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RESEARCH

Persistent pain and sensory disturbances after treatment for breast cancer: six year nationwide follow-up study

Mathias Kvist Mejdahl *research assistant*[1], Kenneth Geving Andersen *physician research fellow*[1], Rune Gärtner *physician*[2], Niels Kroman *professor*[2], Henrik Kehlet *professor*[1]

[1]Section for Surgical Pathophysiology, 7621, Rigshospitalet, University of Copenhagen, Blegdamsvej 9, DK-2100 Copenhagen, Denmark ; [2]Department of Breast Surgery, 3104, Rigshospitalet, University of Copenhagen, Copenhagen, Denmark

Abstract

Objective To examine the development of persistent pain after treatment for breast cancer and to examine risk factors associated with continuing pain.

Design Repeated cross sectional study in a previously examined nationwide cohort. All eligible women who underwent surgery for primary breast cancer in Denmark in 2005 and 2006 and were examined in 2008 were surveyed again with the same questionnaire.

Setting Surgical centres in Denmark.

Main outcome measures Prevalence, location, and severity of persistent pain after treatment for breast cancer in well defined treatment groups and changes in pain reporting and sensory disturbances from 2008 to 2012.

Participants In 2012, 2828 women were eligible in our database, and 108 were excluded. Exclusion criteria were death; new, recurrent, or other cancer; reconstructive breast surgery; and emigration.

Results 2411 (89%) women returned the questionnaire. Prevalence of persistent pain after treatment for breast cancer ranged from 22% to 53% depending on treatment. In 2012, 903 (37%) women reported such pain, a fall from 45% in 2008. Of these, 378 (16%) reported pain of ≥4 on a numerical rating scale (scale 0-10), a fall from 19%. Among women reporting pain in 2008, 36% no longer reported it in 2012. In contrast, 15% of the women who did not report pain in 2008 reported it in 2012. Risk factors for having pain were axillary lymph node dissection rather than sentinel lymph node biopsy (odds ratio 2.04, 95% confidence interval 1.60 to 2.61; P<0.001) and age ≤49 (1.78, 1.25 to 2.54; P<0.001). No particular method of treatment or age was associated with an increase in pain from 2008 to 2012.

Conclusions Persistent pain after treatment for breast cancer remains an important problem five to seven years later. The problem is not static as it can either progress or regress with time.

Trial registration Clinicaltrials.gov NCT No 01543711.

Introduction

Breast cancer is the most common cancer in women worldwide with more than a million new cases diagnosed every year.[1] The prognosis has improved considerably over the past 30 years, and the five year overall survival of patients with a diagnosis of primary breast cancer has increased to about 85%.[2 3] Consequently, the population of long term survivors is increasing, emphasising the need for knowledge on long term sequelae.

Several studies have shown that persistent pain after treatment for breast cancer is a common problem, ranging between 25% and 60% depending on definition, measurement, and methods of treatment.[4] The term refers to pain in and around the area of surgery lasting beyond three months after surgery[5] when all other causes of pain such as recurrence have been ruled out.[4] Persistent pain after treatment has a considerable negative influence on quality of life in breast cancer survivors,[6 7] and persistent pain in general has important economic consequences for the healthcare system.[8-10] Many potential pre-, intra-, and postoperative risk factors for persistent pain after treatment for breast cancer have been proposed, including young age, pain elsewhere in the body, radiotherapy, and the extent of axillary surgery.[4] Only a few studies, however, have looked at persistent pain in patients five and more years after primary surgery, leaving questions on the natural course of such pain.[6 7 11] After another common surgical procedure, groin hernia repair, persistent postoperative pain decreased from about 25% at one year after surgery to about 12% five or more years after surgery.[12 13] We found no study with long term detailed longitudinal data on patients with and without pain after surgery.

Correspondence to: M K Mejdahl mathias.kvist.mejdahl@rh.regionh.dk, K G Andersen kenneth.geving.andersen@rh.regionh.dk

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Appendix: Questionnaire

In addition to the limited data on the natural time course of persistent pain after treatment for breast cancer, there is a lack of knowledge about specific risk factors for long term persistence as well as changing status of such pain, hindering research in development of treatment and preventive measures.[4] We examined the long term development in prevalence and severity of persistent pain and sensory disturbances in a previously reported large well defined, nationwide cohort of women treated for primary breast cancer.[14] Furthermore, we examined the role and time course of different risk factors associated with persistent pain after treatment for breast cancer and sensory disturbances. The patients in our study represent the majority of breast cancer survivors, but we have excluded those with recurrence, metastasis, other malignancy, or reconstructive surgery.

Methods

Study design

From 2005 to 2005, 5119 women aged 18-70 were treated for unilateral primary breast cancer in Denmark. In 2008, with a mean follow-up of 26 months, a questionnaire was sent to 3754 eligible patients and returned by 3253 (87%).[14] The present questionnaire study was a follow-up of the same cohort in 2012, at which time 2828 of the 3253 patients were eligible in the Danish Breast Cancer Cooperative Group (DBCG) database,[15] according to the inclusion and exclusion criteria below.

Setting

A questionnaire, identical to the one used in the first study,[14] was sent to all eligible patients on 1 February 2012 (see appendix). Those who did not respond received a second questionnaire on 5 March 2012. To minimise selection bias, a second reminder was sent on 30 March 2012 to the patients not responding to the second questionnaire. Data collection ended on 8 May 2012.

Participants

All women who participated in the 2008 study were assessed for inclusion. Exclusion criteria were death and emigration. We also excluded women with recurrent, new primary, and contralateral cancer, metastatic disease, other malignant disease, and reconstructive/corrective breast surgery as they represent different pathophysiological mechanisms for persistent pain and represent only a minority of women who survive breast cancer. Data concerning treatment, cancer recurrence, and demographics were retrieved from the Danish Breast Cancer Cooperative Group database.[15] The database has previously been validated for 1999-2004. Only about 3% of women aged 18-69 with new primary breast cancer are not available in the database.[16] The database receives information from all departments of surgery, pathology, and oncology in Denmark. Data on mortality were retrieved from the Danish Civil Registration System. In 2008, information regarding reconstructive or corrective surgery was retrieved from the Danish National Patient Registry.[17] In the present study, patients could report reconstructive surgery performed after 2008. Linkage between the different registers is possible because of a unique civil registration number assigned to all Danish citizens.

Outcomes

The primary outcome was the prevalence of persistent pain after treatment for breast cancer in well defined treatment groups five to seven years after treatment. It was defined as presence of pain in the breast area, side of the body, axilla, or arm on the operated side. Secondary outcomes were location, intensity, and frequency of pain and prevalence of sensory disturbances. We also investigated the natural time course of persistent pain after treatment for breast cancer by examining the reporting of pain in the previous study compared with the reporting in this study in the different treatment groups. Prevalence of pain was assessed dichotomously with yes/no questions. Women were subsequently asked systematically to specify pain according to site, intensity, and frequency. Intensity was assessed on a numerical rating scale from 0-10. There is no clear consensus on cut off points for mild, moderate, and severe persistent postsurgical pain. We chose to interpret 1-3 as light pain, 4-6 as moderate pain, and 7-10 as severe pain, supported by a recent study on cut off points for postoperative pain suggesting that scores of ≥4 identify patients with pain interfering with mood and activity.[18] Frequency was assessed on a 3 point verbal scale: 1=every day or almost every day, 2=one to three days a week, and 3=more rarely. We indentified and separately analysed a subgroup of patients who reported moderate to severe pain on at least a weekly basis.

Sensory disturbances were assessed by a dichotomous yes/no question and site was then specified.

Treatment

Patients were treated according to the 2004 protocol of the Danish Breast Cancer Cooperative Group,[16] which was based on the recommendations from the international expert consensus on primary therapy of early breast cancer in 2003.[19] There were 12 major treatment groups divided according to the type of surgery and adjuvant radiotherapy and chemotherapy. Treatment details are described elsewhere.[14] Oncological follow-up was performed systematically on all patients according to the protocol and registered in the database.[16]

Questionnaire

The questionnaire used was developed for the assessment of persistent pain after treatment for breast cancer, sensory disturbances, functional impairment, and self reported lymphoedema.[14 20] This questionnaire used accepted means of measuring pain[21] and was content validated in the breast cancer population.[14]

Statistics

All statistical methods were computed with SPSS version 19 (IBM, NY, USA). Univariate analyses were carried out to test for significant associations between covariates and outcomes with Wald χ^2 test. Multivariate logistic regression models were then used to examine the concomitant influence of age and methods of treatment on pain, moderate to severe pain on at least a weekly basis, and sensory disturbances. We excluded year of surgery from all multivariate models and endocrine therapy from all pain models as these were not associated with the outcomes in the univariate analyses. For comparability with the previous study, we included type of surgery in the final multivariate analyses.[14] Factors included in the models were type of surgery (mastectomy *v* breast conserving surgery), extent of axillary surgery (axillary lymph node dissection *v* sentinel lymph node biopsy), radiotherapy (locoregional radiotherapy + breast radiotherapy/anterior thoracic radiotherapy, breast radiotherapy alone *v* none), chemotherapy (cyclophosphamide, epirubicin, and fluorouracil *v* none), age, and, in the analysis with sensory disturbances as outcome, endocrine therapy. Adjusted odds ratios and 95% confidence intervals were

calculated and the Wald χ^2 test was used to test the overall significance of each parameter. Tests for interaction between age and the different methods of treatment and between axillary procedure and breast procedure on pain and sensory disturbances were performed pairwise in separate models applying the Wald χ^2 test. To assess pain progression or regression since the 2008 questionnaire study, we computed the difference in worst reported pain numerical rating score between 2008 and 2012. A difference of at least 2 in pain reporting was considered clinically relevant according to the IMMPACT recommendations.[22] We subsequently performed multivariate logistic regression analysis to examine the influence of treatment modalities and age on pain progression of ≥2. Associations between pain in the surgical area and sensory disturbances, and pain in the surgical area and pain elsewhere, were analysed with Fisher's exact test. Two tailed P values were calculated and the level of significance was set at 0.05. Analyses were carried out to assess possible selection bias of non-respondents. All odds ratios reported in the text are the adjusted values. The adjusted number needed to be exposed and exposure impact number for axillary lymph node dissection versus sentinel lymph node biopsy were calculated with the method suggested by Bender et al.[23]

Results

Participants

Of the 3253 patients participating in the 2008 study, 425 were identified in the database as not eligible according to the exclusion criteria, leaving 2828 patients for the present study (fig 1⇓). Subsequently 108 patients were excluded from the study based on information in the questionnaire or gathered by telephone or email communication, either because they matched the exclusion criteria, did not want to participate, or could not fill out the questionnaire. Of the remaining population, 2411 questionnaires (89%) had been returned by 8 May 2012.

Descriptive data

Mean follow-up time was 72.5 months (range 61-87 months). Tables 1 and 2 show the distribution of the women in the different treatment groups⇓⇓. The median age for the cohort was 64 (range 33-77).

Pain

Of the 2411 women, 903 (37%) reported pain in one or more areas. The prevalence varied between 22% and 53% in the different treatment groups. Women who underwent mastectomy and sentinel lymph node biopsy reported the least pain, and those treated with breast conserving surgery, axillary lymph node dissection, chemotherapy, and breast regional radiotherapy reported the most. In total, 378 (16%) women reported moderate to severe pain on at least a weekly basis. Table 3 shows the frequency and severity of pain in the four areas⇓:195 (22%) women reported pain in all areas, 228 (25%) had pain in three areas, 270 (30%) had pain in two areas, and 208 (23%) had pain in only one area. Among those reporting pain, 203 (22%) used analgesics: 181 women used weak analgesics, 40 used opioids, and 16 used other analgesics (such as gabapentin, amitriptyline, pregabalin). In total, 829 women (34%) reported pain in other parts of the body. Among those who reported persistent pain after treatment for breast cancer, 469 (53%) also reported pain in other parts of the body compared with 358 (25%) in women without pain after treatment. The relative risk for having treatment related pain when reporting pain in a non-surgical area was 2.05 (95% confidence interval 1.85 to 2.27).

In the multivariate logistic regression analysis young age significantly influenced pain reporting (table 4⇓). The only method of treatment that was significantly associated with pain was axillary lymph node dissection versus sentinel lymph node biopsy. The number needed to be exposed to axillary lymph node dissection instead of sentinel lymph node biopsy to have one more woman with long term persistent pain after treatment for breast cancer was 6.12 (95% confidence interval 4.53 to 9.43). The exposure impact number was 6.25 (4.73 to 9.20). Surgical procedure in the breast, radiotherapy, and chemotherapy were not significantly associated with pain. Moderate to severe pain on at least a weekly basis was related to young age and to axillary lymph node dissection (table 5⇓).

Development of pain

In total, 2358 (98%) women had answered questions regarding persistent pain after treatment for breast cancer in both studies. Among these, 1087 (46%) reported such pain in 2008. In the present study, 389 (36%) of these women no longer reported persistent pain after treatment. Furthermore, of 1271 women free from pain in 2008, 185 (15%) reported pain in 2012. Of these, 119 (64%) had developed light pain, 56 (30%) moderate pain, and nine (5%) severe pain (table 6⇓). Among women who had answered all necessary questions in both studies regarding intensity and frequency of pain (n=2335, 97%), 453 (19%) reported moderate to severe pain on at least a weekly basis in 2008, and 218 (48%) of these no longer reported this in 2012. Of 1882 women who did not have moderate to severe pain on at least a weekly basis in 2008, 137 (7%) reported it in 2012. The mean difference in numerical rating scale pain score from 2008 to 2012 was −0.58 among women reporting pain in at least one of the studies (fig 2⇓). Looking at pain progression and regression, 277 (11%) women reported a pain increase of ≥2 on the numerical rating scale, and 488 (20%) reported a pain decrease of ≥2. No methods of treatment or age were significantly associated with a pain increase in a multivariate logistic regression comparing women with pain progression of ≥2 with patients with no increase/decrease.

Among women who did not have persistent pain after treatment for breast cancer in 2008, pain in other parts of the body was a risk factor for subsequently reporting pain after treatment in 2012 (relative risk 1.87, 95% confidence interval 1.42 to 2.54). Also, among women who had persistent pain after treatment for breast cancer in 2008, the co-reporting of pain in other parts of the body was a risk factor for reporting continuing persistent pain in 2012 (1.25, 1.14 to 1.37).

Sensory disturbances

In 2012, 1199 women (50%) reported sensory disturbances: 551 (46%) in the breast area, 401 (33%) on the side of the body, 727 (61%) in the axilla, and 558 (47%) in the arm. Regarding propagation of sensory disturbances, 543 (45%) had sensory disturbances in only one area, 351 (29%) in two areas, 196 (16%) in three areas, and 101 (8%) in all four areas. Seven women did not report location of their sensory disturbances. Among those who had pain, 705 (78% of women with pain) also had sensory disturbances in contrast with 492 (33%) of women with no pain but with sensory disturbances. The relative risk for having pain in women who also reported sensory disturbances was 3.79 (95% confidence interval 3.29 to 4.37).

In the multivariate logistic regression analysis of methods of treatment and age on sensory disturbances, younger age and extent of axillary surgery were significantly associated with sensory disturbances (table 7⇓).

Development of sensory disturbances

Of patients who filled out the questions regarding sensory disturbances in both studies (n=2298, 95%), 1343 (58%) reported having sensory disturbances in 2008. Among these, 331 (25%) no longer reported sensory disturbances in 2012. Of the 955 patients not reporting sensory disturbances in 2008, 164 (17%) reported sensory disturbances in 2012.

Discussion

In this nationwide follow-up study, over a third of women treated for primary breast cancer reported persistent pain after treatment five to seven years after treatment and half reported sensory disturbances. Furthermore, 16% reported moderate to severe pain on at least a weekly basis. Among women who reported persistent pain after treatment in 2008, 36% no longer reported it in 2012, and 48% of the patients who reported moderate to severe pain on at least a weekly basis in 2008 did not report it in 2012. Rather surprisingly, 15% of the women who did not report persistent pain after treatment in 2008 did report it in 2012. Over a four year period, we observed a slight decrease in pain prevalence from around 45% (n=1090) in 2008 to 37% in 2012, and in pain intensity with mean scores in the different locations ranging from 3.4-3.9 in 2008 to 2.9-3.5 in 2012. This was also reflected by 488 women having a relevant decrease in pain compared with only 277 having a relevant progression in pain. Among non-respondents from the present study, 56% had reported persistent pain after treatment in 2008, and among excluded patients had 53% reported it in 2008. These numbers suggest that some selection bias has occurred, both with patients in pain being less inclined to answer the questionnaire and excluded patients having more pain than participants. Therefore it is likely that the prevalence of persistent pain after treatment for breast cancer was slightly underestimated and the decline in prevalence of pain overestimated. If the last observation was carried forward among excluded patients and non-respondents, the prevalence of pain would have been 42%, a fall from 47% in 2008.

The present study has some limitations as to what a woman with breast cancer might expect in the future. Some women might experience recurrence and metastatic disease, and some choose to undergo breast reconstruction. Our sample, however, represents the majority of women who survive breast cancer (>85 %). Recurrence, metastasis, and reconstructive surgery represent an additional layer, which complicates the picture as they all have potential additional effects on pain (metastasis, local effects from reconstruction, etc). Therefore, each will require specific analyses in a different study setup, which was neither the aim of nor possible in our study. Although we observed a small decline in prevalence and intensity of pain, it is remarkable that 20% of the women who reported pain in this study were “new” pain patients. We cannot draw conclusions, however, on whether the women developed late onset of persistent pain after treatment or if it reflects a natural fluctuation in pain symptoms. The finding could also to some extent be explained by potential imprecision in the measurement of pain. The numerical rating scale, however, has a high degree of test-retest stability both within minutes[24 25] and within a two day period.[26] The test-retest stability over three months is less strong possibly because of the fluctuating nature of pain.[26] It has been suggested that the incidence and intensity of persistent pain after treatment for breast cancer decrease over time, though this was based on a relatively small study (n=126) conducted in the early 1990s.[27] The only other recent long term follow-up study (n=113), which reassessed a previously studied cohort reported a prevalence of 17%, a reduction from 43% six years earlier,[6 28] which was potentially explained by a longer follow-up (7-12 years). By not examining pain free patients from the first follow-up, however, this study probably underestimated the prevalence of patients with treatment related pain as the present study shows dynamics in persistent pain after treatment. Another study, by Peuckmann and colleagues, looked at persistent pain in long term breast cancer survivors.[7] They found that 29% experienced persistent pain after treatment and 47% had paraesthesia 5-10 years after treatment. The reason for the slightly lower prevalence of pain after treatment is probably because of different definition and measurement of persistent pain after treatment for breast cancer, as they defined it as pain of more than six months’ duration believed by the patient to be associated with the breast cancer treatment.[7] Furthermore, treatment was different in the period 1989-99 compared with 2005 and 2006, especially the introduction of the sentinel node procedure.[7 14] Our findings suggest that persistent pain after treatment for breast cancer does not decline at a high rate, leaving a high proportion of women with a chronic pain problem long time after the initial treatment. Pain in other parts of the body was highly associated, as was also shown in the 2008 study.[14] Furthermore, women reporting pain in other parts of the body in 2008 were less likely to recover from persistent pain after treatment and more likely to develop it than women without pain in other parts of the body in 2008. When we added it to the multivariate logistic regression analysis, pain in other parts of the body was in itself a major risk factor (adjusted) but not a confounder for either axillary lymph node dissection versus sentinel lymph node biopsy or age as these estimates did not change.

Young age has consistently been shown to be a predictive factor for persistent pain after treatment for breast cancer,[4] as well as a predictive factor for both acute and persistent postsurgical pain in general.[29 30] Our study shows young age to be a risk factor for long term persistent pain after treatment, moderate to severe pain on at least a weekly basis, and sensory disturbances. The 2008 study did not find a relation between increasing pain intensity and young age when it looked at women with moderate or severe pain compared with those with light pain.[14] The difference in the two studies is probably caused by different methods of interpreting pain severity. In our study, we considered it more clinically meaningful to include the temporal aspect of pain and to compare women with more severe pain with the entire cohort. Many explanations have been proposed as to why younger women report more pain, including large tumour size, worse histological grading, negative oestrogen receptor status,[27 31] age related decrease in pain perception,[4 32] differences in how age groups report pain,[33] and different psychological mechanisms.

Axillary lymph node dissection has consistently been shown to be a risk factor for persistent pain after treatment and sensory disturbances compared with sentinel lymph node biopsy.[4] Furthermore, axillary lymph node dissection versus sentinel lymph node biopsy is one of the major risk factors for arm lymphoedema.[20] Our study confirms that the axillary procedure remains one of the main risk factors in predicting the long term persistence of both pain and sensory disturbances. Axillary lymph node dissection, however, was not associated with pain progression during the four year interval between this study and the study performed in 2008. Damage to the intercostobrachial nerve has been proposed as one of the main causes of persistent pain after treatment.[4 27] There have not been enough specific studies on the intercostobrachial nerve, however, to determine the exact role of damage as a risk factor for persistent pain after

treatment.[4] After the publication of the Z0011 trial from the American College of Surgeons Oncology Group,[34] most centres around the world, including Denmark, currently do not carry out axillary lymph node dissection in patients with micrometastases or isolated tumour cells in sentinel nodes. In the present study 18% of women had micrometastases/isolated tumour cells in the sentinel nodes. The omission of axillary lymph node dissection among these women would have spared about three out of every 100 women with breast cancer from developing persistent pain after treatment based on the number needed to expose from this study.

Several studies have found radiation treatment to be a risk factor for persistent pain after treatment, including the previous study from 2008.[4 14] Furthermore, some studies suggested that women with breast cancer who undergo radiotherapy have a lifelong risk of developing brachial plexus neuropathy.[35 36] Surprisingly radiotherapy was no longer a risk factor for having either persistent pain after treatment or sensory disturbances in our follow-up study. A subgroup analysis looking at pain reporting in 2008 among the 2411 respondents from the present study showed that radiotherapy was not significantly associated with pain, unlike the whole cohort in 2008,[14] suggesting that our results might either have been influenced by selection bias or that women with pain in relation to radiotherapy have been excluded because of death or cancer recurrence. Our study, however, does not support notions of a cumulative effect of radiotherapy on development of persistent pain after treatment.

In 2008 and 2012 chemotherapy with cyclophosphamide, epirubicin, and fluorouracil was not associated with persistent pain after treatment or sensory disturbances.[14] A recent study examining the influence of the neurotoxic chemotherapeutic agent docetaxel also showed no influence on persistent pain in the area of surgery but a significant association with peripheral neuropathy.[37] Although chemotherapy has not been shown to be a risk factor for persistent pain after treatment, the influence of neurotoxic chemotherapeutic agents should still be examined in future studies.

A weakness of our study is that even though it was a re-assessment of a previously studied cohort, the design was still cross sectional with no pre-operative information on the women, thereby precluding any conclusions on causality. Furthermore, we had no information on smoking habits, obesity, and psychosocial factors, which could potentially bias the results.[4]

The strengths of our study are that it was based on the entire population of Denmark, that it had a high response rate (89%) limiting potential selection bias, and also that the cohort was large, thereby making it possible to perform multivariate logistic regression analyses to provide more precise risk estimates for the different methods of treatment and age on pain and sensory disturbances. Furthermore, the study was a follow-up of a previously well studied cohort, and we used the same methods of questioning. That enabled us to examine how the same women evolved during the additional four year follow-up period.

Future studies should look into the development of pain and sensory disturbances with a prospective design and, preferably, with several time points to get an even better view on the symptoms and nature of these sequelae to breast cancer. Such studies should also include all the potential pre-, intra-, and postoperative risk factors.[4]

Conclusion

Persistent pain after treatment for breast cancer and sensory disturbances remain a large problem five to seven years after treatment. Persistent pain after treatment is not static but seems to fluctuate considerably over time. Young age and axillary lymph node dissection are risk factors.

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Ethical approval: The study was approved by the Data Protection Agency No 2007-41-1530, and the regional bioethics committee of the capital region in Denmark, H-D-2007-0099

Data sharing statement: No additional data available.

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What is already known on this topic

After treatment for breast cancer 25-60% of women experience persistent pain

There are limited data on the natural time course of persistent pain after treatment

What this study adds

Persistent pain after treatment for breast cancer is not static, but seems to fluctuate considerably over time

A third of the women who reported pain two years after treatment no longer reported pain six years after treatment, but 15% of the women who were pain free two years after treatment reported pain four years later

Young age and axillary lymph node dissection were risk factors for pain six years after treatment

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Tables

Table 1| Pain and sensory disturbances among Danish women who underwent breast conserving surgery for primary breast cancer in 2005 and 2006

	Sentinel lymph node biopsy and breast radiotherapy*		Axillary lymph node dissection				
			Breast radiotherapy*		Breast* and locoregional† radiotherapy		
	No chemotherapy	With chemotherapy	No chemotherapy	With chemotherapy	No chemotherapy	With chemotherapy	Total
Non-responders	70 (9)	46 (14)	26 (15)	6 (6)	21 (9)	32 (14)	201 (11)
Median (IQR) age (years)	65 (60-70)	55 (49-64)	69 (65-73)	47 (43-50)	65 (63-69)	54 (50-57)	63 (54-68)
Responders	690 (91)	288 (86)	148 (85)	90 (94)	219 (91)	205 (86)	1640 (89)
Median (IQR) age (years)	67 (61-71)	56 (50-62)	67 (63-70)	56 (49-62)	66 (63-70)	55 (50-59)	64 (56-69)
Pain‡:							
Yes	199 (29)	106 (37)	67 (45)	47 (53)	83 (38)	104 (51)	606 (37)
No	489 (71)	182 (63)	81 (55)	42 (47)	135 (62)	100 (49)	1029 (63)
Worst pain§:							
Light	101 (52)	49 (46)	39 (58)	25 (53)	44 (54)	50 (48)	308 (51)
Moderate	80 (41)	42 (40)	23 (34)	15 (32)	28 (34)	33 (32)	221 (37)
Severe	13 (7)	15 (14)	5 (8)	7 (15)	10 (12)	21 (20)	71 (12)
Sensory disturbances¶:							
Yes	190 (28)	118 (41)	90 (62)	67 (74)	130 (60)	159 (78)	754 (47)
No	487 (72)	168 (59)	55 (38)	23 (26)	88 (40)	46 (22)	867 (53)
Moderate to severe pain on at least a weekly basis**:							
Yes	72 (11)	44 (15)	20 (14)	19 (21)	30 (14)	52 (26)	237 (15)
No	607 (89)	243 (85)	126 (86)	70 (79)	186 (86)	151 (74)	1383 (85)

IQR=interquartile range.

*Corresponding to residual breast tissue.

†Corresponding to periclavicular, axillary level 3, and for right side breast cancers, internal mammary nodes.

‡Not reported by 5 patients.

§Defined as highest pain score of four regional pain scores. Scores 1-3=light pain, scores 4-6=moderate pain, scores 7-10=severe pain.

¶Not reported by 19 patients.

**Not reported by 20.

Table 2| Pain and sensory disturbances among Danish women who underwent mastectomy for primary breast cancer in 2005 and 2006

	Sentinel lymph node biopsy		Axillary lymph node dissection				
					Anterior thoracic* + locoregional† radiotherapy		
	No chemotherapy	With chemotherapy	No chemotherapy	With chemotherapy	No chemotherapy	With chemotherapy	Total
Non-responders	13 (11)	13 (17)	11 (9)	8 (10)	35 (13)	28 (13)	108 (12)
Median (IQR) age (years)	66 (63-71)	57 (50-69)	68 (61-72)	58 (56-58)	68 (64-73)	52 (49-57)	63 (55-69)
Responders	108 (89)	63 (83)	112 (91)	75 (90)	229 (87)	184 (87)	771 (88)
Median (IQR) age (years)	68 (64-73)	60 (54-66)	66 (62-71)	55 (49-63)	67 (64-71)	56 (51-62)	64 (57-70)
Pain‡:							
Yes	24 (22)	17 (27)	40 (36)	35 (47)	101 (44)	80 (44)	297 (39)
No	84 (78)	46 (73)	72 (65)	40 (53)	128 (56)	104 (56)	474 (61)
Worst pain§:							
Light	11 (46)	7 (41)	19 (48)	17 (49)	39 (39)	41 (51)	134 (45)
Moderate	12 (50)	6 (35)	16 (40)	14 (40)	45 (45)	24 (30)	117 (40)
Severe	1 (4)	4 (24)	5 (12)	4 (11)	16 (16)	15 (19)	45 (15)
Sensory disturbances¶:							
Yes	41 (39)	29 (47)	61 (56)	57 (80)	130 (58)	127 (70)	445 (59)
No	63 (61)	33 (53)	49 (44)	14 (29)	95 (42)	54 (30)	308 (41)
Moderate to severe pain on at least a weekly basis**:							
Yes	12 (11)	8 (13)	17 (15)	16 (22)	53 (23)	35 (19)	141 (18)
No	96 (89)	55 (87)	95 (85)	58 (78)	175 (77)	149 (81)	628 (82)

IQR=interquartile range.

*Corresponding to anterior thoracic wall.

†Corresponding to periclavicular, axillary level 3, and for right sided breast cancers, internal mammary nodes.

§Defined as highest pain score of four regional pain scores. Scores 1-3=light pain, scores 4-6=moderate pain, scores 7-10=severe pain.

¶Not reported by 18 patients.

**Not reported by 2 patients.

Table 3| Pain intensity and frequency among 886 (in total 903 patients reported having pain*) long term breast cancer survivors treated for primary breast cancer in 2005 and 2006. Figures are numbers (percentage) of patients

Pain intensity† by area	Light	Moderate	Severe	Total
Breast				
Every day or almost every day	126 (43)	124 (43)	40 (14)	290
1-3 times/week	106 (54)	75 (39)	14 (7)	195
More rarely	155 (72)	52 (24)	7 (3)	214
Total	387	251	61	699
Side of body				
Every day or almost every day	92 (45)	91 (45)	21 (10)	204
1-3 times/week	69 (52)	62 (46)	3 (2)	134
More rarely	108 (77)	27 (19)	5 (4)	140
Total	269	180	29	478
Axilla				
Every day or almost every day	97 (46)	85 (41)	27 (13)	209
1-3 times/week	86 (57)	59 (39)	6 (4)	151
More rarely	124 (82)	23 (15)	5 (3)	152
Total	307	167	38	512
Arm				
Every day or almost every day	72 (35)	90 (44)	43 (21)	205
1-3 times/week	62 (49)	52 (41)	13 (10)	127
More rarely	93 (76)	21 (17)	8 (7)	122
Total	227	163	64	454

*10 patients did not report pain frequency, 5 patients reported neither pain frequency nor pain severity, 1 patient did not report anything but pain “yes,” and 1 patient did not report pain severity.

†Light=1-3 on numerical rating scale; moderate pain=4-6; severe=7-10.

Table 4| Multivariate logistic regression analysis of effects of method of treatment and age on pain in women after treatment for breast cancer. Figures are odds ratios (95% confidence interval)

	No (%) of women		Unadjusted		Adjusted*	
	With pain	Without pain	OR (95% CI)	P value	OR (95% CI)	P value
Age group (years):						
≤49	104 (46)	124 (54)	1.91 (1.39 to 2.62)	<0.001	1.78 (1.25 to 2.54)	<0.001
50-59	285 (46)	331 (54)	1.96 (1.55 to 2.49)		1.86 (1.43 to 2.43)	
60-69	337 (34)	645 (66)	1.19 (0.95 to 1.48)		1.12 (0.90 to 1.41)	
≥70	177 (31)	403 (69)	1 (reference)		1 (reference)	
Breast procedure:						
Mastectomy	297 (39)	474 (61)	1.06 (0.89 to 1.27)	0.49	1.02 (0.77 to 1.34)	0.89
BCS	606 (37)	1029 (63)	1 (reference)		1 (reference)	
Axillary procedure:						
ALND	557 (44)	702 (56)	1.84 (1.55 to 2.17)	<0.001	2.04 (1.60 to 2.61)	<0.001
SLNB	346 (30)	801 (70)	1 (reference)		1 (reference)	
Radiotherapy:						
LRRT + BRT/ATRT	368 (44)	467 (56)	1.64 (1.27 to 2.13)	<0.001	1.18 (0.86 to 1-62)	0.20
BRT	419 (35)	794 (65)	1.10 (0.86 to 1.42)		1.43 (0.97 to 2.10)	
None	116 (32)	242 (68)	1 (reference)		1 (reference)	
Chemotherapy:						
With	389 (43)	514 (57)	1.46 (1.23 to 1.73)	<0.001	1.01 (0.82 to 1.25)	0.91
Without	514 (34)	989 (66)	1 (reference)		1 (reference)	
Year of surgery:						
2005	423 (37)	712 (63)	0.98 (0.83 to 1.15)	0.80	—	—
2006	480 (38)	791 (62)	1 (reference)		—	
Endocrine therapy:						
With	601 (39)	943 (61)	1.18 (0.99 to 1.41)	0.06	—	—
Without	302 (35)	560 (65)	1 (reference)		—	

ALND=axillary lymph node dissection; ATRT=anterior thoracic radiotherapy corresponding to anterior thoracic wall; BCS=breast conserving surgery; BRT=breast radiotherapy, corresponding to residual breast tissue; LRRT=locoregional radiotherapy corresponding to periclavicular, axillary level 3, and for right sided breast cancers, internal mammary nodes; SLNB=sentinel lymph node biopsy.

*Adjusted for age, mastectomy/BCS, ALND/SLNB, radiotherapy, and chemotherapy.

Table 5| Multivariate logistic regression analysis of effects of method of treatment and age on moderate to severe pain on at least a weekly basis in women after treatment for breast cancer. Figures are odds ratios (95% confidence interval)

	No (%) of women		Unadjusted		Adjusted*	
	With pain	Without pain	OR (95% CI)	P value	OR (95% CI)	P value
Age group (years):						
≤49	45 (20)	182 (80)	2.08 (1.37 to 3.18)	<0.001	2.07 (1.29 to 3.32)	<0.001
50-59	138 (22)	475 (78)	2.44 (1.76 to 3.39)		2.43 (1.69 to 3.50)	
60-69	134 (14)	841 (86)	1.34 (0.97 to 1.85)		1.29 (0.94 to 1.79)	
≥70	61 (11)	513 (89)	1 (reference)		1 (reference)	
Breast procedure:						
Mastectomy	141 (18)	628 (82)	1.31 (1.04 to 1.65)	0.02	1.18 (0.84 to 1.66)	0.35
BCS	237 (15)	1383 (85)	1 (reference)		1 (reference)	
Axillary procedure:						
ALND	242 (19)	1010 (81)	1.76 (1.41 to 2.21)	<0.001	1.48 (1.06 to 2.06)	0.02
SLNB	136 (12)	1001 (88)	1 (reference)		1 (reference)	
Radiotherapy:						
LRRT + BRT/ATRT	170 (20)	661 (80)	1.48 (1.05 to 2.07)	<0.001	1.30 (0.87 to .94)	0.40
BRT	155 (13)	1046 (87)	0.85 (0.61 to 1.19)		1.12 (0.68 to 1.83)	
None	53 (15)	304 (85)	1 (reference)		1 (reference)	
Chemotherapy:						
With	174 (19)	726 (81)	1.51 (1.21 to 1.89)	<0.001	0.95 (0.72 to 1.26)	0.73
Without	204 (14)	1285 (86)	1 (reference)		1 (reference)	
Year of surgery:						
2005	194 (17)	932 (83)	1.22 (0.98 to 1.52)	0.08	—	—
2006	184 (15)	1079 (85)	1 (reference)		—	
Endocrine therapy:						
With	257 (17)	1276 (83)	1.22 (0.97 to 1.55)	0.09	—	—
Without	121 (14)	735 (86)	1 (reference)		—	

ALND=axillary lymph node dissection; ATRT=anterior thoracic radiotherapy corresponding to anterior thoracic wall; BCS=breast conserving surgery; BRT=breast radiotherapy, corresponding to residual breast tissue; LRRT=locoregional radiotherapy corresponding to periclavicular, axillary level 3, and for right sided breast cancers, internal mammary nodes; SLNB=sentinel lymph node biopsy.

*Adjusted for age, mastectomy/BCS, ALND/SLNB, radiotherapy, and chemotherapy.

Table 6| **Intensity of pain* in 2008 and 2012 in women after treatment for breast cancer. Figures are numbers (percentage) of women**

	Pain intensity in 2012					
Pain intensity in 2008	No pain	Light pain	Moderate pain	Severe pain	Missing	Total
No pain	1086 (72)	119 (27)†	56 (17)†	9 (8)†	3 (25)	1273
Light pain	259 (17)‡	199 (45)	76 (22)†	13 (11)†	3 (25)	550
Moderate pain	108 (7)‡	99 (22)‡	155 (46)	41 (35)†	4 (33)	407
Severe pain	16 (1)‡	14 (3)‡	44 (13)‡	49 (42)	1 (8)	124
Missing	34 (2)	11 (2)	7 (2)	4 (3)	1 (8)	57
Total	1503	442	338	116	12	2411

*Light pain=1-3 on numerical rating scale; moderate pain=4-6; severe pain=7-10.

†Increase in pain.

‡Decrease in pain.

Table 7| **Multivariate logistic regression analysis of effect of methods of treatment and age on sensory disturbances in women after treatment for breast cancer. Figures are odds ratios (95% confidence interval)**

	No (%) of women		Unadjusted		Adjusted*	
	With sensory disturbances	Without sensory disturbances	OR (95% CI)	P value	OR (95% CI)	P value
Age group (years):						
≤49	165 (73)	62 (27)	5.05 (3.60 to 7.09)	<0.001	5.35 (3.60 to 7.96)	<0.001
50-59	402 (66)	207 (34)	3.69 (2.90 to 4.69)		3.97 (2.99 to 5.27)	
60-69	435 (45)	532 (55)	1.55 (1.25 to 1.92)		1.46 (1.17 to 1.84)	
≥70	197 (35)	374 (65)	1 (reference)		1 (reference)	
Breast procedure:						
Mastectomy	445 (59)	308 (41)	1.66 (1.40 to 1.98)	<0.001	1.67 (0.89 to 3.13)	0.11
BCS	754 (47)	867 (53)	1 (reference)		1 (reference)	
Axillary procedure:						
ALND	821 (66)	424 (34)	3.85 (3.24 to 4.56)	<0.001	—	—
SLNB	378 (34)	751 (66)	1 (reference)		—	
Breast surgery by axillary procedure:						
BCS			—	—		<0.001
ALND	446 (68)	212 (32)	—		4.78 (3.47 to 6.60)	
SLNB	308 (32)	655 (68)	—		1 (reference)	
Mastectomy:						
ALND	375 (64)	212 (36)	—	—	2.48 (1.58 to 3.90)	<0.001
SLNB	70 (42)	96 (58)	—		1 (reference)	
Radiotherapy:						
LRRT + BRT/ATRT	546 (66)	283 (34)	1.63 (1.26 to 2.11)	<0.001	0.96 (0.66 to 1.41)	0.97
BRT	465 (39)	733 (61)	0.54 (0.42 to 0.68)		0.94 (0.56 to 1.58)	
None	188 (54)	159 (46)	1 (reference)		1 (reference)	
Chemotherapy:						
With	557 (62)	338 (38)	2.15 (1.81 to 2.55)	<0.001	0.96 (0.77 to 1.21)	0.75
Without	642 (43)	837 (57)	1 (reference)		1 (reference)	
Endocrine therapy:						
With	817 (54)	702 (46)	1.44 (1.22 to 1.71)	<0.001	0.91 (0.75 to 1.11)	0.38
Without	382 (45)	473 (55)	1 (reference)		1 (reference)	
Year of surgery:						
2005	557 (50)	558 (50)	0.96 (0.82 to 1.13)	0.61	—	—
2006	642 (51)	617 (49)	1 (reference)		—	

ALND=axillary lymph node dissection; ATRT=anterior thoracic radiotherapy corresponding to anterior thoracic wall; BCS=breast conserving surgery; BRT=breast radiotherapy, corresponding to residual breast tissue; LRRT=locoregional radiotherapy corresponding to periclavicular, axillary level 3, and for right sided breast cancers, internal mammary nodes; SLNB=sentinel lymph node biopsy.

*Adjusted for age, mastectomy/BCS, ALND/SLNB, radiotherapy, endocrine therapy, and chemotherapy.

†Interaction between ALND/SLNB and type of breast surgery significant at P=0.02.

Figures

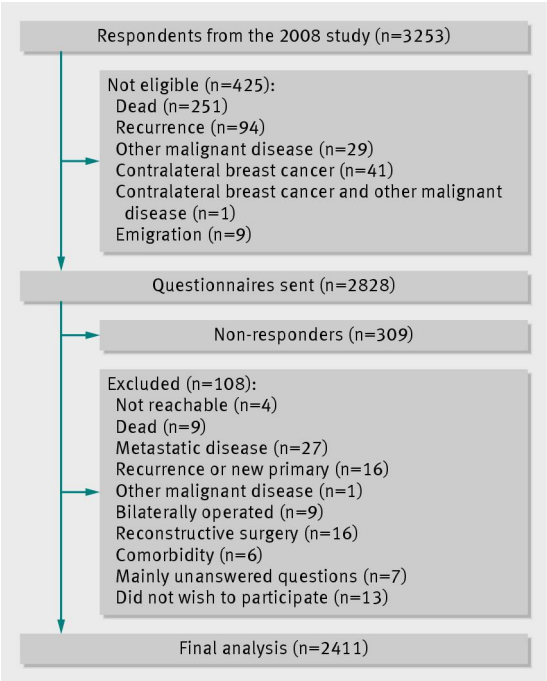

Fig 1 Identification of women included in follow-up study of persistent pain after treatment for breast cancer

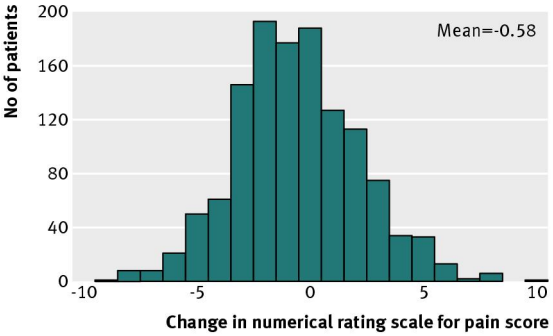

Fig 2 Change from 2008 to 2012 in development of pain after treatment for breast cancer. Excludes 1086 women who reported no pain in 2008 and in 2012