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The Relationship between Anger Regulation, Mood, Pain, and Pain-Related Disability in Women Treated for Breast Cancer

Running title: Anger Regulation, Mood, and Pain

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Abstract

Objective

Anger, depressive symptoms, and anxiety are known reactions to cancer, and suggested to modulate pain experience. We examined the association between anger regulation, mood and pain in 952 breast cancer patients followed for 3 years.

Methods

Preoperatively, the patients completed questionnaires about depressive symptoms (BDI), state anxiety (STAI), anger regulation (STAXI-2), and pains in the surgical and other areas. Experimental pain sensitivity was tested. In the follow-up, BDI and STAI were assessed at 1 and at 6 months, and at 1, 2, and 3 years after surgery. Pain in the surgical area was evaluated during the first 7 days, and at 1 and 3 years after surgery. Pain-related disability was assessed at 3 years after surgery. Latent profile analyses were performed to identify mood profiles, and regression analyses to find independent predictors for mood and pain variables.

Results

Anger-inhibition and pain had associations with ongoing depressive symptoms and anxiety. Pain-related disability was associated with high anxiety at a hazard ratio (HR) of 2.24(95% CI1.17-4.27), with older age (HR1.07, 95% CI1.01-1.13), and with pain in the surgical area (HR3.04, 95% CI2.41-3.85), but not with anger variables. Any relationship between anger regulation and pain intensity disappeared after controlling for age and mood.

Conclusions

Different forms of pain are important to recognize and treat to support breast cancer patients' psychological well-being. Anger-inhibition could be a target for psychotherapeutic intervention, to help with ongoing mood symptoms. The relationship between anger regulation and pain is not straightforward.

Background

The quality of life of cancer survivors has become an important issue as improvements in cancer treatments have increased the survival rates (1). Both depression and anxiety are well-recognized reactions to a breast cancer diagnosis (2). Feelings of anger are also natural in connection with serious conditions such as cancer and pain (3). Anger regulation, referring to how a person usually behaves when feeling angry, is thought to be a fairly stable trait (4). Anger-inhibition (anger-in) reflects a tendency to suppress angry feelings, whereas expression of anger (anger-out) reflects the opposite tendency. Previous studies suggest that anger regulation interrelates with quality of life (5,6), somatic wellbeing (5,7,8), and pain (9,10).

Persistent pain after breast cancer treatments is common. Approximations of the prevalence vary from 14% to 60%(11,12). Systematic risk factors have been found to include, for example, anxiety, radiotherapy, more invasive surgery, and greater preoperative and acute postoperative pain (11,12).

Research suggests that there is an association between anger regulation and both acute and chronic pain (9,10,13-15). Compared with anger-in, anger-out has been reported to have a more independent effect on pain (14-16). However, negative findings also exist (16-18).

Pain experience consists of cognitive, affective, and physiological mechanisms, and anger regulation is thought to influence pain experience through all of these (14,19-22). The connection between anger-out and pain has been suggested to be mediated by, e.g. increased muscle reactivity (23), activation of the sympathetic nervous system (14), and endogenous opioid system dysfunction (20). Anger-in is thought to be associated with generalized negative affect, which would also mediate its influence on pain and especially on coping behavior (3,21). In a previous study in which we used a machine-learning-approach to identify factors that associate with persistent pain after breast cancer surgery, we found that higher anger-in was associated with pain intensity at 3 years after surgery (13).

The aim of the current study was to analyze the association of anger regulation with mood and pain more thoroughly in a large breast cancer cohort. Two dimensions of mood, depressive symptoms and state anxiety, were subjected to latent profile analyses to derive mood profiles. The more specific aims were: First, to examine whether we could recognize

latent mood profiles in the 3-year follow-up and to discover if anger regulation is associated with persistent depressive symptoms and anxiety; the second aim was to examine the role of anger regulation in the experience of both experimental and clinical acute pain intensity; the third aim was to study whether mood and anger regulation associate with pain-related disability.

Better understanding of the role of psychological characteristics behind unfavorable coping and pain, and on the other hand, of the role of pain in mood could help in the development of more specific interventions to support breast cancer survivors.

Methods

Patients

The Coordinating Ethics Committee of the Helsinki University Hospital approved the study protocol (136/E0/2006). Women aged 18 to 75 years, having histologically-proven newly-diagnosed invasive breast cancer (T1-4N0-3M0) were recruited at the Breast Surgery Unit of the Helsinki University Hospital between 08/2006 and 12/2010. The surgical procedure was either modified radical mastectomy or breast-conserving surgery, each with either sentinel node biopsy, axillary lymph node dissection, or both. Women who had oncoplastic breast-conserving procedures and immediate reconstruction surgery were excluded from the study. Women who had breast reconstruction within the past 12 months were excluded from the follow-up analyses.

Background and cancer-related information

Age was recorded and body mass index (BMI) was measured preoperatively. After surgery, the patients' records were reviewed for the type of surgery. The type of surgery in the axilla was included in the acute pain regression analyses as a covariate because it was demonstrated to influence pain intensity in our earlier studies (11,25). The presence of metastases and/or recurrences related to primary breast cancer, other cancers, and metastases and/or recurrences related to other cancers were searched for in the patient records and the data were coded as a categorical variable "cancer status" (0=no incidence, 1=at least one incidence). This categorical variable was used as a covariate in multivariate analyses. Each type

of adjuvant treatment received (radiotherapy, chemotherapy, endocrine therapy) was coded as a categorical variable (yes/no).

Anger regulation, depressive symptoms, and anxiety

The Anger Expression Inventory (STAXI-2)(4) was used to assess anger regulation. The patients were asked to answer the inventory twice, before and at 6 months after surgery. The Beck Depression Inventory was used (BDI)(26) to measure depressive symptoms, and the State-Trait Anxiety Inventory (STAI)(27) to evaluate the intensity of state anxiety. Both inventories were administered preoperatively, and after the surgery at 1 month, and at 6, 12, 24, and 36 months (see online supplemental materials for more detailed description of these measurements).

Pre- and postoperative pain and experimental pain

To assess pre- and postoperative pain in the surgical area, the patient was asked to report the current intensity of pain on a Numerical Rating Scale (NRS) from 0 to 10(0=not at all, 10=the worst pain imaginable). Pain was recorded for three separate regions: the breast, the axilla, and the upper arm. The highest rating in any one of these locations was used as an indication of pain intensity ("worst pain"). Pain in these areas was asked preoperatively, on days 1-7 postoperatively, and at 12 and 36 months after the surgery. The average for the first week of pain ratings was calculated. The presence of possible preexisting chronic pain conditions (e.g., fibromyalgia, headaches) was asked before surgery with categorical yes/no questions.

Experimental cold and heat pain tests were performed 1 to 3 days before surgery (see online supplemental materials for further details).

Pain-related disability

At 3 years after the primary operation the patients evaluated on an NRS from 0 to 10 "*if, and how much the pain in the surgical area (the breast, the axilla, and the upper arm) has affected your life."* They, similarly, evaluated "*if, and how much the pain has disturbed your sleep."* The three surgical areas were asked separately and the highest score indicated was used in the analyses. With a categorical yes/no question the patients were asked *"have you given up on something because of the pain in the surgical area, e.g., hobbies, work, specific*

clothing, etc.?" If a patient answered "yes" for any of the three surgical areas she was coded as having had to give up something. A new variable "pain-related disability" was formed by combining these three questions as follows: the answer to all questions NRS 0 to 3 or no (no or low disability), answer to one of the questions NRS 4 to 10 or yes (moderate disability), and answer to all of the questions NRS 4 to 10 and yes (high disability).

Statistical analyses

The test-retest validity of anger-in and anger-out was tested by using paired samples t-tests and by estimating correlation coefficients.

To determine homogenous subgroups, latent profile analyses (LPA) with one latent variable were run separately on different measures of depressive symptoms and anxiety. The analyses were conducted with Mplus. The model fit was estimated by the Akaike Information Criterion (AIC), the Bayesian information criterion (BIC), a sample-size adjusted BIC(SSABIC), and entropy. A good-fitting model has a small AIC, BIC, and SSABIC (indicating parsimonious models) and high entropy (indicating precision in assigning participants into appropriate classes). To compare models with different numbers of classes, we used the Vuong–Lo–Mendell–Rubin likelihood ratio-test.

Univariate group comparisons were performed by using univariate ANOVA and t-tests for normally distributed variables, and U-tests and Kruskall-Wallis tests for non-normally distributed variables.

Multivariate analyses were performed using either linear regression or binary or multinomial logistic regression analyses depending of the outcome variable. Pain variables with significant independent association with anger-out and anger-in were chosen for multivariate analyses. Age, preoperative state anxiety, and depressive symptoms were set in the experimental pain (heat pain and cold pain tolerance) and acute postoperative pain (first week average pain) models as covariates.

Two different models were formed to find factors associating with latent mood profiles. Goodness-of-fit and model fitting information were detected for all models. SPSS software version 22.0 for Windows (SPSS Inc., Chicago, IL) was used to conduct group comparisons and multivariate statistical analyses. Group comparisons were corrected using the Bonferroni

correction.

Results

The characteristics of the patients are presented in Table 1. 1149 patients were invited to participate. 126 declined and 23 failed to meet the study inclusion criteria. From the total of 1000 patients, preoperative data was available from 952, and three-year follow-up from 709 patients. The detailed patient flow is presented in Figure 1, see online supplement materials. The whole cohort of 1,000 patients has been described in detail earlier (24). The mean value for anger-in was higher than that for anger-out (11.01vs.8.78, p<0.001). Patients in the high anger-in group were older than patients in the low anger-in group (58.0vs 55.0 years, p=0.010). The mean age of the group reporting high anger-out was lower than that of those reporting low anger-out (53.7 years vs.60.6 years, p<0.001).

Anger-in and anger-out subscale scores decreased between the preoperative measurement and those at the 6-month follow up, with means for anger-in 11.0(SD4.2) vs. 10.3(SD4.5)(t=5.60,p<0.001), and means for anger-out 8.7(SD3.8) vs. 7.7(SD3.9)(t=8.7p<0.001). Correlation coefficients were r=0.62(p<0.001), and r=0.59(p<0.001), respectively.

Depressive symptoms and state anxiety

LPAs were able to assort profiles for two mood variables. There were two profiles for depressive symptoms (low and high) and four profiles for anxiety (low, mild, moderate, severe). The frequencies for the depressive symptom profiles were n=774(81.3%) for the low profile and n=178(18.7%) for the high profile. For the anxiety profiles the numbers were as follow: low, n=282(29.7%); mild, n=431(45.3%); moderate, n=179(18.8%); and severe, n=59(6.2%).

The mean ages in the low and high depressive symptom groups were similar, being 57.3(SD 9.3) and 56.1(SD 9.8) with t=1.47(p=0.144), respectively. There were modest differences in age between the anxiety profile groups, with means of 57.9(SD9.0) in the low anxiety group, 57.2(SD9.3) in the mild anxiety group, 55.5(SD10.1) in the moderate anxiety group, and 59.0(SD56.7) in the severe anxiety group (F=2.6, p=0.050).

Table 2 displays the results of the binary logistic regression analyses where the outcome variable was depressive symptom group. Nagelkerke's r^2 for the preoperative model was pseudo r^2=0.13 and for the follow-up model pseudo r^2=0.25.

Table 3 displays the results of the multinominal regression analyses for anxiety. Nagelkerke's r^2 for the preoperative model was pseudo r^2=0.15, and for the follow-up model was pseudo r^2=0.25

Anger regulation and pain intensity

Preoperative chronic pain of any kind was not associated with either anger-out (8.87[SD3.8] vs. 8.49[3.8], p=0.186) or anger-in (10.95[SD4.3] vs. 11.17[SD4.2], p=0.498). Neither was preoperative pain in the surgical area associated with anger-out (8.74[SD3.8] vs 9.3[SD3.9], p=0.281) or anger-in (11.02[SD4.2] vs. 10.92[SD5.0], p=0.861).

Experimental cold pain tolerance was not associated with either anger-out (p=0.827) or anger-in (p=0.090). Experimental heat pain intensity had a univariate association with anger-out (r^2=0.07, p= 0.030) and anger-in (r^2=0.08, p=0.020). After controlling for depressive symptoms and state anxiety in a linear regression model, the independent effect of anger-in on heat pain was no longer statistically significant (p=0.214). Age did not have an effect on the association. Anger-in was not associated with the mean pain intensity for the postoperative first week (p=0.938). The associations between anger-out and both heat pain and pain during the first postoperative week were not significant after controlling for age (p=0.053 and p=0.645, respectively).

Pain-related disability

The results on the associations between pain-related disability, depressive symptoms, state anxiety, anger regulation, and pain are presented in Table 4. Nagelkerke's r^2 for the model was pseudo r^2= 0.426.

Discussion

The relationship between anger regulation, mood and pain among breast cancer patients was studied. We found that there was a group of patients whose depressive symptoms and anxiety

did not diminish in a 3-year follow-up period. Furthermore, we confirmed an association between anger-inhibition and pain in persistent mood symptoms. Anxiety was associated with pain-related disability. The relationship between anger regulation and pain intensity was affected by age and mood.

Even though anger regulation has been described to be quite stable, as far as we are aware there are no follow-up studies on how anger regulation evolves after dramatic life experiences like cancer diagnosis. In the present study the test-retest validity of the anger regulation scales was not as good as expected. This may reflect the fluctuating nature of anger regulation that varies between situations and can plausibly change over a lifetime. The preoperative situation may be psychologically so exceptional for cancer patients that the "baseline" for trait features, like anger-inhibition and expression that explain how a person copes with her disease should also be measured after all primary treatments are over.

Earlier evidence that anger-in reflects negative affect and therefore overlaps with depressive symptoms (18,21) was supported in the present study. Previous research has also revealed an association between anger-in and depressive symptoms shortly after diagnosis in breast cancer patients (6), but our finding of an association between anger-in and high depressive symptoms after a long follow-up is novel. Nearly one fifth of the patients in our study reported repeatedly over time higher scores on the depression measure. Expression of negative emotions may be beneficial to overall health outcomes in breast cancer patients by relieving distress(8,28). However, depression and suppression of emotions may, conversely, have an unfavorable effect on cancer survival (29,30). Julkunen et al. reported in their study of cancer patients that anger-in was negatively associated with perceived partner support (5). Lack of spousal support and increased depressive symptoms may have a crucial influence on how well a person adjusts to life with cancer.

It is commonly acknowledged that negative affect also modulates pain perception, and that depressive symptoms and anxiety influence persistent postsurgical pain and associate with poorer rehabilitation results (31-33). The negative role of high anxiety in perceived pain-related disability was established also in the present study. Pain and mood share many common health-related comorbidities, for example, high BMI, smoking, and physical inactivity (34). Therefore, women at risk for persistent pain and negative affect should be recognized during the early phase of breast cancer treatments.

Previous studies have reported inconsistent results regarding the association of anger regulation with experiences of pain (16-18). Our results suggest that anger regulation has only a minor independent effect on pain intensity in women treated for breast cancer, and the associations between anger-in and pain were no longer significant after controlling for mood. This finding is in agreement with that of a previous study showing an association between anger-in and pain in fibromyalgia patients when mood was not controlled for (35). Another study, on patients having limb pain, demonstrated that after controlling for depressive symptoms the association between anger-in and pain disappears (14). Burns et al.(21) concluded in their review article that anger-in overlaps with negative affect, by which it influences pain experience.

It has been suggested (20) that people with higher anger-out have deficient endogenous opioid regulation that contributes to their pain experience. In the present study, higher anger-out was associated with experimental pain (heat) and with higher average pain during the first postoperative week. However, when controlling for age, this association was no longer significant. This suggests that the relationship between anger-out, pain, and age is more complex than previously acknowledged. The endogenous opioid system has been reported to deteriorate with increasing age (36,37). Anger-out may therefore differently influence pain in different age groups. The number of young patients was too small to allow a comparison of young and older patients in the present study.

Younger patients reported more anger-out, while anger-in was more typical in older patients. This association between anger regulation and age was also reported by Spielberger (4). However, most previous studies examining the association between anger regulation and pain have not controlled for age (9,14,38). The mean age of the individuals studied has usually been much lower than in our study (14,15,17,18). However, Sayar et al.(15) reported that anger-out was related to higher pain scores in fibromyalgia patients, even when age was taken into account. These results may be due to the different nature of pain after breast cancer surgery and the widespread pain of fibromyalgia. It has been suggested that the association of anger regulation with pain is partly related to the pathophysiology of different types of pain (14,15,22).

Study limitations

Some researchers suggest that the role of anger regulation is more pronounced when anger is aroused before asking about pain(17,22). We did not investigate state-anger or its effect on pain intensity, which may partly explain the modest effect of anger on pain in our cohort. In the present study, the mean scores for both anger-out and anger-in were lower than in previous studies with female cohorts (15,39) and particularly so in comparison with cohorts that included men (14,40). Therefore, the results of the current study cannot be generalized to groups other than breast cancer cohorts. The modest test-retest validity may also reflect this. Due to the nature of our study, no conclusion about the causality between mood disturbances and pain can be made.

Clinical Implications and conclusions

We showed that nearly 20% of the patients treated for breast cancer had depressive symptoms and anxiety that persisted throughout the three-year follow-up. Our results suggest that pain intensity and anger-inhibition are closely associated with ongoing negative mood and that anxiety has a strong role in pain-related disability. Thus, it is important to monitor psychological well-being at follow-up visits and to pay special attention to pain management and psychotherapeutic interventions in these breast cancer patients.

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Conflicts of interest

The authors have no conflicts of interest.

Data availability

Dataset analyzed in this study is not publicly available. Further information about the dataset is available from the senior author (EK) on reasonable request.

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Table 1. Patient Characteristics

	N	Min	Max	Mean	SD	Median
Age	952	28	75	57.1	9.4	58
BMI§	952	16	42.8	25.5	4.3	24.8
Preoperative pain intensity in the surgical area (NRS¶)	951	0	8	1.2	1.4	1
Preoperative expectation of intensity of acute postoperative pain (NRS)	546	0	10	5.3	2.1	5
Experimental pain, heat (NRS)	943	0	10	3.5	2.4	3
Cold pain tolerance (seconds)	870	5	90	45.8	29.3	37
Worst pain during the 1st week (NRS)	952	0	9.4	2.6	1.8	2.3
Worst pain at 12 months (NRS)	845	0	10	1.6	1.9	1
Worst pain at 36 months (NRS)	709	0	10	1.4	1.8	1
Anger-inhibition (anger-in)	947	0	24	11.0	4.2	11
Low (≤ 7-11)	520					
High (12- ≥16)	427					
Anger-expression (anger-out)	946	0	21	8.8	3.8	9
Low (≤ 5-9)	466					
High (10- ≥14)	480					
Preoperative chronic pain	952	**%**				
Yes	232	24.3				
No	720	75.6				
Type of surgery (axilla)						
SNB# only	528	55.5				
ALNDŧ	424	44.5				
Radiotherapy						
Yes	698	73.6				
No	250	26.4				
Chemotherapy						
Yes	546	57.4				
No	406	42.6				
Endocrine Therapy						
Yes	641	67.3				
No	311	32.7				

Abbreviations: §BMI=Body Mass Index; ¶NRS=Numerical Rating Scale (0-10); #SNB=Sentinel Node Biopsy; ŧALND=Axillary Lymph Node Dissection; SD=Standard Deviation.

Table 2. The Associations of Age, Anger Regulation, and Pain With Persistent Depressive Symptoms

Preoperative	df	HR	95% CI¶		Sig.
Age	1	0.98	0.96	1.00	0.044
Anger-out	1	1.01	0.96	1.06	0.737
Anger-in	1	1.15	1.10	1.20	<0.001
Chronic pain	1	1.90	1.30	2.78	0.001
Preoperative pain (surgical area)	1	1.24	1.11	1.39	<0.001
Follow-up					
Age	1	0.99	0.97	1.01	0.385
Anger-out at 6 months	1	1.02	0.96	1.07	0.582
Anger-in at 6 months	1	1.26	1.20	1.32	<0.001
Chronic pain	1	1.50	0.96	2.35	0.077
Worst pain at 12 months	1	1.22	1.11	1.35	<0.001
Cancer status	1	1.76	0.84	3.65	0.132

The outcome variable is the latent profile grouping(low/high) for depressive symptoms. The reference category is low depressive symptoms. ¶CI=confidence interval.

Table 3. The Associations of Age, Anger Regulation, and Pain with Persistent Anxiety

Preoperative		df	HR	95% CI¶		Sig.
Mild	Age	1	0.99	0.97	1.01	0.280
	Anger-out	1	1.03	0.99	1.08	0.162
	Anger-in	1	1.11	1.07	1.16	<0.001
	Chronic pain	1	1.05	0.71	1.54	0.813
	Preoperative pain (surgical area)	1	1.36	1.19	1.56	<0.001
Moderate	Age	1	0.97	0.95	0.99	0.006
	Anger-out	1	1.04	0.99	1.10	0.135
	Anger-in	1	1.18	1.12	1.24	<0.001
	Chronic pain	1	0.57	0.36	0.90	0.016
	Preoperative pain (surgical area)	1	1.57	1.35	1.82	<0.001
Severe	Age	1	0.97	0.94	1.01	0.116
	Anger-out	1	1.02	0.95	1.11	0.574
	Anger-in	1	1.27	1.18	1.37	<0.001
	Chronic pain	1	0.71	0.36	1.40	0.324
	Preoperative pain (surgical area)	1	1.22	0.96	1.54	0.101
Follow-up						
Mild	Age	1	1.00	0.98	1.02	0.883
	Anger-out at 6 months	1	1.06	1.01	1.11	0.030
	Anger-in at 6 months	1	1.14	1.09	1.19	<0.001
	Chronic pain	1	0.99	0.64	1.52	0.965
	Worst pain at 12 months	1	1.22	1.09	1.36	0.001
	Cancer status	1	0.43	0.18	0.99	0.047
Moderate	Age	1	0.98	0.95	1.00	0.072
	Anger-out at 6 months	1	1.10	1.03	1.17	0.003
	Anger-in at 6 months	1	1.29	1.22	1.37	<0.001
	Chronic pain	1	0.70	0.41	1.19	0.185
	Worst pain at 12 months	1	1.37	1.20	1.56	<0.001
	Cancer status	1	0.41	0.15	1.11	0.079
Severe	Age	1	1.00	0.96	1.04	0.884
	Anger-out at 6 months	1	1.08	0.99	1.18	0.088
	Anger-in at 6 months	1	1.43	1.31	1.56	<0.001
	Chronic pain	1	1.15	0.50	2.64	0.748
	Worst pain at 12 months	1	1.42	1.19	1.70	<0.001
	Cancer status	1	0.39	0.09	1.66	0.202

The outcome variable is the latent profile grouping for state anxiety(low/mild /moderate/severe). The reference category is low state anxiety. ¶CI=Confidence Interval.

Table 4. The Associations of Age, Pain, Anger Regulation, and Mood with Pain-Related Disability.

		df	HR	95% CI¶		Sig.
Moderate disability	Age	1	0.99	0.96	1.02	0.542
	Anger-out	1	0.98	0.91	1.06	0.652
	Anger-in	1	1.04	0.97	1.12	0.304
	Depressive symptoms (low/high)	1	1.59	0.64	3.94	0.316
	Anxiety (low/mild/moderate/severe)	1	1.39	0.89	2.17	0.149
	Chronic pain	1	0.62	0.33	1.16	0.133
	Worst pain at 36 months	1	1.84	1.56	2.15	<0.001
	Cancer status	1	0.79	0.24	2.55	0.687
High disability	Age	1	1.07	1.01	1.13	0.026
	Anger-out	1	1.01	0.89	1.13	0.935
	Anger-in	1	0.94	0.85	1.04	0.229
	Depressive symptoms (low/high)	1	1.58	0.45	5.52	0.478
	Anxiety (low/mild/moderate/severe)	1	2.24	1.17	4.27	0.015
	Chronic pain	1	0.31	0.13	0.78	0.012
	Worst pain at 36 months	1	3.04	2.41	3.85	<0.001
	Cancer status	1	1.26	0.22	7.24	0.795

Results of multivariate logistic regression analyses. The reference category is no or low pain-related disability. ¶CI=Confidence Interval.