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REVIEW

Magnitude of late effects of breast cancer treatments on shoulder function: a systematic review

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Abstract Late effects of treatment for breast cancer on shoulder function have been documented by a number of investigators; however, many studies include only prevalence data. When comparisons are provided that assess differences between treatment groups, only *P*-values without magnitudes of effect are often reported. The purpose of this systematic review was to identify literature that could be used to examine the magnitude of late effects of breast cancer treatments on shoulder function with a particular focus on axillary lymph node dissection (ALND) and on radiotherapy. A comprehensive search of online databases was performed for research papers published between 1980 and 2008 that provided comparison data between treatment groups, between the affected and unaffected side of individuals, or between pre-operative and subsequent assessments 12 months or more after diagnosis of breast cancer. Papers that met inclusion criteria were reviewed using a methodological checklist. Standardized effect sizes were computed for continuous data; odds ratios and 95% confidence intervals were computed for dichotomous data if not already available. Twenty-two papers met the inclusion criteria. With a few exceptions, most analyses showed excess shoulder morbidity with breast cancer treatment, ALND, or radiotherapy. Although effect sizes varied, moderate to large effects predominated across the different outcomes. There is sufficient evidence of late effects of ALND or radiotherapy post-breast cancer to warrant careful attention to shoulder function across time in individuals who have had breast cancer. Implications for future shoulder dysfunction are discussed.

Keywords Breast neoplasm · Shoulder morbidity · Radiotherapy · Lymph node biopsy · Effect size · Odds ratio

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Introduction

Current evidence suggests that upper extremity impairments from treatment for breast cancer can extend beyond the acute stages of recovery and may be considered a component of chronic illness [1, 8, 21, 43]. Investigators have found that a proportion of women treated for breast cancer continue to experience upper extremity functional limitations two or more years after treatment [18, 20, 26, 41]. Of particular concern relative to shoulder morbidity in the breast cancer patient are nodal dissection and radiotherapy.

Upper extremity lymphedema following breast cancer treatments is a well-documented phenomenon that has received considerable attention [7]. However, the magnitude of shoulder impairments as late effects from breast cancer surgery and radiotherapy independent of lymphedema has received considerably less attention. Moreover, most studies on shoulder impairments post-treatment for breast cancer do not account for pretreatment shoulder morbidity or control in some way for the effects of aging. Because both factors are related to long-term shoulder morbidity in the breast cancer population [16, 30, 42], prevalence data on shoulder morbidity may be inflated and potentially dismissed as weak evidence. Studies that attempt to control for selected covariates by conducting comparisons over time, between groups, or between affected and unaffected arms often report only *P*-values rather than magnitude of effects. The actual impact of breast cancer treatment on shoulder function cannot be ascertained from *P*-values alone. Further, the acknowledged variability of effects among patients may mask potentially important impairments for many individuals with relatively high *P*-values.

Both axillary lymph node dissection (ALND) and radiotherapy have been reported to affect long term shoulder function. Studies indicate that sentinel node biopsy (SNB) reduces shoulder morbidity as compared to ALND [19, 21, 31, 40], although both procedures may contribute to shoulder impairments [19]. Shoulder impairments following radiotherapy may occur after "latent periods" of several months to several years, with late reactions continuing beyond that period in some individuals [1, 10, 47]. Patients receiving axillary radiation (as opposed to chest wall radiation alone) are at higher risk for late arm morbidity [3, 35, 41]. Cheville and Tchou noted that failure to recognize lasting sequelae from treatment for breast cancer delays treatment referrals and may lead to greater long-term shoulder morbidity [7]. Inattention to such morbidity may be an issue for both individuals who have been treated for breast cancer and their health care providers. The purpose of this systematic review was to identify literature that reported or would allow assessment of the magnitude of late effects of breast cancer treatments on shoulder function 1 year or more after diagnosis, with a particular focus on lymph node dissection and on radiotherapy. Presentation of such data in one place will assist health care professionals who have periodic contact with individuals treated for breast cancer in understanding the extent to which late effects on the shoulder may affect such an individual.

Methods

Literature search

Eligible papers had to include breast cancer subjects at least 1 year post-diagnosis as the minimum criterion for late effects. Papers had to be published after 1980 and could not include pre-1980 radiotherapy to minimize the likelihood of including subjects receiving older forms of radiotherapy no longer meeting current standards. Outcomes had to include assessment of impairments or functional activities of the shoulder and, to the extent to which they can be separated, were not to include symptoms related to lymphedema. Pain was accepted as an outcome only if it was reported with functional activity. Quality of life outcomes were not considered because the study focus was to isolate the physical effects of shoulder morbidity. Studies required at least two comparison groups or comparisons to the unaffected side. Comparisons across time were acceptable only when baseline measures were performed preoperatively or pre-radiotherapy. Randomized controlled trials, prospective, retrospective and cross-sectional designs were considered acceptable. The available data had to include means and standard deviations (SDs) or 95% confidence intervals (CIs) for both groups, or group data that would permit computation of odds ratios if not reported by the authors.

Search engines used were PubMed, Medline, CINAHL, Cochrane, Health Source Nursing, Google, and Google Scholar. Search terms were limited to the title, abstract, or keywords and included combinations of breast neoplasm, breast cancer, shoulder, arm, scapula, or humerus, along with sentinel node, brachial plexopathy, pectoralis major, pectoralis minor, latissimus dorsi, rotator cuff, teres minor, late effects, ROM, range of motion, radiotherapy, and radiation. Retrieved abstracts were reviewed for possible inclusion. When warranted, full articles were obtained for review. All full articles were reviewed by the two authors. Any differences in opinion on eligibility were resolved by discussion. There was agreement on all papers that were finally accepted as eligible for inclusion in the systematic review. A methodological checklist was adapted from several sources to assess quality of the included papers [27, 33, 44]. Each eligible paper was subjected to methodological review using the checklist (Table 1).

Data analysis

When means and standard deviations were reported for groups, standardized effect sizes were calculated as $(M_1 - M_2)/\mathrm{SD}$, where M is the mean for each group and the mean difference is standardized using the standard deviation of the referent or control group [34]. Although there is no consensus on the interpretation of standardized effect sizes [34], the guidelines proposed by Cohen were used; an effect size of 0.20 is considered to be small, 0.50 to be moderate and 0.80 to be large [9]. When data were dichotomous, odds ratios were computed to estimate effect size using frequency counts. If frequency counts were not available, reported proportions were used and so noted.

Results

The searches yielded a total of 375 citations from January 1980 through May 2008. After review of all abstracts, 88 papers available in English were retrieved for further examination. Of those, 22 were determined to meet eligibility criteria [3, 6, 12–14, 16, 17, 19, 20, 22, 25, 28–31,

Table 1 Methodological criteria check-list

Criterion	References																					
	[3]	[6]	[12]	[13]	[14]	[16]	[17]	[19]	[20]	[22]	[25]	[28]	[29]	[30]	[31]	[33]	[37]	[38]	[39]	[40]	[42]	[45]
1. *Study population*																						
Source of subjects and recruitment period specified		✔	✔	re	✔	re	✔	✔	re	✔	re	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔
Eligibility criteria specified	re	re	✔	✔		re	✔	✔	✔		✔	✔	✔	✔	✔		✔	re	✔	✔		✔
Loss-to-follow-up identified		✔	✔	✔	✔		✔		✔		✔	✔	✔		✔	✔	✔	✔	✔	✔	✔	✔
Sample size determination made and met											ts											✔
2. *Design*																						
Cross-sectional	✔	✔								✔		✔		✔					✔		✔	
Prospective					✔	✔	✔	✔	✔						✔	✔	✔	✔			✔	
Retrospective																				✔		
Case–control																	✔	✔				
Randomized clinical trial			✔	✔							✔		✔									✔
3. *Allocation*																						
RCT: concealed/ randomized sequence			nr	nr							✔		✔									
Comparability at baseline described			✔	✔						✔					✔		✔	re				✔
4. *Description of treatments*																						
Surgical interventions described	✔	✔	✔	✔	✔	✔	✔		✔	✔	✔	✔	✔	✔	✔	re			✔	✔	✔	✔
Lymph node dissection described	✔	✔	✔	✔		✔			✔	✔	✔	✔	✔	✔	✔	re			✔	✔		✔
Radiation therapy described	✔	✔	✔	✔	✔	✔	✔		✔	✔		✔	✔	✔	✔	re			✔	✔	✔	✔
Chemo/hormonal therapy described			✔	✔	✔	✔	✔			✔		✔	✔	✔	✔	re			✔	✔		
5. *Tests and measurements*																						
Baseline measurements taken			✔				✔	✔			✔		✔		✔	✔					✔	
Impairment outcomes objectively measured and adequately described							✔	✔		✔	✔	✔	✔	✔	✔	✔					✔	
Functional outcomes assessed using standardized tool(s)			✔								✔			✔	✔	✔						

Table 1 continued

Criterion	References																					
	[3]	[6]	[12]	[13]	[14]	[16]	[17]	[19]	[20]	[22]	[25]	[28]	[29]	[30]	[31]	[33]	[37]	[38]	[39]	[40]	[42]	[45]
Reliability of outcomes addressed*	re		✔				✔								✔	✔			✔			
Validity of outcomes addressed*			✔								✔				✔	✔			✔			
Rater(s) masked			na	sr		sr	sr		na								na	na	na			na
6. Statistical Analyses																						
Outcomes analyzed at level collected	✔		✔				✔				✔		✔		✔	✔						
Intention-to-treat analyses (RCT)			✔								✔		✔									✔
Statistical control for covariate(s)	✔		✔	✔		✔			✔			✔			✔	✔	✔	✔	✔		✔	
Total checks	6	6	16	9	6	6	11	8	7	8	12	10	13	9	16	10	7	5	11	8	9	10

re, cited as reported elsewhere; nr, not reported; na, not applicable (patient self-report only); sr, single rater (masking not reported); ts, trial stopped before full enrollment

* Either in text or by citation

33, 37–40, 42, 45]. The results of the methodological review are shown in Table 1.

Overall breast cancer treatment effects on shoulder function

Four studies were found that permitted comparison of the affected shoulders of subjects treated for breast cancer to the same shoulder pre-treatment [33], to the uninvolved shoulder [30] or to subjects without breast cancer [36, 37]. In these studies, specific treatments were not evaluated; rather, the effects of all treatments were assessed. Effect sizes are reported in Table 2. For two of the studies, standardized effect sizes were computed from available data [30, 33]. For one study, crude odds ratios and 95% CIs were computed for each of the presented age groups and are reported along with the adjusted odds ratios given by the authors [36]. For one paper, the authors reported odds ratios and 95% CIs for each age group using ridit analyses for ordinal data and logistic regression [37]. In Table 2, the effect size represents the additional morbidity associated with treatment for breast cancer compared to the referent of pretreatment condition, the untreated arm, or subjects without breast cancer. All data show increases of varying magnitudes in morbidity with breast cancer with the exception of selected tasks in the 75–84 year old group in the Satariano et al. study [37].

Magnitude of effect on shoulder function from ALND

Twelve studies included shoulder morbidity data for subjects who were randomized to or underwent either ALND or SNB (or no axillary dissection) [6, 12, 19, 20, 22, 25, 29, 31, 33, 39, 40, 45]. As shown in Table 3, crude odds ratios and 95% CIs were estimated from available data from eight studies [6, 12, 19, 20, 22, 39, 40, 45], while standardized effect sizes were computed for two [29, 31]. The SNB group was considered the referent group with the exception of Lash and Sillman [20] and Caban et al. [6] where the referent to ALND was no axillary surgery. Each of these effect sizes represents the excess shoulder morbidity of ALND over the referent. Mansel et al. [25] reported 95% CIs rather than SDs so effect sizes could not be computed. The magnitude of changes after 1 year in the affected arm for each group are reported in Table 3. Reitman et al. [33] reported the means and SDs of change scores for each group after 2 years (Table 3) but did not include the SD for preoperative (baseline) measures. If the SD of the change score for the SNB group is used in lieu of the SD of the SNB group's preoperative measures, the standardized effect sizes for the difference between groups in reduction from preoperative to 2 year values can be obtained. Using this strategy, the standardized effect size for reduction in ranges of shoulder abduction and abduction/external rotation and for reductions in grip strength are 0.73, 0.46 and 0.50, respectively, with ALND showing higher morbidity.

Table 2 Breast cancer compared to non-breast cancer shoulder outcomes

Author	Number of subjects	Comparison(s)	Shoulder outcomes	Effect size		
Rietman et al. [33]	181 subjects at 2 years post-op	2 years to Pre-op	Change from pre-op to 2 years:	Mean change (SD)	Std. effect size	
			Flexion (°)*	−4.4 (12.6)	**0.37**	
			Abduction(°)*	−16.2 (31.0)	**0.72**	
			Abduction/ER(°)*	−6.0 (12.3)	**0.91**	
			ER(°)	−5.9 (13.6)	**0.45**	
			Strength of abduct (Nm)*	−10.0 (29.9)	**0.27**	
			Grip strength (Nm)*	−33.6 (51.7)	**0.53**	
					Referent: pre-op	
Rietman et al. [30]	55 subjects with a mean follow-up of 2.7 (SD = 0.7) years. post-op	Side of BCa to contralateral side	Contralateral-BCa side	Affected side	Unaffected side	Std. effect size
			Active flexion(°) *	153.2 (26.2)	158.9 (23.1)	**0.25**
			Active abduction (°) *	156.6 (30.1)	164.1 (19.4)	**0.39**
			Passive ER(°) *	57.3 (14.6)	63.5 (12.6)	**0.49**
			Grip Strength(N)	171.6 (64.2)	183.9 (73.4)	**0.17**
						Referent: contralateral side
Satariano [38]	843 BCa cases at 12 months post-dx; 887 population-based controls	Cases to controls	1 or more upper body limitations (pushing, lifting, reaching)	OR (95% CI)	Adjusted OR[a]	
		40–54 years old		**1.83 (.98–3.41)**	1.5 ($P = 0.005$)	
		55–64 years old		**2.21 (1.2–4.09)**	1.7 ($P < 0.001$)	
		65–74 years old		**2.34 (1.32–4.16)**	1.6 ($P < 0.001$)	
		75–84 years old		**2.13 (1.20–3.77)**	1.4 ($P < 0.001$)	
Satariano et al. [37]	422 cases at 12 months post-dx; 478 controls 8–10 months after first interview	Cases to controls		ORs (95% CIs)		
				55–64 years old	65–74 years old	75–84 years old
			Strength in pushing	1.54 (1.23–1.93)	1.67 (1.30–2.18)	0.92 (0.64–1.30)
			Lifting <10 pounds	1.14 (0.97–1.34)	1.36 (1.10–1.69)	1.23 (0.90–1.71)
			Lifting >10 pounds	1.51 (1.22–1.88)	1.45 (1.14–1.87)	1.25 (0.88–1.80)
			Reaching	1.12 (0.93–1.34)	1.20 (0.98–1.48)	0.84 (0.62–1.12)
			Increasing number of 4 tasks identified as difficult	1.23 (1.02–1.49)	1.56 (1.24–2.0)	1.05 (0.74–1.48)

BCa, breast cancer; SD, standard deviation; ER, external rotation

Bold: Calculated from authors' data

*$P < 0.001$ in favor of pre-op

*$P < 0.006$ for differences in favor contralateral side

[a] demog. variables and co-morbidities

Most of the data in Table 3 show an increase in morbidity with ALND with at least selected functions. Caban et al. [6] did not demonstrate an effect on flexion range of motion. Lash and Sillman [20] found a paradoxical protective effect in both the crude and adjusted odds ratios of ALND compared to no nodal dissection on self-reported decline in one or more of three tasks compared to preoperative status. Schulze et al. [40] found a slight protective effect of ALND compared to SNB when self-reported loss of mobility was assessed, although objective data showed a strong positive association for reduced abduction range of motion.

Magnitude of chest wall and axillary radiotherapy effect on shoulder function

Ten studies were found that permitted one or more comparisons of shoulder morbidity between radiotherapy and no radiotherapy, or between differing radiotherapy fields [3, 6, 13, 14, 16, 17, 20, 28, 39, 42]. Five of the papers included comparisons of a subject group with any radiotherapy (or unspecified radiotherapy) to a group without radiotherapy [3, 6, 13, 14, 20]. Three papers compared chest wall radiotherapy alone to a group without radiotherapy [17, 39, 42], while four compared a group with chest wall radiotherapy to a group with both chest wall and at least axillary radiotherapy [16, 17, 39, 42]. One paper compared a group with multiple radiation fields including the full axilla to a group with multiple radiation fields but only at the apex of the axilla [28]. Johansson et al. [17] also compared a group with chest wall and axillary radiotherapy to a group with no radiotherapy. For eight of the studies, effect sizes were computed from published data or data provided by the authors (Table 4). Standardized effect sizes were computed when appropriate measurement data were available (two studies); crude odds ratios and 95% CIs were estimated when only frequencies were available (seven studies). Adjusted odds ratios obtained via logistic regression were reported in five studies and are included in Table 4 [6, 13, 16, 28, 39]. For all calculated effect sizes, the referent was the no radiotherapy group (compared to a radiotherapy group), or the chest wall radiotherapy group (compared to a chest wall and axillary radiation group). The effect sizes, therefore, represent the excess shoulder morbidity associated with radiotherapy or more extensive radiotherapy. The only exception to this generalization is the adjusted (logistic) odds ratio reported by Caban et al. [6]. Their odds ratio and 95% CI represents the reduction in morbidity (protective effect) associated with *not* having radiotherapy because their referent was the radiotherapy group. Unless otherwise noted in Table 4, the extent of radiotherapy (inclusion of the axilla or additional fields) was not specified.

The majority of studies in Table 4 show increased morbidity associated with more extensive radiotherapy in at least some of the assessed functions. The exceptions are Johannson et al. [17] whose data showed some small but protective effects of chest radiation compared to no radiation on selected range and strength measures, and the Lash and Sillman [20] data where the crude odds ratio showed a protective effect of radiotherapy compared to no radiotherapy on decline in upper body function. The adjusted odds ratio reported by Lash and Sillman, however, showed a small excess of morbidity associated with radiotherapy.

Discussion

Review of Tables 2, 3, and 4 show, with the few noted exceptions, that there is an excess morbidity associated with treatment for breast cancer with ALND compared to SNB, and with radiotherapy or more extensive radiotherapy. However, the effect sizes vary dramatically from small standardized effect sizes (0.20 or less or odds ratios near 1.0) to substantial standardized effect sizes well in excess of 0.80 and odds ratios of 2.0–3.0 or more. Moderate to large effects predominate, especially where abduction and flexion ROMs were reported. This review would largely appear to reinforce the conclusion of Blomqvist et al. [3] that shoulder morbidity, while most evident at the individual level, is sufficient to be seen at the group level. The variations in magnitude and in the size of standard deviations and confidence intervals also reflect the variations in morbidity that exist between studied individuals.

Variability in shoulder morbidity effects may be attributed in part to the diversity of outcome measures and the diversity of methods by which even similar outcomes were assessed and reported. In ten studies, patient self-report of loss of strength, range of motion (ROM) or functional ability were used [11, 13, 14, 20, 22, 36, 37, 39, 40, 45]. In these instances, data were either dichotomized or categorized. When categorical data were collected, data were collapsed by the study authors or by the authors of this paper into impairment as present or absent because of small cell numbers. Only the ridit analyses of Satariano et al. [37] maintained categories of effect within a functional limitation. Two studies subjectively assessed observed impairment and dichotomized the outcomes [6, 16]. Of the studies that measured ROM objectively, seven reported actual ranges [3, 17, 25, 29–31, 33], while five dichotomized their findings [13, 19, 22, 40, 42]. Ranges found to be 10°, 20° or 10% less than the contralateral limb or full ROM were considered to be impaired. This is a strategy similar to that used in other studies [5, 15, 43, 46]. Box

Table 3 Axillary lymph node dissection compared to sentinel node biopsy or no axillary dissection

Author	Number of subjects	Comparison(s)	Shoulder outcomes	Effect size	
Caban et al. [6]	158 ALND; 29 None at 12 months post-diagnosis	ALND to none	Any observed decrease	Proportions	OR (95% CI)
			Decreased flexion ROM	24% vs. 24%	**0.99 (0.39–2.51)**
			Probability of _full_ flexion ROM	Logistic regression	
				OR = 1.02 (0.33–3.13)	
Fleissig et al. [12]	$N = 605$ @ 18 months post-op	Std. node dissection to SNB	Somewhat/quite a bit/very much in last 7 days on:	Proportions	OR (95% CI) for proportions
	Orig group: 405 ALND; 424 SNB (of which 72 went on to ALND)		↓ROM at 12 months	8.8% vs 3.1%	**3.02 (0.80, 11.35)**
			at 18 months	8.4% vs 3.8%	**2.32 (0.66, 8.06)**
			pain w/motion at 12 months	11.8% vs 3.4%	**3.80 (1.08, 12.99)**
			at 18 months	8.6% vs 3.1%	**2.94 (0.77, 11.11)**
			stiffness at 12 months	10.7% vs 2.7%	**4.32 (1.10, 16.91)**
			at 18 months	8.1% vs 3.5%	**2.43 (0.67, 8.79)**
Langer et al. [19]	431 SNB alone; 204 SNB/ALND at median ≈ 30 months post-op	SNB/ALND to SNB	Any shoulder ROM deficit >20° compared to standard and unaffected side.	Proportions	OR (95% CI)
				11.3% vs. 3.5%	**3.53 (1.80–6.91)**
Lash [20]	219 ALND; 30 No dissection at	ALND to None	Late effects: decline from preop in ≥1 of three tasks	Proportions	OR (95% CI)
	473–1,092 days post-op			34% vs. 50%	**0.52 (0.24, 1.22)**
				Logistic regression	
				OR = 0.8 (0.2–2.2)	
Leidenius et al. [22]	47 ALND; 92 SNB at 3 years post-op	ALND to SNB		OR (95% CI)	
			Restriction ≥ 10° Flexion[a]	**2.65 (1.17, 6.01)** ($P = 0.0175$)	
			Self-report of reduced arm function since pre-op	**9.23 (1.87–45.46)** ($P = 0.0014$)	
Mansel et al. [25]	403 ALND; 413 SNB (of which 83 went on to ALND) at baseline and 12 months post-op	ALND to SNB	[1 mo.–12 mo.] measure ipsilaterally	Mean (95% CI)[c]	
				ALND	SLNB
			Flexion[b]	2.7° (1.2–4.2)	0.1° (–1.2–1.5)
			Abduction[b]	2.5° (0.6–4.4)	1.9° (0.2–3.5)
			External rotation	0.6° (–0.8–2.0)	0.7° (–0.8–2.1)
			Internal rotation	1.7° (0.4–3.0)	0.4° (−1.0–1.8)

Table 3 continued

Author	Number of subjects	Comparison(s)	Shoulder outcomes	Effect size	
Purushotham et al. [29]	143 ALND; 134 SNB (of which 57 went on to ALND) at 12 months post-op	ALND to SNB	Reduction in ranges from pre-op to 12 months	ALND change-SNB change (95% CI)	Effect Size (*P* value)
			Flexion	6.3° (0.1–12.6)	**0.40** ($P = 0.04$)
			Extension	0.7° (–1.5–3.3)	**0.0** ($P = 0.6$)
			Abduction	3.2° (−0.5–6.3)	**0.20** ($P = 0.08$)
			Internal Rotation	1.4° (−1.5–4.4)	**0.11** ($P = 0.3$)
			External Rotation	1.4° (−1.5–4.4)	**0.12** ($P = 0.3$)
Rietman et al. [31]	131 ALND; 58 SNB at 12 months from pre-op baseline	ALND to SNB	[Pre-op-12 mo.] measure	ALND change-SNB change	Effect Size (*P* value)
			Flexion	5.0°	**0.50** (.005)
			Abduction	14.5°	**0.72** (<0.001)
			Abduction/ext rot	4.3°	**0.54** (.11)
			External rotation	2.0°	**0.16** (.324)
			Strength of abduct	14.9 Nm	**0.62** (.001)
			Grip strength	25.6 Nm	**0.56** (.001)
Rietman et al. [33]	124 ALND; 57 SNB at 2 years	ALND to SNB	Reduction in ranges from pre-op to 2years:	ALND	SNB
				Mean difference (SD)	Mean difference (SD)[e]
			Abduction[d]	21.0° (33.5)	5.5° (21.0)
			Abduction/ext rot[d]	7.2° (13.7)	3.5° (8.0)
			Grip strength (Nm)[d]	41.3 (51.7)	17.2 (48.2)
Schijven et al. [39]	213 ALND; 180 SNB alone 1–3 years Post-op	ALNB to SNB		Crude OR (95% CI)	Logistic regression ORs
			Painful shoulder/arm	**3.54 (1.88–6.66)**	3.23 ($P = 0.03$)
			Strength loss (arm/hand)	**8.82 (3.90–19.91)**	7.14 ($P = 0.00$)
			Loss of full active ROM	**3.44(1.71–6.95)**	3.57 ($P = 0.01$)
			Not using arm as before	**3.18 (1.68–6.00)**	2.94 ($P = 0.00$)
Schulze et al. [40]	56 ALND; 19 SNB alone >20 months post-op.	ALNB to SNB	Objective (contralateral referent)	Proportions (ALND vs. SNB)	OR (95% CI) for proportions
			↓Abduction ROM (>10°)	19.6% vs 0%	**9.0 (0.50, 161.33)**[f]
			Resist'd abduction (>10°)	48.2% vs 15.8%	**5.14 (1.34, 19.67)**
			Subjective (compared to pre-op)		
			Loss of force (≥ occass.)	66.0% vs 47.3%	**2.28 (.78, 6.60)**
			Loss of mobility (yes/no)	28.6% vs 31.6%	**0.87 (0.28, 2.68)**

Table 3 continued

Author	Number of subjects	Comparison(s)	Shoulder outcomes	Effect size	OR (95% CI) for proportions
Veronesi et al. [45]	100 ALND; 100 SNB alone at 24 months post-op	ALND to SNB	Self-reported rating of restriction in shoulder motion from 0–100%[g]	Proportions (ALND vs. SNB)	
			80–100%	79% vs 100%	**54.35 (3.24–911.32)**[h]
			<80%	27% vs. 0%	

ALND, axillary lymph node dissection; SNB, sentinel node biopsy; OR, odds ratio; SD, standard deviation; CI, confidence interval; ROM, range of motion

Bold: Calculated from authors' data

[a] Other motions $P > 0.05$ (no data reported)

[b] $P < 0.05$ in favor of SLNB

[c] SD of pre-op values not available

[d] $P < 0.025$ in favor of SLNB

[e] SD of pre-op values not available

[f] Using 0.5 correction all cells

[g] 100% = No perceived restriction

[h] Using 0.5 correction all cells

et al. and Voogd et al. [5, 46] specifically addressed losses of 20° from preoperative or contralateral measures as associated with decreased function. Some variability in effect size can be attributed to estimates of crude as opposed to adjusted odds ratios. In six of the studies, odds ratios computed from logistic regression indicated morbidity associated with radiotherapy after adjusting for other covariates including number of nodes dissected, or ALND adjusted for other covariates including radiotherapy. Another source of variability in effect may be the different follow-up periods. Caban et al. [6] used a 12 month follow-up; however, they suggested that this observation period may be insufficient to see the full impact of radiation-induced fibrosis and recommended a follow-up period of 5 years to show the late effects of radiotherapy. Lastly, self-reported estimates of morbidity may be affected by individual expectations associated, for example, with age and by the individual's ability to adapt over time to limitations [1, 37, 38].

The methodological checklist was not intended to be a quantitative assessment; however, it included 20 possible checks for randomized controlled trials and 19 for other designs. Of note was that only two studies achieved 16 checks [12, 30]. While thirteen studies obtained fewer than 10 checks (see Table 1). Given the variability in magnitudes of effect for ascertainment of morbidity and in methodological quality among these papers, it was determined that attempts to summarize the data using meta-analytic techniques were inappropriate. Rietman et al. [32] came to a similar conclusion in their systematic review of late morbidity after treatment for breast cancer.

Most of the studies included in this review followed subjects out for 3 years or less. Bentzen et al. [2] found that time to expression of 90% of the ultimately expected damage from radiotherapy was 3.7–4.2 years depending on the clinical covariates in the model (although radiotherapy techniques in their subjects may have varied from current standards). Fathers and Thrush [10] encountered symptoms of brachial plexopathy in the affected limb 8–20 years after radiotherapy. Because many of the studies included in this review assessed subjects only 1–2 years post-diagnosis or treatment, it may be that morbidity will continue to increase over time for some percentage of the subjects who received radiation. No reference to potential time effects of morbidity related to ALND or SNB were found in the literature although increases over time cannot be ruled out.

Current and future shoulder morbidity may be linked to radiation-induced changes. Bentzen et al. [2] hypothesized that damage to the pectoralis major muscle from radiotherapy was a significant factor in shoulder movement impairment even without clinically detectable subcutaneous tissue fibrosis. Shamley et al. [41] found that pectoralis major and minor muscles decreased in size on the affected

Table 4 Radiotherapy compared to none or chest wall and axillary radiation compared to chest wall radiotherapy alone

Author	Number of subjects	Comparison(s)	Shoulder outcomes	Effect size		
			Self-reported impairment of ADL	XRT: No XRT **OR = 1.48 (0.56, 3.87)**		
Blomqvist et al. [3]	30 XRT; 45 no XRT at 15 months post-MRM	XRT to no XRT		XRT	No XRT	Std ES[a,b]
			Opp. side—MRM side[c]			
			Extension ROM	2.3° ($P < 0.05$)	1.5° (NS)	0.15
			Flexion ROM	17° ($P < 0.001$)	3.0° ($P < 0.05$)	1.30
			Abduction ROM	33° ($P < 0.001$)	6.9° ($P < 0.05$)	1.85
			ER ROM	10.8° ($P < 0.01$)	−0.1° (NS)	1.35
			IR ROM	4.2° ($P < 0.01$)	0.2° (NS)	0.40
			Extension strength	4.8 ($P < 0.01$)	1.0 (NS)	0.47
			Flexion strength	4.9 ($P < 0.001$)	2.0 ($P < 0.05$)	0.24
			Abduction strength	2.6 ($P < 0.05$)	0.1 (NS)	0.25
			ER strength	1.5 (NS)	0.9 (NS)	0.08
			IR strength	3.6 ($P < 0.01$)	0.9 (NS)	0.46
			(*strength units not specified*)			
Caban et al. [6]	56 XRT; 131 no XRT at interview 12 months post-dx	XRT to no XRT	Any observed decrease in flexion ROM	Proportions	OR (95% CI)	
			Decreased flexion ROM	34% vs. 20%	**2.07 (1.03–4.18)**	
				Logistic regression[d]		
				OR = 0.35 (0.12–1.02)		
Hørjis et al. [13]	42 XRT; 42 no XRT. All MRM at 6–13 years post-treatment	XRT (4 fields) to no XRT		Proportions	OR (95% CI)	
			Subjective			
			Loss of any mobility	38% vs. 4%	**12.30 (2.61, 58.03)**	
			Sx loss of mobility	17% vs. 2%	**8.20 (0.96, 69.93)**	
			At least weekly pain	26% vs. 4%	**7.10 (1.46, 34.38)**	
			Interference w/function	29% vs. 4%	**8.0 (1.66, 38.45)**	
			Detectable weakness	28% vs. 19%	**1.70 (0.61, 4.72)**	
			Measured			
			Flex or abd <170°	52% vs. 15%	**6.60 (2.30, 18.96)**	
			Detectable weakness	14% vs. 2%	**6.83 (0.79, 59.48)**	
			Impaired mobility with other variables	Logistic OR (95% CI) = 7.0 (2.2, 22.0)		
Isakkson and Feuk [14]	12 XRT; 33 no XRT at 1–2 years post-op	XRT to no XRT		OR (95% CI)		
			Self-report of restricted arm/shoulder movement	**10.67 (0.99–115.36)**		

Table 4 continued

Author	Number of subjects	Comparison(s)	Shoulder outcomes	Effect size	
Johansson et al. [17]	23 No XRT; 15 Chest XRT; 18 chest/axillary XRT at 2 years			Std ES (mean diff in change)[e]	
		Chest XRT to no XRT (preop to 2 years change)	Abduction ROM	**−0.3 (−7.1°)**	
			Flexion ROM	**−0.5 (−2.5°)**	
			IR ROM	**−0.1 (−1.7°)**	
			ER ROM	**0.1 (0.8°)**	
			Abduction Strength	**−0.5 (−0.7 kp)**	
			Flexion Strength	**0.1 (0.1 kp)**	
			Extension Strength	**0.1 (0.1 kp)**	
			IR Strength	**−0.2 (−0.5 kp)**	
			Grip Strength	**0.1 (0.6 kp)**	
		Chest/axillary XRT to no XRT (preop to 2 years change)	Abduction ROM	**1.8 (38.7°)**	
			Flexion ROM	**2.4 (11.8°)**	
			IR ROM	**0.2 (3.0°)**	
			ER ROM	**2.2 (22.7°)**	
			Abduction Strength	**0.2 (0.2 kp)**	
			Flexion Strength	**0.1 (0.1 kp)**	
			Extension Strength	**0.3 (0.5 kp)**	
			IR Strength	**0.1 (0.3 kp)**	
			Grip Strength	**0.0 (0.1 kp/cm^2)**	
		Chest/Axillary XRT to Chest XRT (preop to 2 years change)	Abduction ROM	**6.0 (45.8°)**	
			Flexion ROM	**2.6 (11.8°)**	
			IR ROM	**0.5 (4.7°)**	
			ER ROM	**1.2 (21.9°)**	
			Abduction Strength	**0.8 (0.9 kp)**	
			Flexion Strength	**0.0 (0.0 kp)**	
			Extension Strength	**0.3 (0.4 kp)**	
			IR Strength	**0.3 (0.8 kp)**	
			Grip Strength	**−0.1 (−0.5 kp/cm^2)**	
Johansen et al. [16]	121 chest and axillary XRT; 145 chest XRT alone. All BCT at 3.5–10.5 years post-diagnosis	Chest/axillary XRT to chest XRT alone		Proportions	OR (95% CI)
			≥Mild flex or abd ROM deficit	20% vs. 4%	**3.37 (1.16, 9.74)**
			≥Mild strength deficit	59% vs. 40%	**1.68 (0.91, 2.92)**
			Impaired mobility controlling for other variables	Logistic RR (95% CI) = 4.6 (1.5, 13.8)	
			Impaired strength controlling for other variables	Logistic RR (95% CI) = 1.7 (0.19–3.0)	

Table 4 continued

Author	Number of subjects	Comparison(s)	Shoulder outcomes	Effect size	
Lash and Silliman [20]	168 XRT; 27 no XRT. All BCT at 473–1,092 days post-op	XRT to no XRT	Late effects: decline from preop in ≥1 of three tasks	Proportions 35% vs. 41%	OR (95% CI) **0.78 (0.34, 1.80)**
			Adjusted for other variables	Logistic regression	
				OR (95% CI) = 1.3 (0.4–4.3)	
Nesvold et al. [28]	99 chest/full axillary XRT; 164 chest/apex of axilla only. 32–87 months post-XRT	XRT including full axilla to XRT with axillary apex only		OR (95% CI)	
			Flexion deficit ≥25° compared to contralateral	2.97 (1.54–5.7)[f] ($P = 0.001$)	
				1.22 (0.51–2.75)[g] ($P = 0.64$)	
			Abduction deficit ≥25° compared to contralateral	2.22 (1.25–3.88)[f] ($P = 0.006$)	
				1.19 (0.54–2.6)[g] ($P = 0.67$)	
Schijven et al. [39]	44 Chest/axillary XRT; 133 Chest XRT only; 31 no XRT[h] 1–3 years post-op			Logistic regression ORs (90% CI where given)	
		Axillary/supra vs. chest only XRT	Not using arm as before	2.64 (1.41–4.96) ($P = 0.01$)	
		No XRT vs. Chest only	Not using arm as before	1.32 ($P = 0.48$)	
Sugden et al. [42]	49 Chest/axillary XRT; 92 Chest XRT only at ~18 months post-XRT	Chest/axillary XRT to chest XRT only	Impairment: <90% of contralateral	Proportions	OR (95% CI)
			Flexion*	39% vs. 4%	**13.93 (4, 38, 44.22)**
			Abduction*	49% vs. 8%	**11.65 (4.4, 30.2)**
			Extension*	45% vs. 14%	**4.95 (2.19, 11.16)**
			ER*	29% vs. 11%	**3.28 (1.32, 8.09)**
			IR	27% vs. 21%	**1.38 (0.61, 3.12)**
			Flexion*	24% vs. 5%	**6.23 (1.38, 28.05)**
			Abduction*	35% vs. 7%	**7.18 (1.95, 26.23)**
			Extension*	41% vs. 13%	**4.70 (1.48, 14.94)**
			ER*	35% vs. 11%	**4.60 (1.37, 15.46)**
			IR	6% vs. 20%	**0.25 (0.03, 2.01)**

XRT, radiotherapy; Std ES, standardized effect size; MRM, modified radical mastectomy; BCT, breast conserving therapy; ADL, activities of daily living; IADL, instrumented activities of daily living; ROM, range of motion; ER, external rotation; IR, internal rotation; dx, diagnosis; flex, flexion; abd, abduction; SD, standard deviation. Bold: calculated from authors' data

[a] Difference between groups in side-to-side differences

[b] SD for Std ES estimated from SEMs reported by authors

[c] Significance for side-to-side differences

[d] Odds ratio for *NO* limitation w/multiple covariates, including independent IADL

[e] Data provided by authors upon request

[f] Univariate

[g] Multivariate (logistic)

[h] Numbers estimated from authors' percents

* $P < 0.01$

side in a series of 57 breast cancer patients from 6 months to 6 years post-surgery, most of whom had chest wall radiation. However, surgery in the vicinity of the pectoralis major or minor may also create fibrotic changes with healing. Fibrosis in the pectoralis major and minor may be a factor in range of motion limitations which may also increase the risk for shoulder impingement syndrome or rotator cuff tears [23]. Ludewig and Cook [24] found that subjects with symptoms of impingement showed greater scapular anterior tipping, decreased upward rotation, and increased scapular medial rotation under load conditions. Borstad and Ludewig [4] found that subjects with a clinically determined short pectoralis minor muscle demonstrated scapular kinematics similar to those found for subjects with shoulder impingement. Decreased scapular upward rotation and increased anterior tipping may be critical in limiting adequate clearance for the rotator cuff tendons. Ludewig and Cook [24] hypothesized that even small limitations in scapular motion (4–6°) may be clinically important given the small size of the suprahumeral space, potentially contributing to initiation or progression of shoulder impingement symptoms. These same limitations to scapular motion are likely to reduce available shoulder range of motion given that the scapulothoracic joint contributes 60° to the total shoulder range of flexion and abduction [23]. Consequently, even the small decreases shown in motions like shoulder abduction and flexion among subjects who have had breast cancer may place these individuals at increased risk for shoulder impingement or rotator cuff problems over time. The magnitude of risk may be hypothesized to increase with increases in motion restrictions.

Limitations

Numerous factors prevent precise determination of the contribution of breast cancer treatments to impaired shoulder function. Tables 2, 3 and 4 and the discussion highlight several of these factors, but are not all inclusive. Bentzen and Dische and Langer et al. [1, 19] provide a comprehensive review of confounding and interactive factors that affect study results related to determination of post-treatment shoulder morbidity, including the lack of a uniformly accepted system for recording and grading shoulder morbidity that limits comparisons across treatment types and across studies.

Conclusion

This systematic review demonstrates the magnitude and the variability in effect sizes of shoulder morbidity attributable to treatment for breast cancer, with a focus on ALND and radiotherapy. Although mathematical aggregation of data was not attempted, the large majority of studies indicated increased shoulder impairments as a late effect from these treatments, with effects varying from small to substantial. Given the functional limitations that are described and the hypothesized relation between even minor limitations to shoulder motion and the potential for shoulder impingement or rotator cuff tear, this review supports the importance of health care professionals routinely asking patients about shoulder function, assessing function, and referring patients for remediation when even subtle limitations are present. Chirikos et al. [8] found that a breast cancer group was more likely to experience adverse economic outcomes compared to age-matched controls, with work-related differences narrowly missing statistical significance. This observation suggests that economic benefits of interventions that minimize or prevent problems are potentially high. The authors of this paper also concur with the recommendations of other investigators that use of selected valid and reliable shoulder function measures is required to enable comparisons across studies and to determine meaningful conclusions. Much work remains to be done to confirm the need to attend to late effects of breast cancer treatments on shoulder function.

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