiple measurements over time. Thus, we developed a questionnaire and scoring system to assess the presence and degree of lymphedema (mild or moderate/severe) and the number of months lymphedema was present using the patient's perceived differences in the size of her hands and arms, which we validated against expert clinical therapists' measurement-based criteria for mild and moderate/severe lymphedema (28).

Specifically, at the first in-person interview, interviewers asked respondents whether, between the date of breast cancer diagnosis and the interview date, their right and left hands seemed to differ in size. The question was repeated for the lower arms and upper arms separately. Patients who reported observing no difference at a location were assigned a degree score of 0. For women noting size differences, the interviewer asked, "On average, would you say that the difference in size of your (hands/lower arms/upper arms) was '1: very slight; you are the only person who would notice this'; '2: noticeable to people who know you well but not to strangers'; or '3: very noticeable'?" The degree score was summed over the three locations and could range from 0 to 9. Subsequent telephone interviews covered the time period back to the previous interview.

Respondents who reported a size difference provided information on the month and year it was first noticed, whether they still noticed the difference, and if not, the month and year it returned to being the same size for each part (hand/lower arm/upper arm) separately, allowing us to assign a lymphedema degree score from 0 to 9 to each month of follow-up.

Based on the validation study, lymphedema was defined as present in any month in which the degree score was >0 and the limb on the side of surgery was larger. If the score was ≥4, the patient had moderate/severe lymphedema; otherwise, the diagnosis was mild lymphedema (sum from 1 to 3). A score of ≥4 required size differences at two or more locations because the largest score possible at any one location was 3 (28).

Cancer treatments. Treatments were classified according to the best information available, whether from operative reports, flow sheets, physician correspondence, or hospital tumor registries. Radiation therapy was categorized into the largest volume reported: breast/chest wall only; breast/chest wall plus supraclavicular field (including the apex of axilla, but not the full axilla); or breast/chest wall, supraclavicular field, and full axilla (including a posterior axillary boost field). Chemotherapy regimens were recorded as specified and later grouped as anthracycline based or not. Because 81% of the chemotherapy received was anthracycline based, we focused on anthracycline-based regimens. Axillary surgeries were combined into three categories: SLNB only, SLNB followed by ALND, or ALND only.

Stage at diagnosis. Stage at diagnosis was classified according to the American Joint Commission on Cancer

Published OnlineFirst October 26, 2010; DOI: 10.1158/1055-9965.EPI-09-1245

(AJCC) criteria (35). If needed information was not available, such as whether a metastatic workup was done, stage was coded as unknown.

Analysis plan

Each woman's follow-up was divided into months (0 through 59) from the reference date (date of histologic diagnosis of breast cancer). Occurrences of subsequent treatment exposures or lymphedema events were converted from calendar time into months from the reference date. We defined end of follow-up as development of lymphedema, loss to follow-up, or completion of 5 years of follow-up. If, during follow-up, a woman was diagnosed with breast cancer or had a mastectomy or lymph node surgery on the side opposite to the original surgery, she was censored at that time because there was no longer an unaffected side for comparing hand and arm sizes.

For most analyses, the outcome was the time to the first occurrence of any lymphedema, mild or more severe. We also restricted the outcome to moderate/severe lymphedema in sensitivity analyses. The effective exposure for all patient characteristics present at the reference date, such as medical conditions and demographic and lifestyle factors, was assumed to begin at month 0 and extend throughout all months of follow-up. Similarly, we considered the potential effects of each cancer treatment on lymphedema risk to be lasting, continuing from initiation of that treatment to the end of follow-up.

Statistical analysis

Incidence rate ratios [hazard ratios (HR)] of lymphedema (yes/no) were estimated using Cox proportional hazards models to accommodate time-varying exposures, censoring events, and loss to follow-up (36, 37). Person-months of a given exposure were combined over study subjects to estimate risk associated with that exposure. Only exposures occurring before lymphedema developed were counted in evaluating risk factors for lymphedema.

We used two main analytic approaches: standard multivariable analyses with no interaction terms (referred to as standard multivariable analyses throughout) and models with interaction terms. For example, standard multivariable analyses treat person-months of exposure to SLNB the same regardless of whether other treatments have been added over time. However, the role of SLNB might differ depending on whether it is the sole exposure or a part of a sequence of exposures. Thus, to model risk of lymphedema associated with combinations of exposures, we included clinically plausible two- and three-way interactions between treatments, asking, for example, whether the degree of association between SLNB and lymphedema depended on subsequent chemotherapy and/or radiation, or whether the degree of association between radiation therapy and lymphedema depended on having had prior lymph node removal and/or chemotherapy. Levels of these exposures were collapsed when necessary to achieve model fit.

We used two different types of interaction models to describe the role of exposure sequence: HRs, which show on a ratio scale the relative contribution of treatment sequences to risk of lymphedema compared with no treatment (no axillary surgery, no chemotherapy, and no radiation), and then cumulative incidence of lymphedema according to treatment. To estimate and plot cumulative incidence, we implemented an equivalent generalized linear model for discrete time survival analysis, but with a prespecified set of times to maintain model parsimony: each month 0-5 and months 6-11, 12-17, 18-23, and 24 or more, grouped as shown.

Potential confounding was addressed by including in our models factors previously reported as risk factors for lymphedema, those significant or close to significant in our unadjusted analyses, or those that seemed to act as confounders in stratified analyses. Because protocols for treatment were based on stage at diagnosis, we did not include stage and treatment in our models. Rather, we modeled the associations of cancer treatments and lymphedema risk, our primary objective, and then performed a series of sensitivity analyses to clarify the separate contributions of stage and treatment to lymphedema risk.

Results

We ascertained 4,551 breast cancer cases from hospitals, locating 97% of breast cancer diagnoses in the two counties during the study period (38). The median time from breast cancer diagnosis to ascertainment for the study was 2 months (range, 0-33 months). Among 1,589 randomly selected potentially eligible patients, 649 (41%) were enrolled. Patient refusal represented 25% of the nonresponse; the remainder included physician noncooperation (35%), inability to locate a physician to give consent (8%), restrictive hospital requirements for patient contact (13%), death (6%), illness (3%), ineligibility due to physical or mental incapability (3%), and inaccessibility (8%). Eighteen enrolled study subjects were discovered to be ineligible at the start because there was no unaffected comparison side to evaluate lymphedema (17 patients with simultaneous bilateral mastectomies at the reference date and 1 with a preexisting size difference affecting the entire arm), resulting in 631 patients in the study. The average time from breast cancer diagnosis to first interview was 12.2 months (median, 11; range, 1-28 months). Of the 631 study subjects, 94% completed 1 year of follow-up, 85% completed 2 years, 69% completed 3 years, and 57% completed all 5 years (29).

Demographic, lifestyle, and medical characteristics potentially related to lymphedema that were present at breast cancer diagnosis are given in Table 1, along with unadjusted associations of each factor with subsequent lymphedema. Statistically significant ($P < 0.05$) positive associations with the presence and degree of lymphedema were observed for younger age, black race, higher body mass index (BMI), lower levels of education and income, Medicaid/public assistance/no

Published OnlineFirst October 26, 2010; DOI: 10.1158/1055-9965.EPI-09-1245

health insurance, greater perceived difficulty getting medical care, and stage at diagnosis.

More than 98% of lymph node surgery, breast surgery, chemotherapy, and radiation began in the first year after breast cancer diagnosis, as did 93% of hormonal therapy. The prevalence of cancer treatments potentially related to lymphedema is shown in Table 2 overall and by stage at diagnosis. When modeling the association of lymphedema with patient characteristics and cancer treatment, we first adjusted for potential confounding ignoring potential interactions (standard multivariable analyses; Table 3) and then introduced interaction terms to estimate the association of specific treatment sequences and lymphedema (Table 4; Fig. 1).

Several patient characteristics significantly associated with lymphedema without adjustment (age, race, health insurance, and perceived difficulty getting care) were no longer significant after adjustment by all other factors (Table 3). ALND [HR, 2.61; 95% confidence interval (95% CI), 1.77-3.84] and chemotherapy, specifically multiagent therapies with anthracycline (HR, 1.46; 95% CI, 1.04-2.04), were the only treatments significantly associated with increased lymphedema risk in standard multivariable analyses. Risk was not significantly increased following irradiation, whether to breast/chest wall only (HR, 1.18; 95% CI, 0.80-1.73) or breast/chest wall plus supraclavicular nodal field +/- full axilla (HR, 0.86; 95% CI, 0.48-1.54). No significantly increased risk was observed for hormonal therapy, SLNB, or type of breast surgery (Table 3).

To further assess whether chemotherapy represented an independent risk factor for lymphedema, as opposed to a marker for more aggressive disease, we performed a number of sensitivity analyses, first stratifying by stage at diagnosis and then stratifying by number of positive lymph nodes regardless of stage. The proportions of women with stages IIa, IIb, and III/IV receiving chemotherapy were similar, around 80% (Table 2), and among these, the proportion with anthracycline-based chemotherapy was also the same, about 85% to 95%. The proportion of women experiencing lymphedema was approximately the same for stages IIa, IIb, and III/IV (Table 1), although 5-year relative survival rates by stage differed markedly (39). Lymphedema did not occur as frequently among women diagnosed at stage I (Table 1) but only 27% received chemotherapy (Table 2). Among women taking anthracycline chemotherapy, the percentages experiencing lymphedema were, for stage I, 58% (37% mild, 21% moderate/severe); stage IIa, 56% (31% mild, 24% moderate/severe); stage IIb, 58% (25% mild, 33% moderate/severe); stage III/IV, 47% (26% mild, 21% moderate/severe); and stage unknown, 45% (26% mild, 19% moderate/severe). These percents did not differ significantly whether lymphedema was categorized as any or none ($P = 0.63$) or as moderate/severe, mild, or none ($P = 0.58$).

When we repeated our original multivariable analyses of the association between anthracycline chemotherapy and lymphedema (Table 3), stratified, in addition, by stage, adjusted HRs remained elevated, although confidence intervals were wide in some strata due to limited sample size [stage I ($n = 182$): HR, 2.52; 95% CI, 1.33-4.76; stage IIa ($n = 102$): HR, 1.99; 95% CI, 0.82-4.81; stage IIb/III/IV ($n = 73$): HR 1.95; 95% CI, 0.55-6.89].

Parallel adjusted analyses of the association of anthracycline chemotherapy and lymphedema controlling for the number of positive lymph nodes instead of stage showed similar elevated HRs for chemotherapy, whether the number of positive nodes was treated as a continuous (HR, 1.50; 95% CI, 1.06-2.11) or categorical (HR, 1.44; 95% CI, 1.01-2.06) variable, with the number of positive nodes grouped as 0, 1-3, 4-9, and 10 or more. These HRs are virtually identical to the estimate from the comparable model for chemotherapy and lymphedema that did not include number of positive nodes (HR, 1.46; 95% CI, 1.04-2.04; Table 3). Conversely, we found no association between number of positive nodes and lymphedema (adjusted HR per positive node, 0.98; 95% CI, 0.93-1.03).

HRs for treatment combinations from a complex model that allowed interactions of lymph node surgery, chemotherapy, and radiation are shown in Table 4. All hazards compare the indicated combination of therapy against a reference group of person-months with no risk factors, that is, no axillary surgery (no ALND or SLNB), no chemotherapy, and no radiation (row I, Table 4). Overall, several treatment scenarios resulted in approximately 4- to 5-fold increases in risk of lymphedema when compared with no treatment, with confidence intervals that excluded 1.0 (Table 4, rows A-D, F, and H). All involved ALND or chemotherapy or both, including combinations with SLNB and chemotherapy (Table 4, rows F and H). None of the HRs for these categories differed significantly from each other.

Plots of standardized cumulative incidence of lymphedema for six representative treatment combinations over the first 36 months of follow-up (Fig. 1) reinforce these findings, suggesting two broad categories of risk according to treatment combinations. As shown in the upper four curves, cumulative incidence is highest for ALND regardless of subsequent treatment, but is similarly elevated for SLNB followed by chemotherapy, and these curves do not differ significantly, with P values for pairwise comparisons ranging from 0.27 to 0.99. The lowest incidence occurs after SLNB and no chemotherapy (lower two curves), with significantly lower incidence compared with the highest group: $P = 0.012$ for SLNB, no chemotherapy, radiation and $P = 0.006$ for SLNB, no chemotherapy, no radiation. Within this low-risk category of SLNB without chemotherapy, lymphedema incidence seems to be higher when radiation therapy is included in the treatment regimen, but the results do not differ significantly (HR, 5.77; 95% CI, 0.70-47.79).

Discussion

Our results highlight the relevance of breast cancer treatment types and patterns to lymphedema risk and

Published OnlineFirst October 26, 2010; DOI: 10.1158/1055-9965.EPI-09-1245

Table 1. Demographic, lifestyle, and medical characteristics potentially related to lymphedema; percent of persons within levels of each factor; and unadjusted associations of potential risk factors with lymphedema

	Persons		Lymphedema			*P**
	n	%	None%	Mild%	Moderate/severe%	
ALL eligible women						
Total	631	100.0	62.3	24.7	13.0	—
Age (y)						
<50	196	31.1	54.6	27.0	18.4	<0.001
50-79	354	56.1	63.3	25.7	11.0	
80+	81	12.8	76.5	14.8	8.6	
Race						
White + others	409	64.8	66.3	24.0	9.8	0.001
Black	222	35.2	55.0	26.1	18.9	
BMI						
<25	235	37.2	67.7	22.1	10.2	0.002
25-29.99	200	31.7	64.0	24.0	12.0	
30-34.99	116	18.4	54.3	31.9	13.8	
35+	80	12.7	53.8	23.8	22.5	
Education level						
<High school	115	18.2	60.0	23.5	16.5	0.005
High school graduate	231	36.6	58.0	29.4	12.6	
High school + some college	140	22.2	60.7	22.9	16.4	
College graduate	62	9.8	64.5	25.8	9.7	
Postgraduate	83	13.2	78.3	15.7	6.0	
Marital status						
Married	281	44.5	61.2	28.1	10.7	0.12
Divorced or separated	104	16.5	53.8	26.9	19.2	
Widowed	146	23.1	67.8	20.5	11.6	
Unmarried couple	16	2.5	56.3	18.8	25.0	
Never married	84	13.3	67.9	19.0	13.1	
Type of hospital†						
Cancer center	115	18.2	66.1	23.5	10.4	0.42
Teaching	322	51.0	61.5	23.0	15.5	
Community	194	30.7	61.3	28.4	10.3	
Modified Charlson index‡						
0	351	55.6	64.1	22.2	13.7	0.27
1-2	228	36.1	61.4	28.5	10.1	
3+	52	8.2	53.8	25.0	21.2	
Hypertension						
Yes	250	39.6	60.4	26.4	13.2	0.55
No	381	60.4	63.5	23.6	12.9	
Arthritis						
Yes	235	37.2	59.1	27.2	13.6	0.31
Rheumatoid	25	10.6	44.0	36.0	20.0	
Osteoarthritis only	90	38.3	63.3	28.9	7.8	
Unknown type	120	51.1	59.2	24.2	16.7	
No	396	62.8	64.1	23.2	12.6	
Smoking status						
Never smoked	287	45.5	62.0	23.3	14.6	0.45
Ex-smoker	194	30.7	63.9	26.8	9.3	
Current smoker	150	23.8	60.7	24.7	14.7	

(*Continued on the following page*)

Published OnlineFirst October 26, 2010; DOI: 10.1158/1055-9965.EPI-09-1245

Table 1. Demographic, lifestyle, and medical characteristics potentially related to lymphedema; percent of persons within levels of each factor; and unadjusted associations of potential risk factors with lymphedema (Cont'd)

	Persons		Lymphedema			*P**
	n	%	None%	Mild%	Moderate/severe%	
Drinking status						
Nondrinker	336	53.2	62.8	23.5	13.7	0.45
<1 drink/wk	120	19.0	60.0	25.0	15.0	
1 to <7 drinks/wk	116	18.4	61.2	27.6	11.2	
7+ drinks/wk	59	9.4	66.1	25.4	8.5	
Health coverage						
Private insurance only	338	53.6	62.4	24.0	13.6	0.005
Some Medicare	209	33.1	67.5	23.4	9.1	
Medicaid/public assistance/none	46	7.3	39.1	39.1	21.7	
Other/unknown	38	6.0	60.5	21.1	18.4	
Difficulty getting care						
Extremely/very	24	3.8	50.0	25.0	25.0	0.008
Somewhat/not very	135	21.4	56.3	26.7	17.0	
Not at all	470	74.5	64.7	24.0	11.3	
Household income						
<$10,000	67	10.6	46.3	35.8	17.9	0.003
$10,000-$14,999	62	9.8	64.5	24.2	11.3	
$15,000-$19,999	53	8.4	58.5	26.4	15.1	
$20,000-$24,999	58	9.2	56.9	34.5	8.6	
$25,000-$34,999	58	9.2	56.9	24.1	19.0	
$35,000-$49,999	95	15.1	63.2	17.9	18.9	
$50,000-$74,999	79	12.5	55.7	30.4	13.9	
$75,000+	99	15.7	78.8	16.2	5.1	
Unknown	60	9.5	71.7	20.0	8.3	
Stage at diagnosis§						
In situ	84	13.8	82.1	14.3	3.6	<0.001
Stage I	182	30.0	61.5	30.2	8.2	
Stage IIa	102	16.8	47.1	32.3	20.6	
Stage IIb	45	7.4	48.9	22.2	28.9	
Stage III/IV	28	4.6	57.1	25.0	17.9	
Unknown	166	27.3	63.3	21.7	15.1	

*Tests of significance of association between lymphedema (none, mild, moderate/severe) and levels of exposures are based on Mantel-Haenszel χ^2 tests for categorical or ordinal variables as appropriate.

†American Association of Medical Colleges (68).

‡Modified Charlson index (69). Sum of scores, as assigned: Assign 1—myocardial infarction, congestive heart failure, peripheral vascular disease, stroke (no paralysis), chronic pulmonary disease, ulcer, mild liver disease, and diabetes; Assign 2—hemiplegia, moderate or severe renal disease, diabetes with end organ damage, and any cancer other than breast cancer.

§AJCC stage (35). Complete AJCC staging information was not available for 166 patients because we lacked information on one or more components of stage. There were another 24 patients, who lacked information to distinguish between stage I or IIa. Except for descriptive analyses in Tables 1 and 2 that are stratified by stage, all study subjects were included in the analyses. Among the 441 women with known AJCC stage in our study, the distribution of *in situ* (19%) and invasive (81%) cancers was the same as reported by the Pennsylvania Cancer Registry for the counties (Delaware and Philadelphia) and years (1999-2001) covered by our study (70).

raise questions for future research. Reviews published within the last 10 years have reinforced the prevailing view that the most important treatment risk factors for lymphedema are ALND and radiation therapy, particularly radiation involving the axilla (7-15, 40). We found that ALND and chemotherapy, specifically multiagent therapies with anthracycline, were the only treatments significantly associated with increased lymphedema risk in standard multivariable models. Four recently published studies also reported increased rates of lymphedema associated with chemotherapy (41-44). The mechanism by which chemotherapy would increase

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Table 2. Percent (number) of participants with specified exposure, by stage of cancer at diagnosis

	Overall	Stage of cancer at diagnosis*					
	(*n* = 631)	*In situ* (*n* = 84)	I (*n* = 182)	IIa (*n* = 102)	IIb (*n* = 45)	III/IV (*n* = 28)	DK/Unk* (*n* = 166)
Any radiation	65.8 (415)	53.6 (45)	78.0 (142)	68.6 (70)	77.8 (35)	64.3 (18)	53.0 (88)
Among those with radiation:							
%Breast/chest wall only	80.2 (333)	100.0 (45)	99.3 (141)	77.1 (54)	42.9 (15)	11.1 (2)	71.6 (63)
%Breast/chest wall + supraclavicular field	9.6 (40)	0.0 (0)	0.7 (1)	11.4 (8)	22.9 (8)	44.4 (8)	15.9 (14)
%Breast/chest wall + supraclavicular field + full axilla	10.1 (42)	0.0 (0)	0.0 (0)	11.4 (8)	34.3 (12)	44.4 (8)	12.5 (11)
Any chemotherapy	43.6 (275)	1.2 (1)†	27.5 (50)	80.4 (82)	84.4 (38)	78.6 (22)	49.4 (82)
Among those with chemotherapy:							
% with anthracycline	80.7 (222)	100.0 (1)	86.0 (43)	85.4 (70)	94.7 (36)	86.4 (19)	64.6 (53)
Any tamoxifen	63.5 (401)	46.4 (39)	63.7 (116)	73.5 (75)	71.1 (32)	57.1 (16)	65.1 (108)
Any lymph node surgery	74.5 (470)	13.1 (11)	96.7 (176)	99.0 (101)	97.8 (44)	85.7 (24)	68.7 (114)
Among those with any lymph node surgery:							
%Sentinel + axillary	31.1 (146)	9.1 (1)	34.1 (60)	35.6 (36)	43.2 (19)	25.0 (6)	21.1 (24)
%Axillary only	50.2 (236)	63.6 (7)	36.4 (64)	53.5 (54)	54.5 (24)	66.7 (16)	62.3 (71)
%Sentinel only	16.6 (78)	18.2 (2)	29.5 (52)	10.9 (11)	0.0 (0)	4.2 (1)	10.5 (12)
Any breast surgery‡							
Among those with any breast surgery:							
%Mastectomy	30.1 (190)	19.0 (16)	17.0 (31)	31.4 (32)	40.0 (18)	64.3 (18)	44.0 (73)
% with concurrent reconstruction	24.2 (46)	37.5 (6)	32.3 (10)	31.3 (10)	27.8 (5)	22.2 (4)	15.1 (11)
%Breast conservation	69.4 (438)	81.0 (68)	82.4 (150)	68.6 (70)	60.0 (27)	35.7 (10)	54.8 (91)
Any breast/axilla infection	5.5 (35)	3.6 (3)	6.6 (12)	8.8 (9)	6.7 (3)	3.6 (1)	4.2 (7)

*See footnote § in Table 1.

†This participant first received chemotherapy in the third year after diagnosis. Of the 275 participants given chemotherapy, 271 began chemotherapy within the first year of diagnosis.

‡Virtually 100% of participants had breast surgery.

lymphedema risk is not known, and it is possible that chemotherapy might be a marker for more aggressive disease. For example, greater tumor involvement in nodes might predispose to lymphedema by causing lymphatic stasis for some period of time even before the cancer is diagnosed and definitively treated. However, based on our sensitivity analyses, the positive association between anthracycline chemotherapy and lymphedema does not seem to be confounded by stage at diagnosis or number of positive lymph nodes. Lending credibility to our results, the increased rate of lymphedema associated with anthracyclines was even stronger when the criterion for lymphedema was restricted to moderate/severe lymphedema (Table 3). In this subgroup, 89% of women experienced lymphedema lasting ≥6 months. Anthracycline-containing regimens differed in their constituent components, and the proportion of women receiving a non–anthracycline-based chemotherapy regimen in this cohort was small. Therapies, such as taxane without anthracycline, and other newer therapies [e.g., trastuzumab (Herceptin), lapitinib, and bevacizumab] did not occur in sufficient numbers to be evaluated. Overall duration of therapy could be a factor regardless of specific agents.

The lower risk of lymphedema after SLNB has been shown in many clinical studies; our population-based sample of patients seen at community hospitals, as well as teaching hospitals and cancer centers, documents the persistence of this effect when SLNB is more widely practiced. The HRs for treatment combinations suggest that the risk of lymphedema with SLNB depends on the subsequent use of anthracycline chemotherapy. Without chemotherapy, lymphedema risk was low after SLNB; however, the risk of lymphedema after SLNB and chemotherapy was significantly elevated compared with no treatment. As shown in Table 4, in our study, only 25% of the person-months of follow-up after SLNB involved anthracycline chemotherapy, whereas 75% did not, perhaps explaining the overall lower risk of lymphedema with SLNB in this population. The many studies reporting a lower incidence of lymphedema in women receiving SLNB compared with ALND (42, 45-54), for example, lacked detailed information on chemotherapy. Most of these studies recruited patients before or during the mid-1990s, and the proportions of patients receiving anthracycline would have varied considerably.

Like ours, other recent studies found no increased risk associated with radiation therapy (41-44). The relative

Published OnlineFirst October 26, 2010; DOI: 10.1158/1055-9965.EPI-09-1245

Table 3. Patient and treatment risk factors for lymphedema. HRs at end of 5 y of follow-up, unadjusted and adjusted for all variables listed in the table

Potential risk factor*	ANY lymphedema, *n* = 238		Moderate/severe lymphedema, *n* = 82†	
	Unadjusted HRs (95% CI)	Adjusted HRs (95% CI)	Unadjusted HRs (95% CI)	Adjusted HRs (95% CI)
Patient characteristics				
Age group (reference: <50 y)				
80+	0.49 (0.30-0.80)	0.79 (0.43-1.46)	0.49 (0.22-1.11)	1.09 (0.38-3.14)
50-79	0.74 (0.56-0.97)	0.83 (0.60-1.14)	0.56 (0.35-0.88)	0.78 (0.45-1.36)
Race (reference: white)				
Black	1.45 (1.12-1.88)	1.17 (0.87-1.57)	2.10 (1.36-3.24)	1.39 (0.86-2.25)
BMI (reference: <25)				
30+	1.66 (1.23-2.26)	1.45 (1.04-2.02)	1.79 (1.06-3.02)	1.61 (0.91-2.83)
25-29.99	1.20 (0.87-1.66)	1.24 (0.89,1.74)	1.21 (0.69-2.13)	1.30 (0.71-2.37)
Education level (reference: college graduate+)				
<High school grad	1.72 (1.12-2.62)	1.49 (0.92-2.40)	2.61 (1.24-5.50)	1.84 (0.78-4.32)
High school grad or some college	1.69 (1.19-2.39)	1.56 (1.08-2.24)	2.02 (1.05-3.86)	1.79 (0.91-3.52)
Marital status (reference: unmarried)				
Married	1.01 (0.79-1.31)	1.03 (0.78-1.36)	0.67 (0.43-1.05)	0.68 (0.42-1.11)
Health coverage (reference: private insurance)				
Medicaid/public assistance/no insurance	2.22 (1.47-3.34)	1.46 (0.91-2.32)	1.92 (0.97-3.81)	0.93 (0.43-2.00)
Some Medicare	0.88 (0.65-1.18)	1.00 (0.69-1.44)	0.69 (0.41-1.18)	0.94 (0.47-1.85)
Difficulty getting care (reference: not at all)				
Extremely/very difficult	1.85 (1.03-3.33)	1.20 (0.61-2.35)	2.91 (1.25-6.79)	1.65 (0.61-4.51)
Somewhat difficult	1.44 (1.07-1.94)	1.25 (0.91-1.71)	1.73 (1.06-2.82)	1.52 (0.91-2.54)
Treatments				
Lymph node surgery (reference: no lymph node surgery)				
SLNB only	1.08 (0.61-1.92)	1.04 (0.58-1.88)	0.99 (0.31-3.20)	0.99 (0.29-3.40)
Any ALND	3.12 (2.20-4.43)	2.61 (1.77-3.84)	3.96 (1.99-7.86)	2.59 (1.17-5.74)
SLNB and ALND	2.89 (1.93-4.30)	‡	3.18 (1.48-6.86)	‡
ALND only	3.27 (2.27-4.73)	‡	4.46 (2.21-9.02)	‡
Breast surgery (reference: breast conservation)				
Mastectomy	1.25 (0.94-1.65)	1.11 (0.78-1.58)	2.18 (1.40-3.41)	1.60 (0.90-2.86)
Simultaneous reconstruction	1.54 (0.96-2.45)	‡	2.04 (0.96-4.34)	‡
No simultaneous reconstruction	1.16 (0.85-1.59)	‡	2.23 (1.38-3.60)	‡
Chemotherapy (reference: none)				
Anthracycline-based regimen	2.11 (1.59-2.79)	1.46 (1.04-2.04)	5.23 (3.09-8.85)	3.76 (2.01-7.04)
Other/unknown type	1.49 (0.89-2.48)	1.05 (0.62-1.80)	4.37 (1.99-9.56)	3.16 (1.38-7.23)
Radiation therapy (reference: none)				
Breast/chest wall only	1.02 (0.76-1.38)	1.18 (0.80-1.73)	0.60 (0.35-1.04)	0.89 (0.43-1.81)
Breast/chest wall + supraclavicular field	1.32 (0.60-2.87)	0.77 (0.34-1.73)	2.13 (0.92-4.93)	1.06 (0.44-2.60)
Breast/chest wall + supraclavicular field + full axilla	1.33 (0.66-2.68)	0.95 (0.46-1.97)	1.72 (0.70-4.18)	1.03 (0.40-2.69)
Breast/chest wall + supraclavicular field (+/− full axilla).	1.33 (0.77-2.29)	0.86 (0.48-1.54)	1.92 (0.98-3.75)	1.05 (0.50-2.20)
Tamoxifen (reference: none)				
Yes	1.02 (0.76-1.36)	1.03 (0.76-1.39)	1.15 (0.71-1.87)	1.23 (0.73-2.08)
Breast/axillary infection (reference: none)				
Yes	1.80 (1.05-3.10)	1.15 (0.65-2.03)	1.11 (0.40-3.04)	0.70 (0.25-1.97)

*The numbers of patients in each category can be found in Tables 1 and 2.

†Seventy-three (89%) of the 82 women with moderate/severe lymphedema had lymphedema lasting 6 or more months.

‡These sublevels were not included in the final model because there were too few observations to permit cross-classification of factors to support estimation and interpretation.

Published OnlineFirst October 26, 2010; DOI: 10.1158/1055-9965.EPI-09-1245

Table 4. HRs for incidence of lymphedema for combinations of axillary surgery, chemotherapy, and radiation therapy compared with a reference group of no axillary surgery, radiation, or chemotherapy, adjusting for the potentially confounding patient and treatment factors specified in Table 3

	Person-months of exposure (% of all person-months with that exposure)*
(A) ALND, no chemotherapy, no radiation: HR, 3.78 (95% CI, 2.17-6.58)	2,265 (10.9)
(B) ALND, anthracycline†, no radiation: HR, 5.46 (95% CI, 2.97-10.01)	1,470 (7.1)
(C) ALND, no chemotherapy, radiation‡: HR, 4.67 (95% CI, 2.48-8.83)	2,704 (13.0)
(D) ALND, anthracycline, radiation: HR, 4.61 (95% CI, 2.43-8.73)	3.632 (17.5)
(E) SLNB, no chemotherapy, no radiation: HR, 0.30 (95% CI, 0.04-2.27)	718 (3.5)
(F) SLNB, anthracycline, no radiation: HR, 4.06 (95% CI, 1.32-12.45)	222 (1.1)
(G) SLNB, no chemotherapy, radiation: HR, 1.74 (95% CI, 0.70-4.37)	1,714 (8.3)
(H) SLNB, anthracycline, radiation: HR, 4.09 (95% CI, 1.43-11.76)	589 (2.8)
(I) Reference: No ALND or SLNB, no radiation, no chemotherapy: HR, 1.0	3,277 (15.8)

NOTE: Reported HRs are estimates from a model with risk factors nested (a method for examining interaction terms). With a reference group of subjects with no radiation, no chemotherapy, and no axillary surgery (no ALND or SLNB), each of the lettered results (A-H) must be contrasted with this reference (row I). Thus, for example, the reported HR for (A) 3.78 is the relative hazard of developing lymphedema in those having ALND versus having no axillary surgery (no ALND or SLNB), assuming that the patient had no chemotherapy or radiation.

*Total number of person-months in the model: 20,778. The number of person-months in the last column of the table totals to 16,591 because results for some treatment combinations with very few person-months of observation (e.g., chemotherapy but not anthracycline-based) are not shown in the table.

†Anthracycline chemotherapy: any regimen containing anthracycline.

‡Radiation therapy: any radiation therapy regardless of extent.

contribution of radiation therapy to lymphedema may be less evident after chemotherapy. Consistent with current recommendations (24), in our study, chemotherapy generally preceded radiation for women undergoing breast conservation. Ninety-one percent of the 210 patients receiving both chemotherapy and radiation had their chemotherapy first. Our results might be related to improvements in contemporary practice, not just changes in chemotherapy regimens, but pursuing this further was beyond the scope of the study.

Although incidence of lymphedema was lowest for treatments that did not include ALND or chemotherapy, the interaction models presented in Table 4 and Fig. 1 (lower two curves) suggested that in the absence of these exposures, radiation might result in an increase in lymphedema risk. The curves seemed to be different and the HR for the comparison was large, but power was limited and results were not significant. Recently, Hayes and colleagues (55) reported that both chemotherapy and radiation therapy increased the risk of lymphedema, and that the risk increase was greater with axillary radiation. Their study recruited patients from 1970 to 2005, a period over which approaches to radiation and chemotherapy changed dramatically, and the effects of treatment sequence and type of chemotherapy were not explored.

Similar to other reports (9, 11, 13, 15, 56), we found increased risks of lymphedema in women with BMI ≥30 at the reference date compared with those with lower BMI, which remained statistically significant after adjusting for potential confounding by treatment. However, sensitivity analyses showed no effect modification by BMI, that is, the association of any treatment type and lymphedema did not differ by BMI (data not shown).

Recommendations for improving survivorship research have stressed the need for large, population-based studies representing the diversity of the survivor population; information not only on treatments but on sociodemographic factors and underlying comorbidities; and detailed timelines for exposures and adverse events (40). Consistent with these recommendations, our study is observational and population based; it encompasses the diverse population and wide range of treatments present in the community that could influence the risk of lymphedema, which would not be feasible with a randomized trial. Additional strengths are the prospective study design; the relatively long 5-year follow-up; the narrow recruitment time frame of the study, precluding major changes in treatment patterns; comprehensive assessment of potential risk factors; the ability to assign exposures to each month of follow-up so that the temporal order of exposures and outcome could be assessed; the use of a previously validated questionnaire to assess lymphedema from patient self-report; and supplementary medical record reviews to obtain specifics of treatment regimens.

Potential limitations relate to selection bias, information bias, confounding, and sample size. To minimize selection bias, we started with nearly complete enumeration of

Published OnlineFirst October 26, 2010; DOI: 10.1158/1055-9965.EPI-09-1245

newly diagnosed breast cancer patients residing in our well-defined study area and then randomly selected potential participants. Among these, 41% were enrolled. Enrollment was similar for white and black women, but was lower for women ages 80 years and older than for younger women (data not shown). The proportions of enrolled women with *in situ* and invasive breast cancer were the same as in the population as a whole (see footnote in Table 1). Nonresponse resulted mainly from restrictive hospital requirements for patient contact, physician refusal, or inability to find the physician. We have no evidence that physician/hospital noncooperation was related to the risk of lymphedema. Instead, noncooperation reflected global concerns about patient privacy, especially salient as the new Health Insurance Portability and Accountability Act regulations were being discussed (29). Removing from the denominator of potentially eligible patients those not enrolled because they were inaccessible (i.e., physician/hospital noncooperation, died before initial contact, moved or could not be located), the percent enrolled increased to 62% (29). Further, some of the nonrespondents may have been found to be ineligible had they enrolled, increasing the estimated response rate further.

Regarding loss to follow-up, yearly retention overall was generally high, near or above 90%, dropping to 81% by the third year of follow-up, the transition year between the original study and continuation funding (29). The longer time between contacts during this year resulted in more losses to follow-up. Most lymphedema began during the first 2 years of follow-up, and survival analysis maximized the use of follow-up months. Reasons for dropping out varied, with no indication that loss to follow-up occurred predominantly in persons at higher or lower risk of lymphedema.

Finally, as described in Materials and Methods, all models were adjusted for patient and treatment factors that might influence the risk of lymphedema (listed in Table 3), helping to reduce potential bias resulting from imbalances due to nonresponse or loss to follow-up.

Regarding information bias, a potential limitation of our study is that for practical reasons, we relied on patient self-reports instead of directly measuring arm circumference or volume. However, the most appropriate method to assess the presence and degree of lymphedema has been debated for years, and it is increasingly accepted that the patient herself can best judge her condition (31-33, 57-59). In our study, trained interviewers used a structured questionnaire that we developed and validated for this purpose. In the validation study, sensitivity and specificity of self-reported lymphedema were high compared with expert physical therapists' diagnosis based on arm measurements (28, 29). Another advantage of our approach is that, unlike direct arm measurements, use of a structured questionnaire minimizes intra- and inter-observer variability (60).

It is difficult to compare incidence of lymphedema across studies, given the different approaches to measuring and defining lymphedema, as well as the variable lengths of follow-up. Nonetheless, as we reported previously (29), the 35% incidence of lymphedema at 3 years in our study was in the range reported by others for a comparable time period, varying from 15% (61) to 21% (62, 63) to 54% (42). The first two studies used circumferential measurements but with different criteria for lymphedema (61, 62), and the third and fourth used self-reports (42, 63).

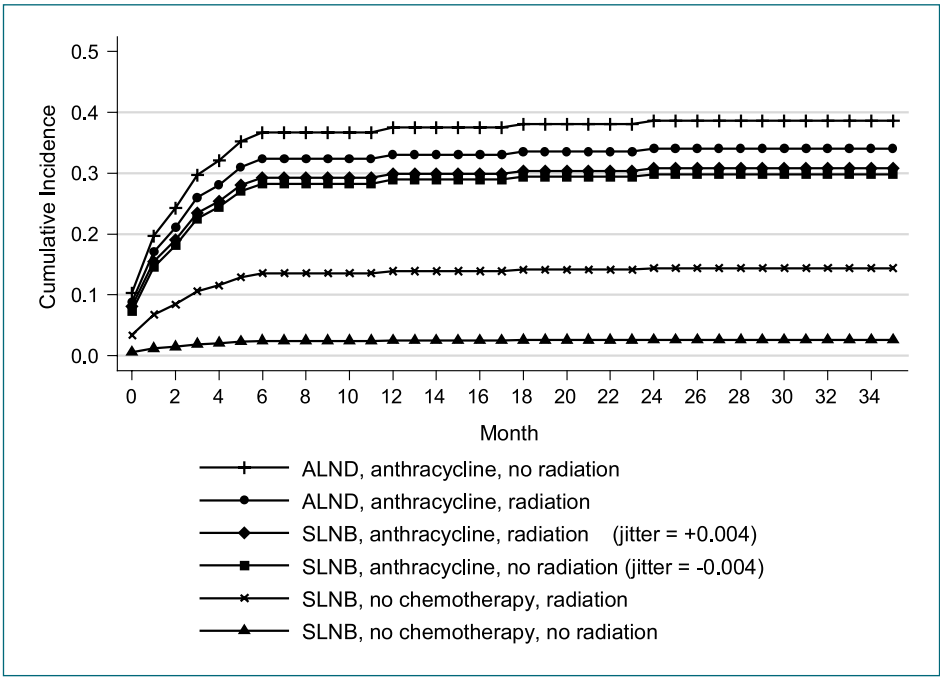

Figure 1. Estimated cumulative incidence of lymphedema according to different treatment scenarios based on discrete time survival models. The jitter represents a small addition/subtraction to the true values to enhance separation of the plotted values for visual clarity. Anthracycline therapy: any regimen containing anthracyclines. Radiation therapy: any radiation therapy regardless of extent.

Published OnlineFirst October 26, 2010; DOI: 10.1158/1055-9965.EPI-09-1245

By design, our measure of lymphedema relies solely on perceived differences in size between the limbs, unlike some other questionnaires developed for self-reported lymphedema assessment in which swelling has been combined with additional factors, such as discomfort, heaviness, tightness, decreased functional activity, movement limitation, and need for a compression sleeve (50, 51, 53, 63). An important objective of our questionnaire development was to design a questionnaire that defined lymphedema independent of its potential effect on quality of life. This was in keeping with the definitions of lymphedema at the time we designed our study, which were based on size. Further, to learn more about the effects of lymphedema on quality of life, we needed to separate size from interference with daily activities (29).

Presence and timing of medical conditions and cancer treatment were also obtained from self-reports to best capture the relative time difference between exposures and lymphedema outcome. Agreement between self-reports and medical records for the presence and dates of breast cancer treatment is high (64-67), and we used medical records for treatment details such as types of chemotherapy, lymph node dissection, and radiation fields that have been shown to be less well remembered.

Potential confounding was addressed by examining a wide range of exposures previously reported as risk factors for lymphedema as well as those that might act as confounders within our data. When evaluating confounding, we distinguished between potential confounders (independent risk factors for lymphedema that were associated with the exposure of interest but were not a consequence of the exposure) and other factors that were intervening variables, not confounders. An example of such a potential physiologic mechanism might be weight gain subsequent to chemotherapy, which in turn triggers lymphedema. Chemotherapy would still increase the risk of lymphedema regardless of the mechanism. Finally, as with all studies, it is possible that there were unidentified confounders that were unaccounted for.

Another limitation relates to sample size. Although our study was large, we lacked power in some subgroup analyses. The number of women with radiation to the supraclavicular fields was small, leaving some open questions about the association of the extent of radiation therapy and lymph node irradiation with lymphedema risk. For example, it seemed, anomalously, that lymphedema risk was lower with more extensive radiation than with radiation limited to the breast/chest wall, but these results did not differ significantly. The study also lacked sufficient power to study the types of chemotherapy in finer detail.

Although our study suggests that the increase in risk of a single therapy may depend on the presence or absence of other therapies, more research is needed to replicate, clarify, and extend these findings to appropriately counsel and monitor breast cancer survivors about lymphedema risk associated with breast cancer treatment. The consistency of recent studies, each with somewhat varying definitions of lymphedema and each conducted in different populations but over a relatively similar time frame, supports further pursuit of potential mechanisms behind the association between cancer treatments and lymphedema.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Grant Support

National Cancer Institute grant R01 CA65422 and American Cancer Society grant ROG-02-259 (S.A. Norman).

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Received 12/10/2009; revised 07/06/2010; accepted 07/12/2010; published OnlineFirst 10/26/2010.

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Published OnlineFirst October 26, 2010; DOI: 10.1158/1055-9965.EPI-09-1245

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