Prevalence of and Factors Associated With Persistent Pain Following Breast Cancer Surgery

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Prevalence of and Factors Associated With Persistent Pain Following Breast Cancer Surgery

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Context Persistent pain and sensory disturbances following surgical treatment for breast cancer is a significant clinical problem. The pathogenic mechanisms are complex and may be related to patient characteristics, surgical technique, and adjuvant therapy.

Objective To examine prevalence of and factors associated with persistent pain after surgical treatment for breast cancer.

Design, Setting, and Patients A nationwide cross-sectional questionnaire study of 3754 women aged 18 to 70 years who received surgery and adjuvant therapy (if indicated) for primary breast cancer in Denmark between January 1, 2005, and December 31, 2006. A study questionnaire was sent to the women between January and April 2008.

Main Outcome Measures Prevalence, location, and severity of persistent pain and sensory disturbances in 12 well-defined treatment groups assessed an average of 26 months after surgery, and adjusted odds ratio (OR) of reported pain and sensory disturbances with respect to age, surgical technique, chemotherapy, and radiotherapy.

Results By June 2008, 3253 of 3754 eligible women (87%) returned the questionnaire. A total of 1543 patients (47%) reported pain, of whom 201 (13%) had severe pain, 595 (39%) had moderate pain, and 733 (48%) had light pain. Factors associated with chronic pain included young age (18-39 years: OR, 3.62; 95% confidence interval [CI], 2.25-5.82; $P<.001$) and adjuvant radiotherapy (OR, 1.50; 95% CI, 1.08-2.07; $P=.03$), but not chemotherapy (OR, 1.01; 95% CI, 0.85-1.21; $P=.91$). Axillary lymph node dissection (ALND) was associated with increased likelihood of pain (OR, 1.77; 95% CI, 1.43-2.19; $P<.001$) compared with sentinel lymph node dissection. Risk of sensory disturbances was associated with young age (18-39 years: OR, 5.00; 95% CI, 2.87-8.69; $P<.001$) and ALND (OR, 4.97; 95% CI, 3.92-6.30; $P<.001$). Pain complaints from other parts of the body were associated with increased risk of pain in the surgical area ($P<.001$). A total of 306 patients (20%) with pain had contacted a physician within the prior 3 months for pain complaints in the surgical area.

Conclusion Two to 3 years after breast cancer treatment, persistent pain and sensory disturbances remain clinically significant problems among Danish women who received surgery in 2005 and 2006.

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PERSISTENT POSTSURGICAL PAIN has been demonstrated to be clinically relevant in 10% to 50% of patients undergoing various common operations, including breast cancer surgery.[1] With breast cancer, the pathogenic mechanisms are multiple, including nerve damage related to surgical technique resulting in risk of intercostobrachial neuralgia, neuroma pain, or phantom breast pain.[2] Different types of sensory disturbances (eg, allodynia, hyperpathia, aftersensations, burning, or sensory loss) are sequelae to other surgical procedures and may be an important part of the pain characteristics in breast cancer.[1]

Pain has also been reported to be associated with adjuvant therapy, such as chemotherapy and radiotherapy.[3] Other risk factors may include age (<40 years), psychosocial status, preoperative breast pain,[4] and acute postoperative pain intensity.[5] However, almost all information is retrospective based on questionnaires, often from single centers or small cohorts, not allowing sufficient analyses of the many risk factors. In addition, surgical principles of treatment have changed in recent years, including more breast-conserving surgery (BCS) and use of the sentinel node technique, and principles for radiotherapy and chemotherapy have been adjusted to more recent scientific data, thereby limiting interpretation of previous studies except for an agreement on persistent pain being a significant clinical problem.

The goal of our study was to examine the prevalence, associated factors, and severity of chronic pain and sensory disturbances after surgery for breast cancer in a nationwide study, taking advantage of the unique possibilities in Denmark with a national database managed by Danish Breast Cancer Cooperative Group (DBCG),[6] which

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prospectively collects detailed clinical data, histopathological status, treatment, and data on recurrence and mortality.[1,4,7] Furthermore, treatment principles are standardized at all Danish breast cancer departments according to European guidelines[8] and national protocols designed by the DBCG.[7]

METHOD

Population

Between January 1, 2005, and December 31, 2006, 5119 women aged 18 to 70 years received surgery for unilateral primary breast cancer in Denmark. Exclusion criteria were nonstandardized treatment (n=797); reconstruction or corrective breast surgery (n=319); emigration (n=5); and cancer relapse, new breast cancer, other malignant disease, or death (n=244). A total of 3754 women matched the inclusion criteria.

A study questionnaire (eAppendix; available at http://www.jama.com) was sent to 3754 eligible women between January and April 2008. Reminders were sent 3 weeks later. In June 2008, 3253 questionnaires (87%) had been returned and were eligible for analysis. Distribution between surgical procedures for responders and nonresponders and median age are shown in Table 1.

Treatment

All women in the study received treatment according to the DBCG 2004 treatment protocol,[6,7] which was based on the International Expert Consensus on Primary Therapy of Early Breast Cancer in 2003.[8] The patients were divided according to type of surgery and adjuvant radiotherapy and chemotherapy into 12 major treatment groups (Table 1). Surgery included mastectomy or BCS with either sentinel lymph node dissection (SLND) or axillary lymph node dissection (ALND) levels I and II.[8]

All patients having BCS received radiotherapy corresponding to a total dose of 48 Gy in 24 fractions to the residual breast tissue (BRT). Those women with at least 1 axillary lymph node macrometastasis (node positive) also received radiation to locoregional lymph nodes (periclavicular, axillary level 3, and for right-side breast cancers, the internal mammary nodes) with 48 Gy over 24 fractions (locoregional radiotherapy [LRRT]). Node-positive patients who had a mastectomy also received radiotherapy to the anterior thoracic wall with 48 Gy in 24 fractions (anterior thoracic radiotherapy [ATRT]).[9] Allocation to antiestrogen treatment and standard chemotherapy (cyclophosphamide, epirubicin, and fluorouracil) followed estrogen receptor status and histopathological criteria according to the DBCG 2004 protocol.[7]

Registries

With approval from all Danish breast cancer departments, demographic and treatment data were retrieved from DBCG's database, which includes more than 95% of patients who underwent surgery for breast cancer in Denmark.[7,10] The database includes primary clinical and histopathological data, data on surgical procedure, postoperative adjuvant therapy, and status at follow-up, including information on site of recurrence, all based on specific case report forms submitted by the departments of surgery, pathology, and oncology in Denmark.

Table 1. Pain and Sensory Disturbances Among 3253 Danish Women Who Had Surgery for Primary Breast Cancer According to 12 Different Treatment Groups

	Treatment Modalities, No. (%)												
	Breast-Conserving Surgery						Mastectomy						
	SLND		ALND				SLND		ALND				
	BRT Without Chemotherapy	BRT With Chemotherapy	BRT Without Chemotherapy	BRT With Chemotherapy	BRT + LRRT Without Chemotherapy	BRT + LRRT With Chemotherapy	None	With Chemotherapy	None	With Chemotherapy	ATRT + LRRT Without Chemotherapy	ATRT + LRRT With Chemotherapy	Total
Nonresponders	118 (12)	56 (13)	22 (10)	14 (11)	39 (12)	35 (11)	40 (21)	15 (15)	36 (20)	7 (7)	62 (15)	56 (16)	500 (13)
Age, median (IQR), y	59 (54-64)	47 (39-53)	59 (55-63)	42.5 (41-45)	61 (57-67)	47 (40-51)	62 (58-66)	54 (41-62)	59.5 (55-64)	48 (46-51)	62 (59-66)	48 (41-52)	
Responders	868 (88)	368 (87)	201 (90)	110 (89)	291 (88)	284 (89)	153 (79)	86 (85)	147 (80)	96 (93)	352 (85)	297 (84)	3253 (87)
Age, median (IQR), y	60 (55-65)	49.5 (44-56)	61 (56-64)	49 (44-54)	60 (57-64)	48 (44-53)	62 (58-66)	53 (48-61)	60 (56-65)	48.5 (43-56)	61 (57-65)	48 (44-55)	
Reporting pain	345 (40)	183 (50)	105 (52)	64 (58)	146 (50)	171 (60)	39 (25)	31 (36)	63 (43)	51 (53)	181 (51)	164 (55)	1543 (47)
Worst pain[a]													
Light	186 (54)	96 (53)	44 (42)	34 (53)	75 (52)	76 (45)	24 (62)	13 (42)	30 (48)	18 (36)	69 (39)	68 (42)	733 (48)
Moderate	123 (36)	61 (34)	44 (42)	22 (34)	58 (40)	65 (38)	14 (36)	14 (45)	22 (35)	26 (52)	73 (41)	73 (45)	595 (39)
Severe	34 (10)	23 (13)	17 (16)	8 (13)	12 (8)	29 (17)	1 (3)	4 (13)	10 (16)	6 (12)	35 (20)	22 (14)	201 (13)
Sensory disturbances	273 (31)	153 (42)	142 (71)	94 (85)	216 (74)	240 (85)	61 (40)	48 (56)	94 (64)	78 (81)	245 (70)	238 (80)	1882 (58)

Abbreviations: ALND, axillary lymph node dissection; ATRT, anterior thoracic radiotherapy corresponding to the anterior thoracic wall; BRT, breast radiotherapy corresponding to residual breast tissue; IQR, interquartile range; LRRT, locoregional radiotherapy corresponding to periclavicular, axillary level 3, and for right-side breast cancers, the internal mammary nodes; SLND, sentinel lymph node dissection.

[a] Defined as the highest pain score of the 4 regional pain scores. Scores of 1 to 3 were regarded as light pain, scores of 4 to 7 as moderate pain, and scores of 8 to 10 as severe pain.

Mortality was retrieved from the Danish Civil Registration System, in which a unique personal identification number is assigned to all persons residing in Denmark. It is used in all national registries, allowing accurate linkage of information between registries. Information for reconstruction or corrective breast surgery was retrieved from the Danish National Patient Registry, which contains information on all patients admitted at clinical hospital departments in Denmark regarding diagnosis, surgical procedures, and date of admission.

The study was performed in accordance with the Declaration of Helsinki and approved by the local ethics committee H-D-2007-0099, the Danish Data Protection Agency, and the Danish National Patient Registry under the Danish National Health Board.

Questionnaire

The literature for existing relevant questionnaires was reviewed to determine prevalence, location, intensity, and frequency of pain, sensory disturbances, and their associations with different treatment modalities. The most commonly used and well-validated questionnaires in breast cancer research were the quality of life questionnaires EORTC QLQ-C30/BR23 (European Organization for Research and Treatment of Cancer, the Core Cancer Quality of Life Questionnaire/Breast Cancer Specific Questionnaire) and FACIT-B (Functional Assessment Chronic Illness Therapy Questionnaire, the breast cancer module).[11] However, these questionnaires were not used because they did not provide detailed information on chronic pain localization or sensory disturbances. No other single standardized questionnaire with documented validity and reliability in comparable populations was found to match these demands.

A detailed questionnaire was designed (eAppendix; available at http://www.jama.com) based on questions or topics identified in the literature and open interviews with 20 women who received surgery for breast cancer. Before the start of the study, the questionnaire was tested and revised twice in accordance with the comments from pilot testing in 11 and 17 patients, respectively. To determine the prevalence of symptoms for each major topic, dichotomous yes or no questions were used. Regarding pain and sensory disturbances, the women were asked systematically to address 4 specific regions of symptoms: (1) area of the breast (defined as either the affected breast or the area from which the breast was removed), (2) the axilla, (3) the arm, and (4) the side of the body, rating pain severity and frequency in each region. To estimate severity of pain, a numeric rating scale from 0 to 10 scores was used in which 0 indicated no pain and 10 indicated worst imaginable pain.[12,13] For the reporting of results regarding severity of pain, scores of 1 to 3 were categorized as light pain, scores of 4 to 7 as moderate pain, and scores of 8 to 10 as severe pain. Worst pain was defined as the highest pain score of the 4 regional pain scores.

The frequency of symptoms was assessed by a 3-point verbal categorical scale: (1) every day or almost every day, (2) 1 to 3 days a week, or (3) more rarely. Questions were asked about physician visits due to pain in the operated region, use of analgesics, other treatment for pain in the affected region, or all 3, and pain in other locations (eg, low back pain, headache).

Statistics

Data analysis was performed by the DBCG data center. Multivariate logistic regression models were applied to examine the concomitant influence of treatment modalities and age on pain, localization, intensity, and sensory disturbances, using the PROC LOGISTIC in SAS version 9.1 (SAS Institute, Cary, North Carolina). Factors included in the models were type of surgery (mastectomy vs BCS), lymph node dissection (ALND vs SLND), radiotherapy (LRRT + BRT/ATRT, BRT vs none), chemotherapy (cyclophosphamide, epirubicin, and fluorouracil vs none), and age. Year of surgery as well as tumor location in the breast had no statistically significant effect and were excluded from the multivariate models.

Adjusted odds ratios (ORs) and 95% confidence intervals (CIs) were calculated (adjusted for age, mastectomy/BCS, ALND/SLND, radiotherapy, and chemotherapy), and the Wald χ^2 test was used to test the overall significance of each parameter. Tests for interaction between covariates on pain and sensory disturbances were performed pairwise in separate models applying the Wald test statistics.

Associations between pain in the surgical area and sensory disturbances, and pain in the surgical area and pain elsewhere were analyzed by χ^2 test. Two-tailed *P* values were calculated and the level of significance was set at 5%.

RESULTS

The overall response rate was 87% (n=3253), varying from 79% to 93% between the 12 treatment groups (Table 1). Mean time from surgery to questionnaire response was 26 months (range, 13-41 months). There was no significant difference ($P=.75$) in pain prevalence between patients operated in 2005 vs 2006 (TABLE 2 and TABLE 3).

Pain

A total of 1543 patients (47%) reported pain in 1 or more areas (Table 1), of which 201 (13%) reported severe pain (scores of 8-10 on the numeric rating scale of 0-10 scores), 595 (39%) reported moderate pain (scores of 4-7), and 733 (48%) reported light pain (scores of 1-3). Fourteen patients (1%) did not rate severity of pain. Among those patients reporting pain, the mean pain score in the 4 different areas varied between 3.5 and 4.0 (range, 0-10). Among women reporting severe pain, 77% experienced pain every day, whereas only 36% of women experiencing light pain had pain every day.

Severity and frequency of pain in the 4 regions are shown in (TABLE 4). A total of 278 patients (18%) reported pain in only 1 area, 435 (28%) in 2 areas, 429 (28%) in 3 areas, and 400

(26%) in all 4 areas. The most frequently reported area of pain was the breast area (n=1331; 86%), followed by axilla (n=975; 63%), arm (n=872; 57%), and side of the body (n=857; 56%).

Of patients reporting pain, 306 (20%) had contacted a physician within the prior 3 months due to pain, 439 (28%) had taken analgesics due to pain in the surgical area, and 397 (26%) had received other treatments for pain (ie, physiotherapy, massage). A total of 1265 women (40%) reported pain in other parts of the body/nonsurgical areas (eg, low back pain, headache). Pain complaints in nonsurgical areas were associated with a higher incidence of chronic postoperative pain because 810 women (65%) had pain in the surgical regions, whereas 674 women (37%) without pain in the nonsurgical area had pain in the surgical area ($P<.001$).

There was a significant association of age on reporting pain, where young age was associated with higher risk, especially for patients receiving BCS, the risk being highest for those women aged 18 to 39 years receiving BCS compared with women aged 60 to 69 years (OR, 3.62; 95% CI, 2.25-5.82; $P<.001$) (Table 2). Although young age was associated with reporting pain, young age was not associated with higher risk of reporting moderate to severe pain compared with light pain (18-39 years: OR, 0.81; 95% CI, 0.50-1.31; $P=.28$).

Table 2. Pain Adjusted for Age, Type of Surgery, Radiotherapy, and Chemotherapy Among 3253 Danish Women Having Surgery for Primary Breast Cancer

	No. (%) of Women		Unadjusted		Adjusted[a]	
	With Pain	Without Pain	OR (95% CI)	*P* Value	OR (95% CI)	*P* Value
Age group, y						
18-39	96 (64)	53 (36)	2.62 (1.84-3.73)	<.001		
40-49	367 (59)	251 (41)	2.11 (1.74-2.57)			
50-59	554 (49)	580 (51)	1.38 (1.18-1.62)			
60-69	526 (41)	760 (59)	1 [Reference]			
Breast surgery by age group, y[b]						
Breast-conserving surgery						
18-39	72 (71)	29 (29)			3.62 (2.25-5.82)	<.001
40-49	240 (60)	160 (40)			2.20 (1.68-2.89)	
50-59	378 (49)	395 (51)			1.42 (1.16-1.74)	
60-69	324 (40)	489 (60)			1 [Reference]	
Mastectomy						
18-39	24 (50)	24 (50)			1.18 (0.64-2.19)	.03
40-49	127 (58)	91 (42)			1.72 (1.21-2.45)	
50-59	176 (49)	185 (51)			1.21 (0.91-1.60)	
60-69	202 (43)	271 (57)			1 [Reference]	
Breast procedure						
Mastectomy	529 (48)	571 (52)	0.98 (0.85-1.14)	.79	1.13 (0.84-1.53)	.41
Breast-conserving surgery	1014 (49)	1073 (51)	1 [Reference]		1 [Reference]	
Axillary procedure						
ALND	945 (54)	795 (46)	1.69 (1.47-1.94)	<.001	1.77 (1.43-2.19)	<.001
SLND	598 (41)	849 (59)	1 [Reference]		1 [Reference]	
Radiotherapy						
LRRT + BRT/ATRT	662 (55)	539 (45)	1.88 (1.51-2.33)	<.001	1.35 (1.04-1.76)	.03
BRT	697 (46)	824 (54)	1.29 (1.05-1.60)		1.50 (1.08-2.07)	
None	184 (40)	281 (60)	1 [Reference]		1 [Reference]	
Chemotherapy						
With	664 (54)	556 (46)	1.48 (1.28-1.71)	<.001	1.01 (0.85-1.21)	.91
Without	879 (45)	1088 (55)	1 [Reference]		1 [Reference]	
Year of surgery						
2005	716 (48)	772 (52)	0.98 (0.85-1.12)	.75		
2006	827 (49)	872 (51)	1 [Reference]			
Tumor location						
Upper lateral quadrant	608 (49)	639 (51)	1.02 (0.89-1.18)	.76		
Other parts of the breast	935 (48)	1005 (52)	1 [Reference]			

Abbreviations: ALND, axillary lymph node dissection; ATRT, anterior thoracic radiotherapy corresponding to the anterior thoracic wall; BRT, breast radiotherapy corresponding to residual breast tissue; CI, confidence interval; LRRT, locoregional radiotherapy corresponding to periclavicular, axillary level 3, and for right-side breast cancers, the internal mammary nodes; OR, odds ratio; SLND, sentinel lymph node dissection.

[a] Adjusted for age, mastectomy/breast-conserving surgery, ALND/SLND, radiotherapy, and chemotherapy.

[b] A statistically significant interaction was observed between age and type of surgery ($P=.03$).

Among women with mastectomies, the highest risk of pain was in the age group 40 to 49 years. A statistically significant interaction ($P=.03$) was observed between age and type of surgery.

Mastectomy had no significant association on OR for reporting pain compared with BCS (Table 2), but those women reporting pain after mastectomy had a higher risk of moderate to severe pain compared with light pain (OR, 1.37; 95% CI, 1.00-1.87; $P=.048$). ALND was associated with an increased risk of pain (OR, 1.77; 95% CI, 1.43-2.19; $P<.001$) compared with SLND, and also a risk factor for moderate to severe pain (OR, 1.39; 95% CI, 1.03-1.88; $P=.03$).

Adjuvant radiotherapy increased the risk of reporting pain (BRT: OR, 1.50; 95% CI, 1.08-2.07; vs LRRT+BRT/ATRT: OR, 1.35; 95% CI, 1.04-1.76; $P=.03$), but without relation to the extension of the radiation field (Table 2) or pain severity (BRT: OR, 1.26; 95% CI, 0.79-2.01; vs LRRT+BRT/ATRT: OR, 1.15; 95% CI, 0.78-1.68; $P=.63$). Use of adjuvant chemotherapy had no independent association on adjusted OR for pain (Table 2), despite consistent differences between subgroups (Table 1).

In the multivariate models, type of surgery of the breast was not significantly related to pain in the axilla (OR, 0.92; 95% CI, 0.66-1.28; $P=.61$), arm (OR, 1.10; 95% CI, 0.80-1.53; $P=.55$), or side of the body (OR, 1.37; 95% CI,

Table 3. Sensory Disturbances Adjusted for Age, Type of Surgery, Radiotherapy, and Chemotherapy Among 3253 Danish Women Having Surgery for Primary Breast Cancer

	No. (%) of Women		Unadjusted		Adjusted[a]	
	With Sensory Disturbances	Without Sensory Disturbances	OR (95% CI)	*P* Value	OR (95% CI)	*P* Value
Age group, y						
18-39	123 (83)	25 (17)	5.09 (3.27-7.94)	<.001		
40-49	443 (73)	167 (27)	2.75 (2.23-3.39)			
50-59	696 (62)	430 (38)	1.68 (1.42-1.97)			
60-69	620 (49)	642 (51)	1 [Reference]			
Breast surgery by age group, y[b]						
Breast-conserving surgery						
18-39	79 (79)	21 (21)			5.00 (2.87-8.69)	<.001
40-49	263 (67)	131 (33)			2.67 (1.97-3.61)	
50-59	437 (58)	321 (42)			1.83 (1.46-2.29)	
60-69	339 (43)	452 (57)			1 [Reference]	
Mastectomy						
18-39	44 (92)	4 (8)			6.06 (2.07-17.7)	<.001
40-49	180 (83)	36 (17)			2.95 (1.90-4.59)	
50-59	259 (70)	109 (30)			1.46 (1.07-1.98)	
60-69	281 (60)	190 (40)			1 [Reference]	
Breast procedure						
Mastectomy	764 (69)	339 (31)	1.86 (1.60-2.18)	<.001	0.84 (0.60-1.17)	.29
Breast-conserving surgery	1118 (55)	925 (45)	1 [Reference]		1 [Reference]	
Axillary procedure						
ALND	1347 (78)	387 (22)	5.71 (4.88-6.67)	<.001	4.97 (3.92-6.30)	<.001
SLND	535 (38)	877 (62)	1 [Reference]		1 [Reference]	
Radiotherapy						
LRRT + BRT/ATRT	939 (79)	256 (21)	2.47 (1.96-3.11)	<.001	0.88 (0.65-1.20)	.02
BRT	662 (45)	819 (55)	0.54 (0.44-0.67)		0.61 (0.42-0.89)	
None	281 (60)	189 (40)	1 [Reference]		1 [Reference]	
Chemotherapy						
With	851 (70)	367 (30)	2.02 (1.73-2.35)	<.001	1.08 (0.89-1.31)	.46
Without	1031 (53)	897 (47)	1 [Reference]		1 [Reference]	
Year of surgery						
2005	875 (60)	595 (40)	0.98 (0.85-1.13)	.75		
2006	1007 (60)	669 (40)	1 [Reference]			
Tumor location						
Upper lateral quadrant	735 (60)	483 (40)	1.04 (0.90-1.20)	.63		
Other parts of the breast	1147 (59)	781 (41)	1 [Reference]			

Abbreviations: ALND, axillary lymph node dissection; ATRT, anterior thoracic radiotherapy corresponding to the anterior thoracic wall; BRT, breast radiotherapy corresponding to residual breast tissue; CI, confidence interval; LRRT, locoregional radiotherapy corresponding to periclavicular, axillary level 3, and for right-side breast cancers, the internal mammary nodes; OR, odds ratio; SLND, sentinel lymph node dissection.

[a] Adjusted for age, mastectomy/breast-conserving surgery, ALND/SLND, radiotherapy, and chemotherapy.

[b] No statistically significant interaction was observed between age and type of surgery ($P=.52$).

Table 4. Pain Among 1515 Danish Women Reporting Light, Moderate, or Severe Persistent Pain in 4 Regions for Primary Breast Cancer[a]

Body Part	No. (%) of Women in Pain		
	Light	Moderate	Severe
Breast area			
Every day or almost every day	278 (47)	243 (41)	66 (11)
1-3 times a week	226 (60)	135 (36)	14 (4)
More rarely	255 (77)	69 (21)	6 (2)
Side of the body			
Every day or almost every day	165 (44)	160 (43)	46 (12)
1-3 times a week	138 (54)	105 (41)	13 (5)
More rarely	141 (75)	42 (22)	5 (3)
Axilla			
Every day or almost every day	183 (42)	190 (44)	60 (14)
1-3 times a week	168 (64)	80 (31)	14 (5)
More rarely	174 (75)	52 (22)	6 (3)
Arm			
Every day or almost every day	144 (33)	191 (44)	96 (22)
1-3 times a week	123 (52)	97 (41)	15 (6)
More rarely	136 (76)	38 (21)	5 (3)

[a]Twenty-eight of 1543 patients (2%) reporting pain did not report severity and/or frequency of pain in any of the 4 locations. Patients scored their pain in 4 different areas on a numeric rating scale, in which 0 indicated no pain, 10 indicated worst imaginable pain; and scores of 1 to 3 were regarded as light pain, scores of 4 to 7 as moderate pain, and scores of 8 to 10 as severe pain.

1.00-1.87; $P=.053$); whereas ALND increased risk of pain in the axilla (OR, 2.17; 95% CI, 1.58-2.99; $P<.001$) and arm (OR, 3.77; 95% CI, 2.73-5.20; $P<.001$).

Sensory Disturbances

A total of 1882 women (58%) reported sensory disturbances or discomfort, ranging from 31% (n=273) among women who had BCS with SLND and BRT to 85% of women who had BCS, ALND, and chemotherapy with BRT (n=94) or BRT and LRRT (n=240) (Table 1). The most frequently reported areas were the axilla (n=1239, 66%), followed by arm (n=986, 52%), breast area (n=816, 43%), and side of the body (n=573, 30%).

After mastectomy and BCS (Table 3), there was a higher incidence of sensory disturbances with decreasing age. Thus, women aged 18 to 39 years had the highest risk compared with women aged 60 to 69 years (BCS: OR, 5.00; 95% CI, 2.87-8.69; $P<.001$; and mastectomy: OR, 6.06; 95% CI, 2.07-17.7; $P<.001$). ALND was associated with increased incidence of sensory disturbances compared with SLND (OR, 4.97; 95% CI, 3.92-6.30; $P<.001$).

A total of 1204 women (65%) reporting sensory disturbances reported pain as well compared with 292 (23%) reporting pain but not sensory disturbances, indicating sensory disturbances and nerve injury were related to an increased risk of chronic pain ($P<.001$).

Adjuvant chemotherapy and radiotherapy did not increase the risk of reporting sensory disturbances in the multivariate model (Table 3).

COMMENT

This large nationwide study shows that 47% of women treated for breast cancer experience pain and 58% of women experience sensory disturbances in the surgical region 1 to 3 years after surgery. Half the women reporting pain reported moderate to severe pain. In general, the prevalence estimates are in agreement with those estimates of the literature varying for pain between 25% and 60%[1-5,14-21] and for sensory disturbances between 20% and 80%.[1-5,18,19]

The wide range of pain complaints in the literature is likely due to differing definitions of persistent pain, differing measurements of pain and its consequences, a varying mix of type of surgery and adjuvant treatment, and variations in time since surgery. Although some studies have tried to differentiate the role and type of surgery and also regarding adjuvant therapy,[3] the number of included patients compared with the many treatment modalities has been insufficient to draw valid conclusions for each treatment-related risk factor.

The goal of the questionnaire designed for our study was the greatest possible simplicity, asking in general whether patients had pain or sensory disturbances in relevant areas according to literature and open interviews. Asking patients how long the pain had been present or demanding the patient to consider whether pain and sensory disturbances were due to the treatment of breast cancer was deliberately avoided. Also avoided was the potential recall bias by retrospectively asking about the intensity of pain experienced in the early postoperative phase.

The most important determinant of persistent pain and sensory disturbances was young age (<40 years), although age was not related to the severity of the pain reported. This association was more clear in our study than in other studies.[5,14,22] Although our univariate analyses showed a strong association between chemotherapy and reporting of pain and sensory disturbances as reported in the literature,[2-4] the effect disappeared in the multivariate analyses. Therefore, the observed association between chronic pain and chemotherapy could be due to age, because young women more often receive chemotherapy. Our results may be regarded as valid for chemotherapy with cyclophosphamide, epirubicin, and fluorouracil, but not for more recent regimens containing taxans with potential neurotoxicity.

In the DBCG 2004 protocol, the standard endocrine treatment was tamoxifen for 2.5 years followed by treatment with aromatase inhibitor for 2.5 years. Thus, very few women in our cohort were receiving aromatase inhibitor treatment, known to cause muscular and joint pain, at the time when the

questionnaire was returned. Hence, treatment with aromatase inhibitor was not included in the statistical models.

Having adjusted for other therapeutic modalities, radiotherapy was an independent and significant risk factor for reporting pain, but the extent of the radiation field did not influence the risk of reporting pain. Although other studies[14,15] have found radiotherapy to be a risk factor for sensory disturbances, this was not confirmed in our study. Altogether, comparison of our results with the literature is difficult because no previous study has indicated exact information about the dose and location of radiotherapy. In the future, intraoperative, localized radiotherapy may be a way to reduce radiotherapy-related persistent pain due to more well-defined anatomical application.

Pain was reported most frequently in "the area of the breast," but similar to other studies,[14] we found that the frequency appeared independent of type of breast surgery, although women who underwent mastectomy reported slightly but significantly more severe pain than women undergoing BCS. An association between location of tumor in the upper lateral quadrant and reporting of pain could not be confirmed in our study.[15]

The strengths of our study are that it is based on the entire population of Denmark with a high response rate and is sufficiently large to provide reasonably precise risk estimates of all treatment modalities, such as surgery, radiotherapy, and chemotherapy. In addition, patients were treated according to the same guidelines. Our results on the effects of age and chemotherapy demonstrate the importance of multivariate analysis to disentangle independent effect on risk factors for chronic pain. Many previous studies have been based on relatively small selected patient series from 1 or a few centers, often focusing on only 1 or 2 elements.[4,5,15,17,22]

The main limitation of our study is that it is a cross-sectional study that provided only 1 estimate of pain prevalence, 1 to 3 years after the primary treatment. It did not follow patients over time and thus does not provide information on if and how the reported pain and sensory disturbances will develop with time since breast cancer treatment. Also, the cross-sectional study design does not allow drawing conclusions regarding causality, but can merely describe factors associated with pain and sensory disturbances. Another limitation is in the 13% of patients who did not complete the questionnaire. If these patients experienced more pain than the responders, our estimates are too low. Additionally, the results might have been biased by the patients who were excluded due to death or cancer relapse who might have had different patterns of pain than survivors included in the study.

Our nationwide study reflects the Danish population, which is generally well-educated, ethnic homogeneous (white), and benefiting from a uniform public health care system covering all citizens, and thus limiting the generalizability to other populations with different health care systems, demographics, or treatment protocols. However, our study with its population-based nature, high response rate, lack of recall bias, and standardized treatment offers very precise estimates of prevalence regarding pain and sensory disturbances and associated factors following breast cancer surgery in Denmark.

Based on the results of our study together with previously reported findings,[1-4,17] chronic pain after breast cancer surgery and adjuvant therapy may predominantly be characterized as a neuropathic pain state and probably related to intraoperative injury of the intercostal-brachial nerve. In accordance with these findings, preliminary observations with nerve-sparing techniques[19-21,23-25] may suggest such approaches to reduce the risk of developing a chronic neuropathic pain state. However, such studies need to be larger and more detailed taking all the different subgroups as studied in our investigation into consideration. Also, there is a need for detailed psychophysical examination of patients with postmastectomy pain, because existing data were from very limited patient groups and included different treatment modalities.[26] Such extensive neurophysiological examinations may also provide a rational basis for mechanism-based pharmacological interventions in the future. Because psychosocial status, preoperative breast pain, and acute postoperative pain intensity are well-known risk factors related to a persistent postsurgical pain state,[1,4,5,27,28] large-scale therapeutic interventions in relevant subpopulations are required to outline rational strategies for prevention and treatment. So far, analgesic and other interventions with paravertebral blocks,[29] topical capsaicin,[30] gabapentin and local anesthetics,[31] *N*-methyl-D-aspartate–receptor antagonists,[32] or glucocorticoids[33] may suggest certain benefits, but large-scale studies including well-characterized relevant subpopulations are required before general recommendations can be made. These results and those of other studies[1] clearly show that a persistent postsurgical pain state may be related to existence of other pain syndromes (headache, low back pain), which may suggest that a preoperative general pain hypersensitivity due to psychosocial or genetic factors may be important pathogenic mechanisms, and therefore to be included in future preventive and therapeutic trials.

In our study, sensory disturbances and specific pain complaints were studied, but other pain syndromes may occur after breast cancer treatment,[4] including phantom breast sensations and pain,[34,35] which were not included in our study.

CONCLUSION

Persistent pain in the surgical area after breast cancer surgical treatment is a clinically significant problem in approximately 25% to 50% of patients. Although BCS and sentinel node dissection have reduced complaints, future strategies for further improvement should include nerve-sparing axillary dissection and attention to patients with other chronic pain symptoms.

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Study concept and design: Gärtner, Nielsen, Kroman, Kehlet.
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Analysis and interpretation of data: Gärtner, Jensen, Ewertz, Kroman, Kehlet.
Drafting of the manuscript: Gärtner, Jensen, Ewertz, Kehlet.
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Additional Information: An eAppendix is available at http://www.jama.com.

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