Acta Oncologica, 2010; 49: 347–353

informa
healthcare

ORIGINAL ARTICLE

Arm/shoulder problems in breast cancer survivors are associated with reduced health and poorer physical quality of life

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Abstract

Background. Except for lymphedema, the consequences of arm/shoulder problems (ASPs), at long-term in breast cancer survivors (BCSs) have hardly been studied. We examined demography, lifestyle, quality of life (QoL) and somatic morbidity in BCSs with and without ASPs. We also compared the associations of restricted shoulder abduction and lymphedema with QoL. *Methods.* We used a cross-sectional case-control design. A sample of 256 BCSs all with lymph node metastases were examined at a mean of 4.1 (SD 0.9) years post-surgery. Based on objective examinations and self-rating the sample were separated into 81 BCSs (32%) with definite ASP (ASP+ group) and 175 (68%) with minimal or no ASP (ASP– group). The self-rating contained among other schedules the Short Form-36 (SF-36) and the Kwan's arm/shoulder problem scale (KAPS). *Results.* In univariate analysis ASP+ was associated with not being employed, having had mastectomy, longer follow-up time, radiotherapy to axilla, poorer self-rated health and physical condition, minimal physical activity, increased body mass index, regularly intake of analgesics, and poorer physical QoL. Multivariate analysis showed that mastectomy, longer follow-up time, minimal physical activity and poorer physical QoL were associated with belonging to ASP+ group. All domains of the SF-36 were significantly associated with having impaired shoulder abduction (≥25° difference) while none of the associations with lymphedema were significant. *Discussion.* In BCSs, at four years after treatment, having ASP was associated with mastectomy, minimal physical activity and poorer physical QoL. Poor physical QoL is strongly associated with reduced shoulder abduction rather than with lymphedema.

Multimodal treatment has increased survival rates in breast cancer patients, resulting in an increasing number of breast cancer survivors (BCSs). As a consequence, much research on health-related quality of life (QoL) of BCSs in general has been published lately. In a recent review on QoL in BCSs, Montazeri found that arm morbidity was among the most common adverse effects in these patients [1]. Reduced prevalence of arm/shoulder problems (ASPs) in BCSs were reported after the introduction of breast conserving therapy (lumpectomy) replacing modified radical mastectomy (mastectomy) [2,3]. Introduction of the sentinel node technique further reduced the prevalence of ASPs [4]. However, axillary dissection due to lymph node metastases and adjuvant radiotherapy to regional lymph nodes stations increase the risk of developing ASPs [5].

Several studies have reported that poor QoL and physical impairment in BCSs in the acute phase will improve during the first year post-treatment [6,7]. In contrast, Mols et al. in their review emphasized that late effects were important when evaluating the total consequences of breast cancer treatment [8]. The relevance of studying ASPs at long-term therefore seem quite relevant.

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(Received 11 March 2009; accepted 1 September 2009)

ISSN 0284-186X print/ISSN 1651-226X online
DOI: 10.3109/02841860903302905

While several studies have reported on the prevalence of ASPs in BCSs after different treatment modalities, few studies have included ASPs in QoL studies. Many studies have reported that presence of lymphedema affects daily activities and social life and implies increased psychological stress in BCSs [9–11]. However, the relative impact of impaired shoulder mobility compared to lymphedema on QoL has not been studied. Therefore, a study of the associations between socio-demographic variables, lifestyle, somatic morbidity, and physical QoL variables and different aspects of ASPs at long-term follow-up (defined as mean follow-up time of >3.0 years) [12,13] eventually should fill a gap in our knowledge. Particularly since Kwan et al. [14] reported that even minimal arm/shoulder problems could have a significant negative impact on QoL at long-term, and Engel et al. [15] also found that self-reported arm/shoulder problems affected QoL several years post-treatment.

In this cross-sectional follow-up study our primary aim was to compare BCSs with and without ASPs at long-term concerning socio-demographic, somatic morbidity, lifestyle, and QoL. Secondly, we wanted to study the associations between lymphedema and impaired shoulder mobility and QoL. As to our primary hypothesis, we held that BCSs with ASPs would be significantly associated with more problems than BCSs without ASPs concerning these factors. Based on the literature our second hypothesis was that lymphedema rather than impaired shoulder mobility would be significantly associated with poor QoL.

Methods

Patient sampling

Women treated for stage II–III breast cancer, between 1998 and 2002 at The Norwegian Radium Hospital, were invited to take part in a follow-up survey in 2004/2005. The survey consisted of a mailed questionnaire and an outpatient clinical examination.

The inclusion criteria were: 1) Curatively intended surgery, either mastectomy or lumpectomy, followed by radiotherapy to the regional lymph node stations and the chest wall/breast; 2) No evidence of relapse since primary treatment; 3) No other malignant diagnosis; 4) Age ⩽75 years at the time of the survey.

Among the 415 BCSs who fulfilled the eligibility criteria, 23 declined participation, and 43 did not respond, resulting in 350 BCSs (84% response rate) delivering questionnaire and 318 (91%) of them had an outpatient examination. A total of 55 primarily inoperable patients with cT3–cT4 tumours, who received neo-adjuvant chemotherapy, were excluded in order to obtain a more homogenous sample concerning treatment regimes. Seven patients were omitted due to incomplete questionnaires. The sample of the present study was therefore restricted to 256 BCSs with pT1–pT2 tumours, all with axillary lymph node metastases.

Treatment modalities

Treatment was based on the guidelines of the Norwegian Breast Cancer Group (NBCG). The primary treatment consisted of mastectomy or lumpectomy and axillary lymph node dissection at level I–II. The target volume of radiotherapy included the breast for lumpectomy, and the chest wall for mastectomy and all patients had radiotherapy to the ipsilateral supraclavicular fossa, the lymph nodes along the ipsilateral internal mammarian artery and the ipsilateral axilla. The post-mastectomy scar was covered by a 6 cm wide bolus.

From October 1999 BCSs who had removed ⩾10 axillary nodes without perinodal infiltration, had irradiation only to the axillary apex, while those with <10 nodes removed or perinodal infiltration, had radiotherapy to the entire axilla. The latter procedure was applied to all BCSs who had radiotherapy before that time.

Post-operative adjuvant chemotherapy with CMF or FEC and/or tamoxifen were administered according to the patients' age and the hormone receptor status of the tumour.

Arm/shoulder morbidity

Clinical physical assessments. During the outpatient follow-up examination BCSs had their arm/shoulder function assessed by two physiotherapists who had extensive experience with such patients. Goniometer-based measurements were performed for flexion (forward elevation of arm) and abduction (lateral elevation of arm) of both arms. Clinical experience had shown that a 10–20° reduced range of motion compared to the contra-lateral side, did not limit the daily activities of the patients [16]. Therefore, we defined a reduced range of motion of ⩾25° difference as impaired shoulder mobility.

The presence of *lymphedema* was assessed by volumetric calculation using five circumferential measurements on both arms, since high correlation with water displacement volumetry ($r=0.96$) and high reliability has been demonstrated [17]. The summed volume of the truncated cones was calculated. Lymphedema was defined as either: 1) a difference of ⩾10% in volume between the two arms; or 2) ⩾2 cm increase of any circumference of the

affected arm versus the other arm and in addition use of compression garment or having had treatment for lymphedema. Additional information of treatment of swelling and impaired shoulder mobility was collected by interview.

Self-rating of ASP. The Kwan's arm problem scale (KAPS) was used for self-rating of persistent ASPs [14]. The KAPS consistsof the *Problem subscale* with eight items rating arm/shoulder function, pain, stiffness and swelling, and the *ADL subscale* with five items rating impairment in daily life functioning due to ASP. All 13 items are rated on five point Likert scales from 1 ("no symptom" or "same as before") to 5 ("severe symptom" or "unable to perform"). Scores on the Problem and the ADL subscales were summed up to give the KAPS total score. The scoring of the Problem subscale ranged from eight to 40 points, and the ADL subscale from five to 25 points. The KAPS has shown good psychometric properties with high reliability and considerable convergent and discriminant validity in our sample of BCSs, and the cut-off of the KAPS total score defining ASPs was found to be $\geq$21.5 based on receiver operating curve analyses [18].

Definition of the ASP groups. The ASP positive group (ASP+ group) was defined by the presence of $\geq$2 of the following criteria based on the definitions given above: 1) impaired shoulder mobility; 2) having lymphedema; or 3) a KAPS total score $\geq$21.5. BCSs who fulfilled $\leq$1 of these criteria were defined as ASP negative (ASP– group). Accordingly 81 BCSs (32%) were classified as belonging to the ASP+ group and 175 (68%) to the ASP– one.

To study the relative impact of lymphedema and impaired shoulder mobility on QoL domains, we chose shoulder abduction as a measure, since this movement showed higher correlation with ASPs ($r=0.80$) than flexion ($r=0.61$).

Demographic and medical data. Information on sociodemography, health and somatic condition, lifestyle issues and use of health services were obtained by questionnaire. Relationship status was dichotomised as paired and non-paired, and level of education into $\leq$12 years or >12 years of education. Employment status was categorized as employed and not employed. The employed category included those working full time and part time, and students. Having disability pension and full time housework was defined as not employed. Level of physical activity was characterized as minimal versus moderate or high activity per week according to published algorithms [19].

Regular and daily use of various medications during the last 12 months was noted. Eventual consultations with various health care providers during the same time period were answered by yes or no. Self-rated health and physical condition were scored on four point Likert scales from 1 (excellent) to 4 (poor) and were then dichotomised into excellent/good versus moderate/poor. Information on cancer treatment and stage was obtained from the medical records.

The Short Form 36 (SF-36). The Medical Outcomes Study Short Form Survey (SF-36) is in common international use as a measure of QoL with well-documented psychometric properties in numerous studies, and established normative data from the Norwegian general population [20].

The SF-36 items are combined to form four physical domain scales: physical functioning, physical role functioning, bodily pain, general health, summarized as the Physical Component Summary Scale (PCS); and four mental domain scales: vitality, social functioning, emotional role functioning and mental health summarized as the Mental Component Summary Scale (MCS) The scale scores are converted to 100 (best QoL) to zero (worst QoL) according to established algorithms. The PCS and MCS have been T-transformed so that the Norwegian general population mean score is set at 50. Scores of 40 and 60 represent one standard deviation from the mean [21].

Statistical analysis

Continuous variables were analyzed with t-tests and categorical variables by χ^2 tests. In case of skewed distributions non-parametric tests were applied. Clinical significance in continuous and 2×2 contingency tables was given by effect sizes (ESs) with a cut-off of ESs $\geq$0.40 [22,23]. Univariate and multivariate logistic regression analyses were used to explore the associations between demographic, lifestyle and morbidity as independent variables and ASP+ versus ASP− (reference) as dependent variable. Only independent variables that were statistically significant in univariate analyses or of particular clinical interest, were included in the multivariate analysis. Stepwise analyses were used to explore the explained variance of the various steps, and explained variance was given by Nagelkerke's R^2 as well as change of explained variance at each step (R^2 change). The strength of the associations was expressed as odds ratios (OR) with 95% confidence intervals (95%CI) at the final step. Multivariate linear regression was used to explore the associations of lymphedema and shoulder abduction and QoL. The analyses were done on SPSS for Windows, version 15.0. The level of significance was set to $p<0.05$, and all tests were two-sided.

Ethical considerations

The study was approved by the Regional Ethical Committee of Health Region South of Norway and by the National Data Inspectorate. All patients gave written informed consent.

Results

Socio-demographic findings

The mean age at survey, the proportions in paired relationships and with lower level of education were similar in both ASP groups (Table I). The proportion being employed was significantly lower in the ASP+ than in the ASP– group, and a significantly higher proportion of the former group was on disability pension.

Cancer-related findings

A higher proportion of the ASP+ compared to the ASP− group had mastectomy ($p<0.001$), and radiotherapy to the entire axilla ($p=0.001$), and the follow-up time was significantly longer in the ASP+ group ($p<0.001$) (Table I). The mean number of axillary lymph nodes and metastatic lymph nodes removed were similar in the two groups. No significant differences were observed concerning cancer stage or the proportion of patients who had received chemotherapy or anti-oestrogen therapy. A similar and high proportion of both groups were still receiving anti-oesterogen therapy at the time of the survey.

All the statistically significant differences were also clinically significant with ESs ≥ 0.40.

Somatic morbidity and QoL

The following analyses were adjusted for follow-up time, employment status, type of surgery, and type of radiotherapy to the axilla. Compared to the ASP− group, the ASP+ group reported a higher proportion with poorer self-rated health ($p=0.01$), minimal physical activity ($p=0.001$), poorer physical condition ($p=0.04$) and used analgesics regularly during the past 12 months ($p=0.01$). The ASP+ group had significantly higher mean BMI and reported poorer QoL on all the physical domains of the SF-36 as well as on the PCS ($p<0.001$) (Table II). Among these findings only the differences in self-rated health and physical activity showed clinical significance.

Table I. Socio-demographic and cancer-related characteristics in breast cancer survivors with (ASP+) and without (ASP−) arm/shoulder problems.

Variables	ASP− n=175	ASP+ n=81	p	ES[a]
	Mean (SD)	*Mean (SD)*		
Age at survey	54.5 (8.2)	54.7 (7.7)	0.82	
Follow-up time- years	3.8 (0.8)	4.3 (1.4)	<0.001	0.50
	N (%)	*N (%)*		
Paired civil status	133 (76)	67 (83)	0.33	
Low level of education (≤12 years)	99 (58)	52 (66)	0.27	
Employment status			0.001	0.47
Employed	119 (69)	37 (46)		
Not employed	54 (31)	44 (54)		
On disability pension[b]	42 (24)	37 (46)	0.001	0.47
Type of breast cancer surgery			<0.001	0.52
Mastectomy	112 (64)	70 (86)		
Lumpectomy	63 (36)	11 (14)		
Adjuvant treatment				
Received chemotherapy	138 (79)	67 (83)	0.58	
Received anti-oesterogen therapy	134 (76)	59 (73)	0.74	
Type of radiotherapy			0.01	0.41
Radiotherapy to axillary apex	121 (69)	40 (49)		
Radiotherapy to axilla	54 (31)	41 (51)		
Stage of cancer			0.17	
Tumour PT 1 (≤2 cm)	102 (58)	39 (48)		
Tumour PT 2 (>2–≤5 cm)	73 (42)	42 (52)		
	Mean (SD)	*Mean (SD)*		
Lymph node status				
Metastatic lymph nodes	2.9 (2.6)	3.4 (3.4)	0.29	
Axillary nodes removed	12.7 (4.3)	12.0 (4.6)	0.27	

[a]Effect size.

[b]In Norway one can hold a small job while on disability pension.

Table II. Somatic morbidity, quality of life and lifestyle characteristics in breast cancer survivors with (ASP+) and without (ASP−) arm/shoulder problems.

Variables	ASP− (n=175)	ASP+ (n=81)	p*	ES[a]
Self-rated health	*N (%)*	*N (%)*	0.01	0.40
Excellent/good	136 (79)	48 (61)		
Moderate/poor	36 (21)	31 (39)		
Life style issues				
Minimal physical activity	11 (6)	16 (20)	0.001	0.43
Poor/very poor physical condition	33 (19)	26 (33)	0.04	0.32
Current smoker	32 (18)	20 (25)	0.31	
Body mass index, mean (SD)	26.1 (4.4)	27.8 (4.9)	0.01	0.37
Use of health service last year				
Visiting a GP	152 (87)	76 (94)	0.15	
Visiting a physiotherapist	63 (39)	41 (51)	0.11	
Use of medication last year				
Analgesics	19 (11)	20 (25)	0.01	0.37
Anti-hypertensives	21 (12)	14 (17)	0.34	
	Mean (SD)	*Mean (SD)*		
Quality of life (SF-36)				
Physical functioning	82.2 (15.8)	67.2 (20.4)	<0.001	0.38
Bodily Pain	71 (26.1)	48.9 (24.9)	<0.001	0.37
Physical Role Functioning	65.7 (39.8)	37.2 (41.4)	<0.001	0.30
General Health	74.9 (20.6)	60.7 (23.7)	<0.001	0.29
PCS	46.7 (9.9)	38.2 (10.3)	<0.001	0.37

[a]Effect size.

*Adjusted for follow-up time, employment status, type of surgery, and radiotherapy to the entire axilla.

Stepwise multivariate model of variables associated with the ASP+ group

Demography, cancer related variables, life style issues, regular use of medication, QoL and health conditions were all significant steps in the stepwise multivariate logistic regression analyses with ASP+ as dependent variable and ASP− as reference. These steps explained 37% of the variance in the ASP+ membership which was significantly associated with increasing follow-up time (p=0.001), having had mastectomy (p=0.01), minimal physical activity (p=0.01) and poorer PCS (p=0.01) (Table III). The greatest contribution was made by the cancer-related step (15%) and the life style variables (9%).

Associations of shoulder abduction and lymphedema with QoL

In multivariate linear regression analyses with impaired shoulder abduction and lymphedema as independent variables (adjusted for surgery, follow-up time, and employment status), all physical and mental dimensions of the SF-36 were significantly associated with impaired abduction, while lymphedema did not show a non-significant association with any of these outcome variables (Table IV). The correlation between having lymphedema and impaired abduction was low (r=0.25).

Discussion

In this cross-sectional follow-up study our hypothesis that BCSs with ASPs would have significantly more problems than those without ASPs concerning demography, lifestyle and somatic morbidity was confirmed. Our second hypothesis was rejected since lymphedema was not associated with any of the SF-36 QoL domains, while we found significant associations between impaired shoulder mobility and all these domains.

As the two ASP groups did not differ in level of education or civil status we conclude that the higher proportion of ASP+ being non-employed and holding disability pension most likely was a consequence of ASPs. We have not observed other studies reporting on employment status related to ASPs, but we assume that our findings indicate disabling consequences of having ASPs at long-term.

Compared to mastectomy, significantly fewer BCSs with lumpectomy belonged to the ASP+ group. Other treatment modalities and disease-related consequences were similar in the two ASP groups, except radiotherapy to the axilla. Among those who had mastectomy 20% had lymphedema compared to 8% in the lumpectomy group, and the corresponding figures concerning impaired abduction were 36% versus 16%. Other studies have also reported significant differences in ASPs between mastectomy and lumpectomy [2,3].

Table III. Stepwise logistic regression analysis of significant independent variables in breast cancer survivors with arm/shoulder problems (ASP+) and without such problems (ASP−) (reference).

Independent variables	OR	95% CI	p	Explained variance/p	Variance change
Step 1. Demographics				0.072/	-
Age	0.99	0.95–1.04	0.72	0.01	
Low level of education (reference >12 years)	0.86	0.41–1.8	0.69		
Not employed (employed as ref)	1.9	0.92–3.88	0.08		
Step 2. Cancer-related variables				0.29/	0.15
Follow-up time	1.07	1.03–1.11	0.001	0.001	
Mastectomy (lumpectomy as ref)	2.98	1.3–6.8	0.01		
RT[a] to axilla (apex axilla as ref)	1.2	0.55–2.7	0.63		
Step 3. Life style issues				0.31/	0.09
Body mass index	1.07	0.99–1.14	0.08	<0.001	
Minimal physical activity (moderate or more as reference)	0.23	0.09–1.38	0.01		
Step 4. Use of medication last year				0.33/	0.02
Analgesics	1.66	0.67–4.14	0.27	0.03	
Step 5. QoL and health condition		0.91–0.98		0.37/	0.04
SF-36 PCS	0.95	0.37–2.3	0.01	<0.001	
Poor health (good=ref)	0.92		0.85		

[a]Radiotherapy.

All socio-demographic and cancer-related variables that showed statistically significant differences between the ASP+ and ASP− groups, reached clinical significance (ESs ≥0.40), thereby strengthening the relevance of our findings.

Defining long-term follow-up as >3.0 years, might be considered as a short period of time. With Bentzen's estimation of 90% of late effects in the arm/shoulder tissue after radiotherapy occuring during the first 3.9 years, we consider the follow-up time as sufficient, although somewhat longer observation-time might have been preferable [24]. Increasing observation time is not reported to be associated with ASPs in other studies, but most of them had shorter follow-up time [6,7]. However, the prospective study by Engel et al. [15], did not find much improvement in self-reported ASPs after five years, with 38% still reporting chronic arm/shoulder problems at that time. All our BCSs had radiotherapy to the regional lymph node stations and the chest wall/breast combined with a relatively long follow-up time. This combination may explain the association between ASP+ and follow-up time in our study.

Table IV. Multivariate linear regression analyses of quality of life SF-36 scores and impaired shoulder mobility* versus lymphedema adjusted for surgery, follow-up time and employment.

Dependent variables	Independent variables			
	Impaired shoulder mobility		Lymphedema	
Continuous variables	beta	p	beta	p
Physical QoL				
Physical function	–0.30	<0.001	–0.05	0.43
Physical role	–0.24	<0.001	0.04	0.53
Bodily pain	–0.29	<0.001	0.01	0.94
General health	–0.24	<0.001	–0.02	0.78
PCS	–0.28	<0.001	–0.01	0.90
Mental QoL				
Vitality	–0.25	<0.001	0.05	0.49
Social function	–0.19	0.001	0.01	0.92
Role emotional	–0.29	<0.001	0.01	0.83
Mental health	–0.18	0.01	0.03	0.69
MCS	–0.16	0.02	0.04	0.57

*≥25° reduction of lateral elevation of ipsilateral arm.

Kwan et al. [14] studied the impact of ASPs on QoL in a small sample of BCSs and found a significant association between ASP+ and reduced physical and social functioning and pain. Our findings are in line with these results by showing a strong association between long-term ASP+ and reduced health condition and QoL.

In a recently published cohort study, Ahmed et al. [10] found that self-reported arm/shoulder problems were associated with low physical and mental QoL eight years after diagnosis. Compared to our findings, these authors reported significantly lower mean values on all SF-36 domains.

Our second hypothesis was rejected by showing a strong association between impaired shoulder mobility and QoL as opposed to the non-significant relation with lymphedema. Our hypothesis was mainly based on the literature, which mostly has focused on the adverse effects of the lymphedema component of ASPs but rarely included concomitant study of shoulder mobility [9,11].

Approximately eight months following surgery, Thomas-Maclean et al. studied the impact of different aspects of arm morbidity, including lymphedema, pain and impairment in range of movement. Using an arm disability instrument they reported that pain and impairment in abduction and rotation, in con-

trast to lymphedema, was associated with disability [25]. Our results in a sample with longer follow-up time complement their results by confirming a strong association between impaired shoulder abduction and poorer PCS, in contrast to lymphedema.

We consider it a strength that our material is homogenous concerning treatment modalities, except for type of surgery to the breast. In addition a high proportion of the patients had received chemotherapy and/or tamoxifen and hence our BCSs represented a group with extensive cancer treatment. The cross-sectional design, which precludes any exploration of causal factors, is a limitation in our study.

Although we cannot definitely say that the impaired abduction found in the BCSs is a consequence of the breast cancer treatment, other explanations are unlikely. Our results have given an indication of women who should have priority for prevention and eventual therapeutic interventions. Breast cancer patients with metastatic axillary lymph nodes will probably in the future continue to have extensive cancer treatment and thereby develop ASPs. The latency in the development of long-term effects in the soft tissue of the shoulder after radiotherapy [24] indicates that the evaluation of eventual treatment has to be considered for a long time after primary treatment. To our knowledge no studies have been published showing results of any interventions for shoulder mobility on a long-term basis. We believe it is relevant to inform the women of potential long-term effects and continuation of stretching of the soft tissue in shoulder/arm for a longer period of time than usually recommended. We see the need for more clinical trials, studying different interventions aimed at preventing long-term ASPs or achieving improvement of ASPs.

Declaration of interest: The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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