Postoperative Chronic Pain Syndrome and Risk Factors in Patients with Breast Surgery

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ABSTRACT

Objective: To investigate the incidence of chronic postoperative pain after different types of breast surgery, and investigate the risk factors associated with chronic postoperative pain.

Study Design: Descriptive study.

Place and Duration of the Study: Ankara University, Faculty of Medicine, Ibnisina Hospital, from January to May 2021.

Methodology: Postoperative chronic pain syndrome and risk factors were investigated in 200 female patients who underwent breast surgery for different reasons. The relationships between preoperative chronic pain, analgesic drug use, number of previous surgeries, anxiety, depression levels, lifestyle, age, height, body mass index, education level, postoperative acute pain, and postoperative sixth--month pain level were statistically analysed.

Results: Chronic postoperative pain was observed at a rate of 30%. Postmastectomy syndrome was observed with a rate of 31.6%. A statistically significant relationship was found between preoperative chronic pain, smoking, analgesic use, and postoperative chronic pain ($p<0.001$). Total mastectomy, mastectomy and simultaneous reconstructive surgery, axillary surgery were associated with chronic pain ($p<0.001$). A strong correlation was observed between preoperative anxiety ($r=0.758$, $p<0.001$), depression ($r=0.773$, $p<0.001$), and chronic pain.

Conclusion: Chronic postoperative pain and postmastectomy pain syndrome are found in almost one-third of the operated patients mainly related to preoperative smoking, analgesic use, breast cancer, and psychological state.

Key Words: *Chronic pain, Breast neoplasms, Mastectomy, Anxiety, Depression.*

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INTRODUCTION

Chronic postoperative pain syndrome (CPPS) was first described in 1998 by Crombie *et al.*; there is no standard protocol for the pathogenesis, causes and management of this syndrome.[1] Post-operative chronic pain syndrome is also defined as the pain that occurs after surgery, associated with the surgical field, and lasting at least 3-6 months.[2]

In addition to the type of surgical intervention, duration of surgery, and the anaesthetic method, there are many other risk factors contribute to the development of this syndrome such as pre-operative pain, psychological factors, *etc*.[3] In recent years, studies investigating the role of psychological factors, especially depression and anxiety in the formation of post-surgical chronic pain syndrome, have been conducted in increasing numbers.[3,4]

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Chronic pain syndrome after breast surgery is a highly prevalent condition that cannot be underestimated.[5] Breast cancer, which is one of the most common cancer types in women, is also one of the top causes of cancer-related death. Conditions such as emotional distress, anxiety, and depression are seen at a high rate in patients with cancer diagnosis and can affect the severity of postoperative pain by increasing patient sensitivity and expectation to pain.[5] The aim of this study was to investigate chronic postoperative pain syndrome and contributing risk factors in patients who underwent breast surgery.

METHODOLOGY

The general surgery operating rooms of Ibnisina Hospital, between January and May 2021. The study was conducted after the approval of the Ethics Committee (decision dated 14.01.2021, No. 1-07-21), in accordance with the Helsinki Declaration criteria.

Written informed consent was obtained from the patients participating in the study and information about the study was given. Patients who did not agree to participate in the study, patients under the age of 18, patients with a diagnosis of cancer other than breast cancer or with metastases due to breast cancer, and uncooperative patients were excluded from the study. Since general anaesthesia was applied to all of the patients, the

agents used in induction and maintenance were similar (remifentanil, propofol and rocuronium bromide in induction, and in the maintenance of anaesthesia, sevoflurane, 40-60% O_2 -N_2O mixture). During the operation, the depth of anaesthesia was monitored with Bispectral Index monitorisation (BIS™, Medtronic, Ireland) (BIS value between 40-60).

A similar pain protocol was applied to all patients for post-operative pain control (intravenous paracetamol and tramadol).

Two hundred and twenty-three patients initially consented to the study and 218 completed the baseline questionnaires. Since 18 patients did not respond at the 6th month postoperatively, the study was continued with 200 patients. At the sixth-month point, the patients were divided into groups with and without chronic pain according to their pain levels (VAS ≥4). The number of patients with VAS ≥4 at 6 months postoperatively was 60. In 140 patients, the pain was either completely absent or at a level that could not affect the quality of life (VAS <4).

Demographic information of the patients (age, weight, height, body mass index, family or living alone, smoking, doing sports, education level), and telephone numbers for communication were recorded. Pre-operative medical information such as any kind of chronic pain (conditions such as diagnosed fibromyalgia, migraine, facet joint or lumbar disc herniation related low back pain, chronic toothache), use of analgesic medicines, if any, and the number of previous surgeries were also recorded. The presence of preoperative anxiety and depression findings of the patients was recorded by evaluating with Beck Anxiety Inventory and Beck Depression Inventory, respectively.

During the follow-up period in the post-anaesthesia recovery unit (PACU), the patients' highest pain levels (VAS score, early postoperative pain) and additional opioid doses (morphine mg equivalent) were recorded. Surgical procedures were classified as breast conserving surgery, total mastectomy and total mastectomy+reconstructive surgery. Patients who underwent partial mastectomy and excisional biopsy were evaluated in the breast-conserving surgery group. According to axillary intervention, the authors classified the procedures as no axillary dissection, axillary dissection and sentinel lymph node biopsy. Surgical indications were classified as invasive cancer, ductal carcinoma *in situ* (DCIS) and benign. The duration of the surgical operation performed was also recorded. At the 6th postoperative month, the patients were called by phone and asked about their pain levels (VAS), and pain characteristics (burning, stinging, throbbing, stabbing). Patients receiving chemotherapy and radiotherapy were also recorded. Patients with VAS ≥4 at 6 months were considered as patients with CPPS. The effects of preoperative anxiety and depression on CPPS were analysed. At the same time, the relationship between the demographic information of the patients and CPPS was statistically analysed.

Sample size was determined by performing power analysis with the G-Power 3.1 program. According to Power (1-β) =0.80 at a confidence level of 95%, the number of samples to be taken in each group was determined as 55. The total sample size of the two groups was determined as a minimum of 110.

Statistical analysis was performed using SPSS version 23.0 software (SPSS Inc., Chicago, IL, USA). In descriptive statistics, normal distribution is determined by one-sample Kolmogorov-Smirnov test and the continuous variables that are not normally distributed were expressed as median (min-max), while categorical variables were expressed in numbers and percentages. The Mann Whitney-U test was used to compare the continuous variables of two groups. The difference between categorical variables are calculated by Chi-Square test. Correlation of two continuous variables was calculated by Spearman Rho correlation.; r value between 0.0.3 was considered weak, 0.3-0.7 as moderate and 0.7-1 was accepted as strong correlation. A p-value of <0.05 was considered statistically significant.

RESULTS

Although the study started with 223 patients, the number of patients who answered all the questionnaires and could be reached at the 6th month control was 200. CPPS was observed in 60 patients (30%) at the 6th month postoperatively (VAS score ≥4). These patients had complaints of pain at the operation site. Other patients participating in the study had no or mild pain (<4/10).

A statistically significant relationship was observed between age and BMI and CPPS. In the group of patients who developed CPPS, the mean age was younger and the mean BMI was higher (p<0.05, Table I).

Twenty-two (37.3%) of the patients who developed CPPS were primary school graduates and 22% (n=13) were secondary school graduates; this rate was equal in the group without chronic pain 11.3% (n=16). The relationship between education level and chronic pain was statistically significant (p<0.001, Table I).

The effect of lifestyle on CPPS was not statistically significant (p>0.05). It was observed that chronic pain developed in 27 (90%) of 30 patients who smoked preoperatively. The effect of smoking on CPPS was statistically highly significant (p<0.001).

The relationship between regular exercise and CPPS was statistically significant (p=0.002, Table I).

There was no statistically significant relationship between the number of previous surgeries for other reasons and chronic pain after breast surgery in 200 patients who completed the study (p=0.128, Table I).

In the postoperative chronic pain group, 47.5% (28 patients) of the patients were using analgesic drugs before surgery, while this rate was 10.6% 815 patients) in the other group (p<0.01, Table I).

Table I: Demographic properties and the comparison of CP and NCP groups.

	Total	Chronic pain (CP) (n=60)	No Chronic Pain (NCP) (n=140)	p*
	Median (min-max) / n(%)			
Age (years)	47 (20-78)	46 (20-75)	52 (30-78)	0.001
Weight (kg)	65 (47-100)	72 (47-88)	63 (48-100)	0.014
Height (m)	1.6 (1.5-1.82)	1.59 (1.5-1.74)	1.64 (1.5-1.82)	0.076
BMI (kg/m2)	25.3 (19-270)	26.1 (20.3-36.6)	24.3 (19-270)	0.001
Education level				<0.001
Primary school	38 (19 %)	22 (37.3 %)	16 (%11.3)	
Secondary school	29 (14.5 %)	13 (22 %)	16 (%11.3)	
High school	73 (36.5 %)	12 (20.3 %)	61 (%43.3)	
University	60 (30 %)	12 (20.3 %)	48 (34%)	
Living type				0.555
Family	177 (88.5 %)	51 (86.4 %)	126 (89.4%)	
Alone	23 (11.5 %)	8 (13.6 %)	15 (10.6%)	
Exercise	40 (20 %)	4 (6.8 %)	36 (25.5%)	0.002
Smoking	30 (15 %)	27 (45 %)	3 (2.1 %)	<0.001
Preoperative analgesic use	43 (21.5 %)	28 (47.5 %)	15 (10.6 %)	<0.001
Preoperative pain	60 (30 %)	55 (91.7 %)	5 (3.6 %)	<0.001
No preoperative pain	140 (70 %)	5 (8.3 %)	135 (96.4 %)	
Radiotherapy	40 (20 %)	33 (55 %)	7 (5%)	<0.001
Chemotherapy	30 (15%)	27 (45 %)	3 (2.1%)	0.128
Previous surgery number	1(1-4)	1(1-4)	1(1-4)	

**Mann Whitney-U test, Chi-square test, min-minimum, max-maximum.*

Table II: Comparison of operative parameters, anxiety and depression status between CP and NCP groups.

	Total	Chronic pain (CP) (n=60)	No Chronic Pain (NCP) (n=140)	p*
	Median (min-max) / n(%)			
Surgery type				<0.001
Total mastectomy	29 (14.5%)	29 (48.3%)	-	
Mastectomy with reconstruction	17 (8.5%)	17 (28.3%)	-	
Breast conservation surgery:	154 (77%)	14 (23.3%)	140 (100%)	
1. Partial mastectomy	144 (%93.5)	14 (100%)	130 (92.9%)	
2. Excisional biopsy	10 (6.5%)	-	10 (7.1%)	
Axillary surgery				<0.001
No axillary surgery	79 (39.5%)	-	79 (56%)	
Axillary dissection	46 (23%)	46 (78%)	-	
Sentinel lymph node biopsy	75 (37.5%)	13 (22%)	62 (44%)	
Indications for surgery				<0.001
Invasive cancer	65 (32.5%)	50 (83.3%)	15 (10.7%)	
DCIS	125 (62.5%)	10 (16.7%)	115 (82.1%)	
Benign	10 (5%)	-	10 (7.2%)	
Surgery duration (min)	85 (50-190)	120 (60-190)	80 (50-110)	<0.001
Preoperative anxiety				<0.001
Absent	18 (9%)	-	18 (12.8%)	
Mild	106 (53%)	6 (10.2%)	100 (70.9%)	
Moderate	46 (23%)	26 (44.1%)	20 (14.2%)	
Severe	30 (15%)	27 (45.8%)	3 (2.1%)	
Preoperative depression				<0.001
Absent	18 (9%)	-	18 (12.8%)	
Mild	105 (52.5%)	6 (10.2%)	99 (70.2%)	
Moderate	45 (22.5%)	22 (37.3%)	23 (16.3%)	
Severe	32 (16%)	31 (52.5%)	1 (0.7%)	
Highest VAS score in PACU	3 (0-7)	5 (3-7)	3 (0-5)	<0.001
Morphine dose in PACU (mg)	2 (0-8)	4 (2-8)	1.5 (0-3)	<0.001

**Mann Whitney-U test, Chi-square test, min-minimum, max-maximum.*

Of the 200 study patients, 60 (30%) had preoperative chronic pain conditions (conditions such as diagnosed fibromyalgia, migraine, facet joint or lumbar disc herniation-related low back pain, and chronic toothache). It was observed that chronic pain developed after surgery in 55 (91.7%) of these patients. A statistically significant relationship was observed between the presence of chronic pain preoperatively and CPPS (p<0.001, Table I).

It was observed that the rate of CPPS development was high among patients receiving chemotherapy and radiotherapy. This was statistically significant (p<0.001, Table I).

All patients with total mastectomy and mastectomy with reconstruction (11 directly implanted patients and 6 tissue expander patients) developed chronic pain. The rate of CPPS was 23.3% in the group of patients who had undergone breast-conserving surgery. The rate of development of post-mastectomy pain syndrome (PMPS) in 190 patients who underwent mastectomy (total or partial, except for patients who underwent excisional biopsy) with the diagnosis of cancer was 31.6% (60 patients). The relationship between the type of surgical intervention performed CPPS was statistically significant ($p<0.001$, Table II).

Axillary dissection was performed in 46 patients. The rate of development of CPPS was 100% in this patient group. The rate of development of chronic pain was 22% in the sentinel lymph node biopsy group (Table II).

Surgical indications were classified as invasive cancer, ductal carcinoma *in situ* (DCIS) and benign. It was observed that 50 (83.3%) of 65 invasive cancer patients developed chronic pain. Only 10 (16.7%) of DCIS patients (125 patients) developed CPPS ($p<0.001$, Table II).

The correlation between the duration of surgery and CPPS was statistically significant ($r=0.542$, $p<0.001$, Table II).

It was observed as a statistically highly significant correlation between preoperative anxiety ($r=0.758$, $p<0.001$) and depression ($r=0.773$, $p<0.001$) and CPPS.

It was observed as a statistically significant correlation between early postoperative acute pain ($r=0.712$, $p<0.001$) and opioid use ($r=0.690$, $p<0.001$) and CPPS.

It was observed burning pain in 35 (58.3%), stinging in 5 (8.3%), throbbing in 6 (10%), stabbing pain in 10 (16.7%), and a combination of stinging + burning in 4 (6.7%) of 60 patients who developed chronic pain in the 6th month postoperatively. Pain was localised in the breast in 16 (26.7%) patients and in the axilla in 14 (23.3%) patients. Thirty (50%) patients had in both breast and axilla.

DISCUSSION

The study was conducted with 200 female patients who had undergone breast surgery. It was observed CPPS at a rate of 30% (60 patients) at 6 months postoperatively. PMPS developed in 31.6% (60 patients) of 190 patients who had undergone surgery for cancer. Patients with a VAS score of ≥4 at 6 months postoperatively were considered as patients with chronic pain. The pain developed after surgery persisted for at least 3 months and was localised in the axilla, breast or upper arm.

PMPS is a long-lasting condition that occurs immediately or weeks to months after surgery.[6] PMPS is seen as a wide range with frequency of 20% to 68%.[7,8]

Factors contributing to PMPS formation can be classified as patient and surgery. Among the surgical factors, the surgical method (mastectomy, axillary dissection, *etc*.) and the duration of surgery are important factors contributing to the development of postoperative pain. Wilson *et al*. emphasised the importance of the surgical method (axillary surgery, axillary lymph node dissection) among the determining factors of CPPS. As a result of the examination of 470 patients who had undergone breast surgery, the incidence of CPPS was found to be high after axillary surgery and axillary lymph node dissection.[9] Possible nerve damage (eg, intercostobrachial nerve) at the time of axillary dissection may be a cause of PMPS.[10]

Wallace *et al*. studied 282 female patients who had undergone breast surgery. The incidence of CPPS was found to be higher in patients who underwent mastectomy+ reconstructive surgery compared to those who underwent only mastectomy (49% *vs*. 31%).[8]

In this study, PMPS was found to be high in patients who had undergone total mastectomy, mastectomy and reconstructive surgery, and axillary surgery. The rate of development of CPPS is lower in the group of patients who did not undergo axillary intervention, sentinel lymph node biopsy and partial mastectomy. Wide surgical areas, chest wall muscles or a possible nerve damage during total mastectomy, axillary dissection may be the causes of CPPS. On the contrary, less tissue damage in breast-conserving surgery is an important factor in preventing chronic pain.

In this study, it was observed a statistically significant relationship between young age and CPPS ($p=0.01$). This correlation was also present between high weight ($p=0.014$) and BMI values ($p=0.001$) and CPPS.[10,11]

Smith *et al*. showed an inverse relationship between the incidence of PMPS and age. In the same study, the authors argued that larger tumour sizes seen in the younger patient population may result in longer-lasting and severe acute postoperative pain.[7] A higher risk of nerve damage due to wider surgical dissection in younger patients, a higher tendency to anxiety, and a more morbid course of breast cancer pose a risk for the development of CPPS.[11]

Karki *et al*. found that high BMI values were associated with chronic pain after breast cancer surgery.[12] It was also seen in this study that obesity with high subcutaneous fat ratio had complicated the surgical intervention.

Most of the patients in the group with CPSS were primary and secondary school graduates (37.3% and 22%,

respectively). There is a statistical relationship between education level and postoperative chronic pain (p<0.001). Lanitis *et al*., claimed in a study they conducted that there is a relationship between education level and early postoperative pain. Low education level may be associated with high expectation after surgery, high preoperative anxiety, and depression levels, and insufficient medical support demand.[13]

No statistically significant relationship was found between lifestyle (living with family or alone) and CPPS (p=0.555). The patient group who developed chronic pain mostly consisted of individuals who did not do sports constantly and lived a sedentary life (p=0.02). The authors think that regular physical activity has a positive effect on postoperative rehabilitation and prevents chronicity of postoperative pain by modulation of pain.[14] A sedentary lifestyle was associated with increased CPPS in patients who had undergone breast surgery.

It was observed that 30 of the 200 female patients included in the study were smokers and 27 of them developed CPPS. Studies have shown that changes in the neuronal level caused by smoking in the nervous system contribute to the development of CPPS.[15] These changes continue for a long time and contribute more to the development of chronic pain compared to active smokers.[16]

In this study, a statistically significant relationship was found between smoking and CPPS (p<0.001).

Patients' preoperative anxiety and depression were tested with questionnaires and were found to be correlated with CPPS (6 months postoperative pain) (r=0.758, p<0.001 for preoperative anxiety, r=0.773, p<0.001 for preoperative depression).

It was noticed that 27 of 30 patients with severe anxiety developed chronic pain, all of these patients were diagnosed with cancer, 31 of 32 patients with severe depression symptoms developed chronic pain, and 29 of these patients were diagnosed with cancer. It is common for patients to experience symptoms of anxiety and depression after cancer diagnosis.[16] The surgical intervention to be applied and the anxiety of possible changes in the postoperative body appearance negatively affect the psychological state of the patients. At the same time, high anxiety levels may affect the severity of acute pain after surgery.[17]

Tara *et al.* while investigating the incidence of CPPS after breast surgery, found a strong correlation between postoperative 6th month pain levels and preoperative anxiety, depression, and catastrophizing findings.[18]

The relationship between early postoperative acute pain and CPPS was statistically significant (r=0.712, p<0.001). This relationship was also present between the need for opioids in the early postoperative period and CPPS (r=0.690, p<0.001).

The authors think that the neuronal changes caused by postoperative acute pain in the central and peripheral nervous system have an important contribution to the development of CPPS.[19] There are studies showing that acute pain after surgery and its associated opioid use are the determining factors of CPPS.[20]

Of the 200 study patients, 60 were found to have chronic pain in any part of the body before surgery (40 fibromyalgia, 10 chronic migraine, 5 low back pain, 5 chronic toothache). None of the patients had a previous history of breast or axillary pain. It was observed that 55 of these patients developed CPPS. A statistically significant correlation was observed between preoperative chronic painful conditions and CPPS (p<0.001).

Sipila *et al*. in their study, stated that preoperative chronic painful conditions were associated with CPPS.[16] Preoperative chronic painful conditions pave the way for the development of CPPS in patients. Long-term central and peripheral sensitization facilitates the chronicity of postoperative acute pain.[21] The rate of analgesic medicine use for different reasons was 47.5% (28 patients) and 10.6% (15 patients) in the group with and without chronic pain, respectively (p<0.001). Keller *et al*. found a high incidence of chronic pain after thoracotomy in the patient group using preoperative narcotic drugs in their study.[22] Villa *et al*. reported preoperative analgesic drug use as an independent risk factor for CPPS after breast surgery (p=0.018). The authors think that the changes (wind-up of wide dynamic range neurons, sensitization) caused by preoperative chronic pain in the central and peripheral nervous system contribute to the formation of postoperative chronic pain.[23]

General anaesthesia was administered to all patients included in this study. Therefore, no comment could be made on the relationship between the form of anaesthesia and chronic pain.

It is known that additional treatment methods such as radiotherapy and chemotherapy increase the risk of CPPS.[24] In this study, a significant relationship was observed between the incidence of CPPS and radiotherapy and chemotherapy according to the literature (p<0.001).

When the operation times are examined, it is seen that this period is longer in the patient group with CPSS and this is statistically significant (r=0.542, p<0.001). Ashraf *et al*.

showed in their study that the duration of surgical intervention was associated with postoperative acute pain.[25] Since the hospital where the study was conducted is also a training and research hospital, assistant doctors also participated in surgical operations. At certain stages of the surgical intervention, assistant doctors work independently. The difference between the operation times may be due to this. In this study, longer surgical time, especially large surgical area, and major surgery (total mastectomy, axillary dissection) contributed to more tissue damage, prolongation of tissue healing time and chronicity of postoperative pain.

There are limiting factors in this study, such as the fact that the surgical team participating in the operation is not always the same, and that neuropathic pain scales (eg DN4) are not used in the 6th month controls of the patients. Despite improvements in postoperative pain management protocols, the rate of the patient population experiencing severe postoperative pain is still high. The authors think that effective and aggressive treatment of postoperative acute pain will prevent chronic pain. Each patient who is planned for breast surgery should be approached individually, chronic pain status, high anxiety and/or depression symptoms should be investigated before the surgery, and close pain monitoring should be performed in the postoperative period.

CONCLUSION

CPPS after breast surgery remains an important problem. Total mastectomy, axillary dissection, total mastectomy + reconstruction surgery, prolonged surgical procedure, and preoperative high anxiety and depression levels increased the frequency of postoperative chronic pain. In addition, preoperative chronic pain and the use of analgesic drugs are among the factors contributing to the development of CPPS. What makes this study special is the evaluation of demographic, surgical and psychological factors together.

ETHICAL APPROVAL:

Before starting the study, approval was obtained from the Human Research Ethics Committee of Ankara University Faculty of Medicine (Decision No. 1-070-21, dated 14.01.2021).

PATIENTS' CONSENT:

It was shared with the patients who participated in the study that they gave consent for the data to be published by participating in the study.

COMPETING INTEREST:

The authors declare that they have no competing interests.

AUTHORS' CONTRIBUTION:

DA, IA: Idea, design, data collection, writing, analysis, critical revision.

REFERENCES

1. Crombie IK, Davies HT, Macrae WA. Cut and thrust: Antecedent surgery and trauma among patients attending a chronic pain clinic. *Pain* 1998; **76**:167-71.
2. Werner MU, Kongsgaard UE. Defining persistent postsurgical pain: Is an update required? *Br J Anaesth* 2014; **113(1)**:1-4. doi: 10.1093/bja/aeu012.
3. Darin C. Chronic postoperative pain: Recent findings in understanding and management. *F1000Res* 2017; **6**:1054. doi: 10.12688/f1000research.11101.1.
4. Kristin LS, Martel OM, Helen S, John RS, Carol G, Nicole V. *et al*. Persistent pain in postmastectomy patients: Comparison of psychophysical, medical, surgical, and psychosocial characteristics between patients with and without pain. *Pain* 2013; **154(5)**:1-20. doi: 10.1016/j.pain.2012.11.015.
5. Erbin K, Tuğba A, Tünay K, Gonca OT, Suheyla U. The effect of anxiety on postoperative pain expectation and opioid consumption in modified radical mastectomy operations. *Ortadogu Medi J* 2019; **11**:136-42.
6. Yuksel SS, Ava GC, Brandon TJ, Annie BW, Marco FE. Post mastectomy pain syndrome: A systematic review of prevention modalities. *JPRAS Open* 2022; **31**:32-49. doi: 10. 1016/ j.jpra.2021.10.009.
7. Smith WC, Bourne D, Squair J, Phillips DO, Chambers WA. A Retrospective cohort study of post mastectomy pain syndrome. *Pain* 1999; **83(1)**.91-5. doi: 10.1016/s0304-3959 (99)00076-7.
8. Wallace MS, Wallace AM, Lee J, Dobke MK. Pain after breast surgery: A survey of 282 women. *Pain* 1996; **66(2-3)**: 195-205. doi: 10.1016/0304-3959(96)03064-3.
9. Wilson GC, Quillin RC, Hanseman DJ, Lewis JD, Edwards MJ, Shaughnessy EA. Incidence and predictors of neuropathic pain following breast surgery. *Ann Surg Oncol* 2013; **20(10)**:3330-4. doi: 10.1245/s10434-013-3156-6.
10. Andersen KG, Kehlet H. Persistent pain after breast cancer treatment: A critical review of risk factors and strategies for prevention. *J Pain* 2011; **12(7)**:725-46. doi: 10.1016/j.jpain. 2010.12.005.
11. Youwei G, Qixing T, Qinghong Q, Changyuan W. Prevalence of postmastectomy pain syndrome and associated risk factors A large single-institution cohort study. *Medicine* 2020; **99(20)**:e19834. doi: 10.1097/MD.00000000000 19834.
12. Karki A, Simonen R, Malkia E, Selfe J. Impairments, activity limitations and participation restrictions 6 and 12 months after breast cancer operation. *J Rehabil Med* 2005; **37(3)**:180- 8. doi: 10.1080/16501970410024181.
13. Sophocles L, Christina M, Demetris R, Gionous S, George S, Constantine K. The ımpact of educational status on the postoperative perception of pain. *Korean J Pain* 2015; **28(4)**: 265-74. doi: 10.3344/kjp.2015.28.4.265.
14. Kayo AH, Maria SP, Carla MS, Virginia FMT. Effectiveness of physical activity in reducing pain in patients with fibromyalgia: A blinded randomised clinical trial. *Rheumatol Int* 2012; **32(8)**:2285-92. doi: 10.1007/s00296-011-1958-z.
15. Perkins KA, Gerlach D, Michelle B, Mark S. Quitting cigarette smoking produces minimal loss of chronic tolerance to

nicotine. *Psychopharmacol* 2001; **158(1)**:7-17. doi: 10. 1007/s002130100850.

16. Sipila R, Estlander AM, Tasmuth T, Kataja M, Kalso E. Development of a screening instrument for risk factors of persistent pain after breast cancer surgery. *Br J Cancer* 2012; **107(9)**:1459-66. doi: 10.1038/bjc.2012.445.
17. Aysegul B, Gonul S, Elif C. Effects of preoperative anxiety on ıntraoperative hemodynamics and postoperative pain. *J Coll Physicians Surg Pak* 2019; **29(9)**:868-873. doi: 10.29271/jcpsp.2019.09.868.
18. Tara LS, Emily DG, Nantthasorn Z, Tari AK, Laura D, Rob RE. *et al*. Chronic pain after breast surgery: A prospective, observational study. *Ann Surg Oncol* 2018; **25(10)**:2917-24. doi: 10.1245/s10434-018-6644-x.
19. Alexandre L, Miriam SM, Guilherme AMB. Chronic postoperative pain: Ubiquitous and scarcely appraised: narrative review. *Braz J Anesthesiol* 2021; **71(6)**:649-55. doi: 10. 1016/j.bjane.2020.10.014.
20. Katz J, Jackson M, Kavanagh BP, Sandler AN. Acute pain after thoracic surgery predicts long-term post-thoracotomy pain. *Clin J Pain* 1996; **12(1)**:50-5. doi: 10.1097/00002508-199603000-00009.
21. Ru-Rong J, Andrea N, Yul H, Niccolò T, William M. Neuroinflammation and central sensitization in chronic and widespread pain. *Anesthesiol* 2018; **129(2)**:343-66. doi: 10.1097/ALN.0000000000002130.
22. Keller SM, Carp NZ, Levy MN, Rosen SM. Chronic post thoracotomy pain. *J Cardiovasc Surg* 1994; **35(6 Suppl 1)**: 161-4.
23. Gianluca V, Raffaele M, Caterina SC, Valeria R, Martina DD, Diego PM. *et al*. Chronic pain after breast surgery: Incidence, associated factors and impact on quality of life, an observational prospective study. *Perioperative Medicine* 2021; **10(1)**:1-11. doi: 10.1186/s13741-021-00176-6.
24. Poleshuck EL, Katz J, Andrus CH, Hogan LA, Jung BF, Kulick DI, *et al*. Risk factors for chronic pain following breast cancer surgery: A prospective study. *J Pain* 2006; **7(9)**: 626-34. doi: 10.1016/j.jpain.2006.02.007.
25. Ashraf SH, Miklos DK, Mary C, Rachel AG, Shelley H. Risk factors for severe acute pain and persistent pain after surgery for breast cancer: A prospective observational study. *Reg Anesth Pain Med* 2019; **44(2)**:192-9. doi: 10.1136/rapm-2018-000040.