PAIN SENSITIVITY AND FACTORS ASSOCIATED WITH THE PAIN EXPERIENCE AFTER BREAST CANCER TREATMENTS

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Faculty of Medicine
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To my family

Never look for univariate answers to multivariate questions
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LIST OF ORIGINAL PUBLICATIONS


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ABBREVIATIONS

ACC  Anterior Cingulate Cortex
ALND Axillary Lymph Node Dissection
Amy Amygdala
ANS Autonomic Nervous System
BDI Beck’s Depression Index
BG Basal Ganglia
BMI Body Mass Index
BrSt Brain Stem
CI Confidence Interval
CIS In Situ Carcinoma
COMT Catechol-O-Methyltransferase
DNIC Diffuse Noxious Inhibitory Control
DZ Dizygotic
HLA Human Lymphocyte Antigen
IC Insula
MDD Major Depressive Disorder
MI primary motor cortex
MZ Monozygotic
NCF Nucleus Cuneiformis
NMDA N-methyl-D-aspartate
NRS Numerical Rating Scale
OPRM1 Opioid Receptor Mu 1
OR Odds Ratio
PAG Periaqueductal gray
PCA Patient Controlled Analgesia
PFC Prefrontal Cortex
RVM Rostral Ventromedial Medulla
SI Primary somatosensory cortex
SII Secondary somatosensory cortex
<table>
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<tr>
<td>SNB</td>
<td>Sentinel Node Biopsy</td>
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<tr>
<td>STAI</td>
<td>Spielberger’s State and Trait Anxiety Index</td>
</tr>
<tr>
<td>STAXI</td>
<td>Spielberger’s State and Trait Anger Expression Index</td>
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<tr>
<td>TENS</td>
<td>Transcutaneous Electrical Nerve Stimulation</td>
</tr>
<tr>
<td>Th</td>
<td>Thalamus</td>
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<td>VAS</td>
<td>Visual Analog Scale</td>
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ABSTRACT

Breast cancer is the most common cancer among women in the Western world. In Finland, approximately 5000 women are diagnosed with breast cancer each year (Finnish Cancer Registry). Due to advances in treatments, disease prognosis has improved markedly, and increasing numbers of women have undergone treatment for breast cancer. The quality of life of cancer survivors is a growing area of research. Pain after breast cancer treatments is a common adverse symptom. Depending of the study setting, the prevalence of persistent pain after breast cancer treatments ranges from 14% to 60%. Both surgery and adjuvant treatments may increase the risk for persistent pain. The purpose of this prospective study was to identify factors associated with the pain experience in women treated for breast cancer. More specific aims were to uncover clinically feasible factors associated with acute and persistent pain to develop an easy-to-use screening tool to identify women at the highest risk for persistent pain.

The whole cohort included 1000 patients (18-75 years). They were recruited at the Breast Surgery Unit of Helsinki University Hospital and were operated on between August 2006 and December 2010. All patients met the research nurse 1-3 days before the surgery. On that preoperative visit, they filled in questionnaires about medical history, overall health, and pain symptoms. Psychological symptoms were evaluated by using Beck’s Depression Scale (BDI, depressive symptoms) and the Spielberger State-Trait Anxiety questionnaire (STAI, state and trait anxiety). Anger regulation was evaluated by using the Spielberger State-Trait Anger Expression Inventory-2 (STAXI, anger inhibition and anger expression). Experimental pain tests (cold 4°C and heat 48°C) were performed the day before surgery. Anesthesia protocol and perioperative pain treatment (oxycodone consumption) were carefully recorded. Patients documented pain on the first postoperative week (days 1-7) three times daily in the area of surgery. In the follow-ups (1 month, 6 months, 1, 2, and 3 years after surgery) patients completed again the same questionnaires about pain, depressive symptoms, and anxiety.

The range of pain sensitivity between women treated for breast cancer was high. Of the women treated for breast cancer, 12.6% reported significant pain at six months, and 13.5% had developed clinically significant persistent pain at the one-year follow-up. The best predictors of pain of any kind; experimental, acute clinical, or persistent pain, were found to be quite similar. Pain (other
chronic pain condition, pain in the area of surgery, or intensity of acute pain), more invasive surgery (axillary clearance), and psychological distress (mainly anxiety) were found to be consistent predictors of heightened pain experience. In addition to these, pain expectation and higher need for oxycodone to achieve satisfactory pain relief after surgery were associated with higher pain intensity during the first postoperative week. Obesity was associated with persistent pain at six months and one year after surgery. The adjuvant treatments of radiotherapy and chemotherapy added to the risk for persistent pain at one year.

Screening tools for preoperative and acute phase use to identify women at risk for persistent pain at six months and at one year after surgery were developed. The one-year prediction tool was also validated in two other prospective patient cohorts.

The average levels of psychological burden, depressive symptoms, anxiety, and heightened anger expression or inhibition were surprisingly low. However, there was a group of women whose distress remained quite stable during the first year. Anger regulation had only a modest association with pain in this patient cohort, and was influenced by age and mood. However, anger inhibition was associated with higher depressive symptoms throughout the three-year follow-up. COMT rs4680 was associated with anger-out.
TIIVISTERMÄ

Rintasyöpä on naisten yleisin syöpätyyppi maailman laajuisesti. Vuosittain Suomessa rintasyöpään
sairastuu noin 5000 naista (Suomen Syöpärekisteri). Hoitojen kehittymisen myötä eliniän ennuste
sairastumisen jälkeen on noussut huomattavasti. Tämän myötä työssä käynti-ikäisiä naisia, jotka
ovat sairastaneet rintasyövän, on paljon. Leikkaus on tyyppillinen osa rintasyövän hoitoa. Vaikka
leikkaustekniikat ovat kehitettyä ja nykyään selvitätään pienemmällä leikkausilla, siitä huolimatta
leikkausen jälkeinen pitkittynyt kipu on merkittävä kliininen ongelma. Myös muut rintasyöpään
liittyvät hoidot kuten sädehoito ja solunsalpaajahoidot, voivat vaikuttaa kivun pitkittymiseen.
Tutkimuksesta riippuen pitkittynyt kipun esiintyvyys vuosi rintasyöpäleikkausen jälkeen vaihtelee
14–60%.

Tämän prospektiivisen tutkimuksen tavoitteena oli selvittää tekijöitä, jotka vaikuttavat kivun
ekokemiseen rintasyöpään sairastuneilla ja sen vuoksi hoidetuilla naisilla. Selvitimme tekijöitä sekä
akuuttiin kokeelliseen että kliiniseen kipuun liittyen ja pitkittyneeseen kipuun liittyen. Selvitimme
tekijöitä, joita on kliinisessä työssä mahdollista seuloa.

Aineistomme koostui HYKS sairaalassa leikatusta 18-75 vuotiaista naisista. Aineisto kerättiin
vuosina 2006-2010. Potilaat tapasivat tutkimushoitajan 1-3 päivää ennen leikkausta ja täyttivät
laajasti terveyshistoriaa ja muuta voimia kartoittavia kyselylomakkeita. Psykologisten oireiden
kyseynä käytimme depressio-oireita kartoittavaa Beckin Depressioasteikkoa (BDI), ahdistusoireita,
sekä tilanteeseen että yleisempää ahdistustaipumusta kartoittavaa Spielbergerin State-Trait (piirre-
ja tilanne) ahdistuskyselyä (STAI) ja suuttumisen ilmaisutyyliä selvitimme Spielbergerin Anger
Expression Inventory-2 kyselyllä (STAXI-2). Potilaille tehtiin leikkausta edeltävänä päivänä myös
kuuma- (48 °C) ja kylmäkipua (4° C) mittavaat kokeellisen kipun testit. Leikkausen liittyvä
anestesia, sekä akuutin kivun hoito (oksikodonin kulutus) monitoroitiin tarkasti. Potilas kirjasi
ensimmäisen leikkausen jälkeisen viikon ajan kipua leikattaavalta alueelta kolmesti päivässä. Potilaalle
lähetettiin kipua ja osa mielialaan liittyvistä kyselylomakkeista 1kk, 6kk, 1v, 2v ja 3v leikkausen
jälkeen.

Hoidetuista potilaista 12.6 % ilmoitti kipua leikatulla alueella puolen vuoden seurannassa ja vuoden
seurannassa 13.5 %. Akuuttiin ja pitkittyneeseen kipua vaikutavat tekijät olivat melko samanlaisia.
Ai kaisempi kipu, joko muu krooninen tai kipu leikattavalla alueella olivat yhteydessä sekä akuuttiin

Potilaat olivat keskimäärin ennen leikkausta psyykkisesti varsin hyvinvoivia. Kliinisesti merkittävää masennusta ja tilanteeseen liittyvää korostunutta ahdistustaipumusta tai yleisempää ahdistustaipumusta oli melko vähän. Aggression ilmaisu oli hieman tyypillisemmin nuorilla ulospäin ulospäin suuntautuvaa, kun taas vanhemmilla suuntumukseen ilmatsa on ollut vähän. Sisäänpäin suuntautuvan suuttumuksen ilmatsa on ollut vähän säänpäin. Sisäänpäin suuntautuvan suuttumuksen ilmatsa on ollut vähän säänpäin. Sisäänpäin suuntautuvan suuttumuksen ilmatsa on ollut vähän säänpäin. Sisäänpäin suuntautuvan suuttumuksen ilmatsa on ollut vähän säänpäin. COMT (rs4680) geenillä huomattiin yhteys suuttumuksen ulospäin suuntautuvan ilmatsaan.
1. INTRODUCTION

Breast cancer is the most common cancer in women in Western countries, also in Finland (Global Burden of Disease Cancer Collaboration et al., 2016; Finnish Cancer Registry). Pain is not a typical symptom that would lead to breast cancer diagnosis, but pain related to breast cancer treatments, especially breast surgery, is common (Wang et al., 2016; Andersen & Kehlet, 2011). Since the number of women who will undergo surgery for breast cancer each year is high, approximately 5000 women in Finland, many will face the risk of persistent pain.

Both acute and persistent pain is always subjective, but also a multidimensional phenomenon, including physiological and psychological aspects. According to the International Association for the Study of Pain (IASP), pain is “an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage”. The fundamental function of acute pain is to inform a person of a plausible danger. Pain experience related to malignant disease may therefore be different from pain of benign cause. Pain after cancer diagnosis may always remind a person of the serious disease and therefore underlie the threat message of pain. When pain is in transition from an acute to a persistent state, the threat value of pain becomes inconsequential. Psychological factors, especially symptoms of depression and anxiety, are known to be associated with increased pain experience (Edwards et al., 2016). These psychological symptoms are also very natural reactions to cancer diagnosis. This combination contributes to how a person interprets and adapts to pain stimuli. Previous experiences of pain and expectations of pain are also known to influence pain (Colloca & Benedetti, 2006; Bingel et al., 2011; Pan et al., 2013). Apkarian et al. (2005) have shown that anticipation of pain is not only a cognitive construct but a neural process that has an influence on pain. Psychological distress comprising depressive symptoms and anxiety and also the prevalence of pain are higher in women. Therefore, the study of the association between pain and psychological factors in women, especially breast cancer patients, is justified.

Research of factors associated with pain experience in breast cancer patients is important in order to diminish individual suffering and also economically (Gustavsson et al., 2012), as severe persistent pain may cause considerable disability and inability to work. It is important to understand the great
variety of pain sensitivity but also to find factors common to the risk of high intensity of clinical acute pain and its persistence. With increased knowledge, we are able to develop treatments, psychosocial and pharmacological, to prevent pain or at least to diminish suffering and to improve the pain treatment and the quality of life after breast cancer treatments. Moreover, the knowledge of how common the symptom of pain is among breast cancer patients and who is at risk for pain is important to enhance healthcare professionals’ awareness of pain and its adequate treatment.
2. REVIEW OF THE LITERATURE

2.1. BREAST CANCER

In 2014, there were 5008 new breast cancer cases in Finland (Finnish Cancer Registry), compared with 2802 cases in 1994 and 3929 cases in 2004 (Figure 1).

![Figure 1](image.png)

**Figure 1.** Increase in the prevalence of breast cancer over a 60-year period.

The risk of having breast cancer increases with age, and part of the rapid rise in incidence is explained by aging of the population. But even if new incidences are standardized by age, the annual number of women facing a diagnosis of breast cancer is increasing. Thanks to improvements in breast cancer treatments over the past decades (Global Burden of Disease Cancer Collaboration et al., 2016), the survival rates of breast cancer have improved remarkably. The survival rate in Finland at ten years after the diagnosis is 85% (Finnish Cancer Registry). Therefore, the negative consequences related to breast cancer treatment and their significance for the quality of life post-recovery are increasingly important.
2.1.1. TREATMENT

The severity of breast cancer defines the treatment needed. The TNM classification comprises information about size of the tumor (T), presence of positive lymph nodes (N), and metastases (M). In situ carcinoma (CIS) is a local, early stage breast cancer where the malignant cells have not penetrated the cell membrane. Also, the grade of the tumor (1-3) affects the decision of the treatment assigned to a patient. The grade reflects the difference in the appearance of the cancer cells compared with normal breast tissue. Grade 1 is the cell type closest to normal tissue, and grade 3 is the cell type with the worst prognosis.

2.1.1.1. Breast surgery

Surgery is the primary and the most typical treatment for breast cancer. Its purpose is to remove malignant tumor from the breast and positive lymph nodes from the axilla, if needed. During breast surgery sentinel lymph node biopsy (SNB) is performed to determine whether the cancer has invaded the lymph nodes. Axillary lymph nodes (ALN) on the side of the tumor are usually the first targets of metastasis and therefore important for diagnosis. Type of surgery in the breast is either breast-conserving or mastectomy. If the tumor is < 3 cm (Joensuu et al., 2013) and it is possible to remove entirely from the tissue, then the type of surgery is breast-conserving. Mastectomy, amputation of the entire breast, is needed if the tumor is large or if there are several cancer tumors in the breast (multifocal tumor) and they are situated widely apart from each other. Mastectomy is usually done if the risk of cancer recurrence is high according to the tumor specimen and if the patient is aged under 35 years. Type of surgery in the axilla is either only sentinel node biopsy (SNB) or also axillary lymph node dissection (ALND). If the tumor has invaded the lymph nodes, axillary clearance is needed. This means removal of the axillary fat tissue and those lymph nodes that have tumor cells.
2.1.1.2. Adjuvant oncological treatment

2.1.1.2.1. Chemotherapy

Medical adjuvant treatments are recommended if tumor cells are found in the axillary lymph nodes or if there are metastases elsewhere in the body or if the risk of recurrence is increased. Chemotherapy is a systemic treatment and usually administered intravenously in the clinic. The purpose of chemotherapy is to eliminate cancer cells that may have circulated into the blood system and to parts of the body other than where the original tumor was located. Chemotherapy may be delivered with a single drug or with a combination of different drugs. Commonly used drugs are taxanes, anthracyclines, and CEF or CMF combination. The combinations include cyclophosphamide (C), fluorourasimide (F), epirubisine (E), or metotreksatite (M). If the tumor is HER2-gene positive, the LHRH agonists, tratutsumab, is used as an adjuvant treatment. Possible long-term side effects of chemotherapies include cardiomyopathy, neutropenia, and neuropathic pain.

2.1.1.2.2. Radiation therapy

Radiation therapy is a local treatment and the majority of women receives it after breast cancer surgery as an adjuvant treatment. When the visible tumor is removed from the breast, there may be malignant cells left and radiation therapy is given to minimize the risk of local recurrence. The treatment is ionizing radiation and its purpose is to damage the DNA of the cancer cells, which leads to cellular death. If the tumor has invaded the axillary lymph nodes, radiation therapy is also given to the axillary area. The most common side effects related to radiation therapy are local erythema, skin irritation, and pain in the area of radiation.

2.1.1.2.3. Endocrine therapy

Some breast cancer cell types use estrogen in order to multiply. In these hormone-positive cancer types, endocrine therapy can be used either alone or after other adjuvant treatments. Endocrine treatment may include antiestrogens or aromatase inhibitors or combinations of both. These are orally administered and treatment usually lasts five years or even longer. The purpose is to minimize the risk of recurrence. The most commonly reported side effects for endocrine therapy are sweating and pain in the joints. Also risk of thrombosis and osteoporosis are known side effects.
2.2. PAIN

2.2.1. NOCICEPTION, MODULATION, AND EXPERIENCE OF PAIN

The definition of pain by the International Association of the Study of Pain (IASP) is the basis of the conception of the nature of both acute and persistent pain experience. According to that definition pain is “an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage” (Merskey & Bogduk, 1994). Experience of pain is always a complex interplay between the somatosensory output from the nociceptors to the brain and the individual modulatory system that determines the actual experience of pain. Therefore, nociception alone is not necessary or even sufficient for complex pain experience. The foundation of the theory of the relevance of this modulatory system was described already in 1965 by Melzack and Wall when they introduced the gate control theory (Melzack & Wall, 1965). The fundamental idea was that pain transmission from the peripheral nerves through the spinal cord was modulated by both intrinsic neurons and controls emanating from the brain. Therefore, pain experience could be controlled by modulation, and this could be done by reducing excitation or by increasing inhibition. This theory has been tested over the years and its applications are still used in modern pain treatment. For instance, treatment like TENS (Transcutaneous Electrical Nerve Stimulation) basically activates large diameter afferents (responsible for e.g. touch and vibration sensations), which increases the inhibitory effect of interneurons. And this non-painful stimulus decreases pain sensation through interaction between neurons having large and thin diameters, projection neurons, and inhibitory interneurons (Melzack & Wall, 1965). In the 16th century, the philosopher Renè Descartes described pain as a bottom-up ascending sensation without any control along the way. Figure 2 shows a variety of factors that modern pain research knows to contribute to the descending top-down pain modulation.
Figure 2. Factors involved in the descending modulation of pain experience.

With advances in techniques to study brain activation during the actual pain experience, the dynamic process that influences pain perception has been elucidated (Lee & Tracey, 2013; Martucci & Mackey, 2016; Tracey, 2017). Understanding of the neural basis of pain has increased, and it is clear that pain perception is centrally mediated (Tracey, 2008). Pain perception or the experience of pain is not modified by a specific pain area in the brain, but rather by a pain matrix consisting of a network of brain areas contributing to the process (Figure 3) (Lee & Tracey, 2013; Melzak, 1999; Tracey, 2008). Furthermore, pain processing is dynamic, showing a wide variety between individuals, especially in the case of persistent pain (Denk et al., 2014; Lee & Tracey, 2013; Tracey, 2008).
Pain experience is modulated through a descending pain modulatory system. Nociceptive information from the periphery goes through the spinothalamic tract, consisting of the central nervous system, the spinal cord (largely within the dorsal horn), and the thalamus (Apkarian et al., 2005; Tracey & Mantyh, 2007). The brainstem area connects nociception with the autonomic nervous system (ANS) and homeostatic processes (Tracey & Mantyh, 2007). Descending modulation can produce either facilitation (pronociception) or inhibition (antinociception) (Tracey & Mantyh, 2007). Brain areas contributing to the descending modulation consist of many regions, e.g. the frontal lobe, insula, anterior cingulate cortex (ACC), amygdala, hypothalamus, periaqueductal gray (PAG), rostral ventromedial medulla (RVM), and nucleus cuneiformis (NCF) (Lee & Tracey, 2013). The brain areas important in pain modulation are also involved in mood regulation and emotional and cognitive experiences (Figure 2). This has been suggested in part to explain the close connection between psychological factors and pain experience, especially in persisting pain (Bushnell et al., 2013; Mansour et al., 2014). Multiple psychological factors, e.g. cognitive processing, mood, and emotional regulation, influence the descending pain modulation (Figure 3) (Apkarian et al., 2005; Bushnell et al., 2013; Denk et al., 2014; Goffaux et al., 2007; Millan, 2002; Tracey, 2010). Structural anatomical changes in the brain have been reported across different clinical pain conditions when pain persists for a long time (Baliki et al., 2014). Interestingly, these changes have been found to be reversible after adequate pain treatment (May, 2011).
Wide variety of neurotransmitters are also involved in this regulation (Millan, 2002). Serotonin may either facilitate or inhibit descending modulation (Millan, 2002), whereas norepinephrine released from the dorsal horn is connected to descending inhibition (D’Mello & Dickenson, 2008; Millan, 2002). Also, the role of e.g. endocannabinoids (Zogopoulos et al., 2013), endogenous opioids, acetylcholine, and substance P in descending pain modulation are well acknowledged (Millan, 2002).

One explanation for altered pain sensation is central sensitization. It is described as an increased functioning of neurons and circuits in nociceptive pathways, leading to pain from a non-painful stimulus or an excessive perception of pain from low-level painful stimuli. It has been suggested to eventually lead to neuronal plasticity of the peripheral and central nervous system. The altered tissue sensitivity can be seen within the injured area, but also in uninjured tissue around the injury (Latremoliere & Woolf, 2009; Woolf, 1983).
Decades of pain research and findings in clinical work with pain patients suggest that also more psychosocial components of pain should be added to the definition of pain (Williams & Craig, 2016). Pain is generally an emotional experience that causes suffering and widely affects the patient's life. Williams and Craig (2016) have suggested that the definition of pain should therefore also include social and cognitive components. Because pain is such a complex issue, it is difficult to assess, manage, and treat.

2.3. PAIN SENSITIVITY

Sensitivity to pain differs enormously among individuals (Edwards, 2005; Mogil, 1999). The same surgical procedure or other painful stimuli are reported differently, and pain experiences from the same stimuli are not comparable. Variation between individuals within the same painful condition has been stated to be greater than the differences across painful conditions (Nielsen et al., 2009). The definition of pain sensitivity is not clear and it seems to vary within an individual depending on the modality of pain (Nielsen et al., 2009). Pain sensitivity can be studied in a well-controlled experimental pain setting where the intensity of noxious stimuli is the same across tested subjects (Edwards, 2005).

2.3.1. MEASURING PAIN

Since pain is a highly subjective and multidimensional experience, self-report is the gold standard for its measurement. This obviously has limitations and it could be argued that the differences between individuals not only reflect actual differences in physical pain sensation but also individual reporting style and usage of the pain rating scales. These issues have been of interest in pain research. A brain imaging study, performed with healthy participants, showed that those individuals reporting high pain ratings in an experimental pain test activated more frequently and with a greater magnitude the brain regions responsible for processing pain-related information (Coghill et al., 2003). These findings are thought to be a neural proof of individual differences in pain experiences. New suggestions about how to image pain with advanced brain image techniques have inevitably yielded more information about pain processes, but these cannot replace the subjective evaluation given by the person experiencing the pain (Robinson et al., 2013).
2.3.1.1. VAS and NRS

Sensory intensity is the most commonly assessed aspect of pain. The Visual Analog Scale (VAS) and Numerical Rating Scale (NRS) have been shown to be equally reliable estimators of the intensity of especially acute pain (Breivik et al., 2008). The NRS is a commonly used measure in both clinical and research settings, and it has shown good validity when measuring pain intensity in various age groups (Fillingim et al., 2016; Gagliese et al., 2005). It has also been demonstrated to have good reliability and stability across experimental sessions (Rosier et al., 2002). It is an 11-point Likert scale ranging from 0 to 10 where zero indicates “no pain” and 10 “the worst imaginable pain”. NRS cut-off point ≥4/10 has been shown to identify patients with moderate to severe pain in postoperative pain (Gerbershagen et al., 2011). Despite good overall validity, NRS may be prone to biases. Smith et al. (1998) noted in their study with cancer patients that if a patient attributed her/his pain to cancer their estimation of pain was higher than those who did not.

2.3.1.2. Patient-controlled analgesia (PCA)

Patient-controlled analgesia (PCA) can be used as a proxy for the intensity of postoperative pain. The need for analgesics postoperatively is an indirect but clinically relevant way to measure individual sensitivity to pain (Kissin, 2009). However, in addition to pain intensity, there are number of factors that may affect the behavior how a patient uses PCA. For example, younger age (Saari et al., 2012) and psychological variables, e.g. depressive symptoms (De Cosmo et al., 2008) and anxiety (Pan et al., 2006; De Cosmo et al., 2008), have been found to be associated with more frequent demands for opioid doses. In a study with patients operated on mainly for a malignant cause, attentional avoidance of emotionally negative stimuli was found to predict a higher amount of demands (Lautenbacher et al., 2011).
2.3.1.3. Experimental pain

Experimental pain testing is a commonly used setting to explore individual and interpersonal variance in pain experience. The experimental setting uses controlled noxious stimuli, e.g. thermal (cold or heat), mechanical (blunt pressure or sharp), or chemical (e.g. capsaicin), that represent different modalities of pain. Traditionally, two features are measured: pain threshold and pain tolerance. Threshold measures the point where an individual reports the stimulus as painful. In the experiment, the stimulus usually is initially a non-painful sensory perception, with the stimulus intensity increasing until it reaches a painful level. Pain tolerance describes the maximum time a person can tolerate the pain stimulus. The intensity of suprathreshold pain is also used to measure pain sensitivity. This reflects the intensity that an individual reports beyond his/her pain threshold. Temporal summation of pain is a dynamic measure of pain sensitivity. It has been considered to reflect the central sensitization of pain in a situation where experimental pain stimulation is given repetitively, with the difference between the pain evoked after one stimulus and the amount of pain evoked after a series of pain stimuli calculated (Arendt-Nielsen et al., 1995). The physiological mechanism behind temporal summation is the activation of N-methyl-D-aspartate (NMDA) receptors as a result of high levels of nociceptive input. In a clinical condition, this is seen as allodynia and hyperalgesia (Arendt-Nielsen et al., 1995).

Another dynamic measure of pain sensitivity is the Conditioned Pain Modulation (CPM) experiment. It comprises psychophysiological tests believed to represent diffuse noxious inhibitory control (DNIC) and to reflect the altered function of the endogenous pain inhibitory pathway (Shrout & Fleiss, 1979; Yarnitsky et al., 2015). The idea is that “pain inhibits pain”. The experiment could be done in various ways and different pain modalities can be used. In brief, the procedure consists of two subsequent painful stimuli, e.g. cold pressure tests. The hypothesis is that the second noxious stimuli (test part) is experienced as less painful because of an activation of endogenous descending pain control. The wide range of experimental settings has hindered comparison of studies, and therefore, a guideline for applying the experiment has been published (Kennedy et al., 2016; Yarnitsky et al., 2015). Nevertheless, various studies have concluded that low efficiency in DNIC is associated with both acute and persistent postoperative pain (Yarnitsky, 2010).

It would be a very tempting idea that clinical postoperative pain could be predicted by the level of experimental pain sensitivity. There is no clear understanding of what experimental pain modalities
best predict clinical pain sensitivity (Abrishami et al., 2011). The results of the comparability between experimental pain and clinical pain have been controversial. Kim et al. (2004) did not find predictive value of experimental (thermal or cold) pain ratings on pain after oral surgery, whereas Nielsen et al. (2007) found that lower pain threshold for electrical pain was associated with higher pain ratings after Cesarean section. Pan et al. (2006) found that heat pain threshold predicted acute pain at rest after the same procedure. Also, Granot et al. (2003) found a positive association between experimental pain and Cesarean section acute pain. Their finding was related to a specific modality, heat pain, and only suprathreshold pain, not pain threshold, predicted acute pain. Predicting persistent pain with experimental pain testing has yielded conflicting findings (Granot, 2009; Johansen et al., 2014). In a large cohort of surgical patients, the predictive value of decreased cold pain tolerance to persistent pain disappeared after adjusting the analysis for other chronic pain conditions (Johansen et al., 2014). Also age has been shown to be related to the sensitivity of cold pressure pain, with younger healthy volunteers reporting lower thresholds to the pain stimulus than older participants (Lariviere et al., 2002). One study was performed to assess the predictive value of the efficacy of DNIC in breast cancer patients. It found no association between DNIC and postoperative acute pain. However, the authors did find that higher pain intensity in the hot water experiment was associated with higher acute postoperative pain (Rehberg et al., 2017). Divergent findings of the association between experimental and clinical postoperative pain (acute or persistent) reflect well the complex nature of pain. Numerous factors contribute to the intensity of pain and subsequent disability. For instance, the context in which pain is experienced and reported (Blasi et al., 2001), the coping strategies used (de Rooij et al., 2014), and mood (Hinrichs-Rocker et al., 2009; Chapman and Vierck, 2016) may have strong influence on the pain experience. Therefore, a more comprehensive preoperative evaluation than experimental pain sensitivity alone is needed to predict the risk of persistent postoperative pain.

2.3.2. GENETICS

2.3.2.1. Heritability

Heritability may explain some of the interindividual differences in pain sensitivity. The role of genetic variation in pain sensitivity can be studied in animal models (Lariviere et al., 2002; Mogil et al.,
In these models, the social and environmental effect of pain experience remains stable, since laboratory animals are bred in controlled environments and they lack the psychosocial history of humans, which is known to have an effect on pain experience. However, the role of a social environment has been demonstrated also in laboratory mice whose response to pain stimulus was affected by observation of a cage-mate who was exposed to the same test earlier (Langford et al., 2006). In humans, the portion of the variance of pain sensitivity explained by genetic variations can be evaluated with twin studies. Dizygotic (DZ) twins share only 50% of their segregating genes, whereas monozygotic (MZ) twins are genetically identical. By studying twin pairs assuming that they share the same environment the importance of genetic factors may be explained over the variance that is not explained by the environment factors. When examining sensitivity to experimental pain stimulus, greater similarity for a particular response to a painful stimulus within MZ twins, compared with DZ twins, can be considered to be due to genetic factors. In a study done with female twins, heritability for different experimental pain modalities ranged from 22% to 55% (Norbury et al., 2007). In another study, including both genders, genetic variants explained approximately the same amount of pain variance: 60% of cold pressure pain and 26% of contact heat pain (Nielsen et al., 2008). Heritability in chronic pain conditions has also been established. A large Finnish twin cohort study demonstrated that up to 51% of the fibromyalgia-related symptoms were explained by heritability (Markkula et al., 2009). Heritability can also be investigated in population-based studies; e.g. in a study in Scotland the heritability for chronic pain was 38.4% (McIntosh et al., 2016).

2.3.2.2. Gene variants and pain

The research aimed at identifying specific gene variants to explain differences between individuals in vulnerability to pain sensitivity and its persistence has been active (Mogil, 2012a; Montes et al., 2015). There is a hope that with advances in finding genetic variants that are related to pain, pharmacotherapies and other treatments could be improved and new targets for drugs could be discovered. A large challenge has been in replicating different findings in new studies. The difficulty is that gene variants associated with pain are often either relevant only to a specific modality of pain rather than to a specific pain condition or the associations are specific to gender or even ethnicity (Hastie et al., 2012; Mogil, 2012a; Denk et al., 2014). Gene variants responsible for pain modulation are also often associated with psychological variables related to descending modulation of pain, e.g.
pain catastrophizing, depression, and anxiety (Bogdan et al., 2013). McIntosh et al. (2016) found in their wide population-based study that chronic pain and major depressive disorder (MDD) were positively correlated and the shared genetic variations explained a significant part of the association. Mogil (2012a) concluded in an extensive review that the most commonly found variants associated with different pain phenotypes included the gene that encodes the catecholamine catabolizing enzyme catechol-O-methyltransferase (COMT) (e.g. postoperative pain, cancer pain, and musculoskeletal pain), μ-opioid receptor gene OPRM1 (e.g. experimental pain and acute pain), GCH1 that encodes an enzyme called GTP cyclohydrolase (e.g. back pain and experimental pain), and human lymphocyte antigen (HLA) (e.g. inflammatory pain and neuropathic pain). COMT metabolizes, for instance, norepinephrine and dopamine and has been shown to moderate, in addition to pain, also psychological factors such as pain catastrophizing (George et al., 2008), aggressive behavior, anger regulation (Baud et al., 2007; Rujescu et al., 2003), depression, and anxiety disorders (Lacerda-Pinheiro et al., 2014). Studies performed in healthy volunteers have shown that the impact of COMT val158met gene variant on depression- and anxiety-related emotional processing is more prominent in females (Domschke et al., 2012). Also, associations between OPRM1, anger expression, and acute pain have been suggested (Bruehl et al., 2008b). De Gregori et al. (2016) found in their study in patients undergoing abdominal surgery that neither the need for analgesics nor postoperative pain intensity was associated with one gene variant, but rather with a combination of different genes.

2.3.3. GENDER DIFFERENCES IN PAIN SENSITIVITY AND EXPERIENCE

It is well known that women report more experimental, acute clinical, and persistent pain (Bartley & Fillingim, 2013). Women also have a higher prevalence of painful diseases, e.g. fibromyalgia and irritable bowel syndrome, and report more pain related to these conditions (Bartley & Fillingim, 2013), which may explain a portion of the differences in pain prevalence between genders. There is fairly good consistency between studies showing that women are more sensitive to different modalities of experimental pain than men (Mogil, 2012b). This difference has been shown in both healthy volunteers (Kim et al., 2004) and in patients undergoing a surgical procedure (Johansen et al., 2014). A study by De Cosmo et al. (2008) found that, compared with men, women reported also more acute postoperative pain after laparoscopic cholecystectomy. However, in a systematic review
searching for predictive factors for acute postoperative pain and analgesic use, female gender was as often positively correlated as negatively correlated with pain (Ip et al., 2009). Some studies also suggest that gender moderates how different psychological factors, e.g. anger, affects the pain experience and its reporting (Bruehl et al., 2007; Burns et al., 1998). The explanation for why women report more pain in general is suggested to be multifactorial and still partly unclear. A wide range of studies have demonstrated that women have more deficient DNIC than men, although studies reporting no difference also exist (van Wijk & Veldhuijzen, 2010), but interestingly no studies show superior DNIC in women (van Wijk & Veldhuijzen, 2010).

One reason behind the gender differences in pain may be the effect of sex hormones. Rosen et al. (2017) suggested in their review article that the overrepresentation of women in different painful conditions and diseases as well as pain persistence may in part be explained by neuroimmunological factors. They suggested that women may produce a larger proinflammatory immune reaction to tissue damage (such as surgery) and have more inflammation, leading to higher pain reports (Rosen et al., 2017). Mast cells, T cells, and macrophages are found to increase the release of proinflammatory cytokines due to estrogen (Rosen et al., 2017). Testosterone, on the other hand, has been found to have a more antinociceptive influence on pain (Craft, 2007).

Also, differences in pain-related coping and psychological variables are suggested to explain the gender differences. Pain-related catastrophizing and rumination is higher in women (Meints et al., 2016). Both of these are known risk factors related to pain intensity and persistence (Meints et al., 2016; Keefe et al., 1989). Furthermore, social expectations may also cause bias in pain reporting (Robinson et al., 2001); men are expected to report less pain than women. Interestingly, healthcare professionals have been demonstrated to estimate females to have more severe pain than men, which may lead to different decisions in treatments between the sexes (Alqudah et al., 2010; Wandner et al., 2010).
2.4. PSYCHOLOGICAL FACTORS AND PAIN EXPERIENCE

2.4.1 THE BIOPSYCHOSOCIAL MODEL OF PAIN

Psychological factors influence how threatening, intense, or interfering we perceive the noxious stimuli to be, and, most importantly, how we experience pain. The biopsychosocial model of pain was developed to describe the multidimensional nature of pain and to converge the dualistic perspectives of the physical and psychological components of pain. The biopsychosocial model describes the dynamic process between physiological, psychological, and social components that mutually influence each other (Gatchel, 2004). The model reflects cancer-related pain well since a multitude of factors, including medical illness, treatments, and psychological suffering and distress, are involved in the pain experience (Syrjala & Chapko, 1995).

The meaning of psychological factors, such as depression, anxiety, pain catastrophizing, fear, and anger, has been the focus of research for already a couple of decades (Bruehl et al., 2006; Burns et al., 2008; Edwards et al., 2016; Keefe et al., 2004). In addition, cognitive processing, e.g. attentional mechanisms, hypervigilance, and pain anticipation, has been investigated (Eccleston & Crombez, 1999; Lautenbacher et al., 2011; Pan et al., 2013). The traditionally studied psychological aspects of how a person experiences pain and adjusts her/his life to persistent pain could be classified as having a negative valence (Edwards et al., 2016). However, the protective, resilience factors also have a role in the perception of interfering or disabling pain (Goubert & Trompetter, 2017). Important components of resilience in persistent pain are suggested to be psychological flexibility, basic psychological need satisfaction, and positive attitude (Goubert & Trompetter, 2017). These are thought to be associated with how well a person engages in positive coping (de Rooij et al., 2014).

Although the biopsychosocial model of pain is widely supported, it has been criticized for emphasizing psychosocial features, especially when clear anatomic pathology underlying the pain is missing (Weiner, 2008). It is important to be aware that psychological factors, e.g. anxiety and fear related to pain, especially in the acute phase, are mostly normal reactions and normal processing related to possible danger-causing input, not signs of psychiatric illnesses. Anxiety, depressive symptoms, negative mood, and pain catastrophizing have previously been shown to be associated with experimental pain sensitivity (Starr et al., 2010; Strulov et al., 2007; Thompson et al., 2008).
Heightened anxiety and depression have been found to be associated with more intense acute pain and with the transition from acute to persistent pain post-surgically (Hinrichs-Rocker et al., 2009; Chapman and Vierck, 2016).

Psychological factors influence the pain experience and its persistence on many levels; as a risk, protective or moderating factors. A recent comprehensive review describes the interaction between psychological vulnerability and resilience factors in persistent pain, and their associations with neurobiological pathways (Denk et al., 2014). Psychosocial factors are thought to heighten the process of sensitization at the peripheral, spinal, and/or brain levels through cellular priming, epigenetic changes, and alterations in brains networks concerned with motivation, reward, and descending modulatory control (Denk et al., 2014). A negative outlook can influence psychoneuroimmunology (Voscopoulos & Lema, 2010) and the risk of postsurgical complications (Kiecolt-Glaser et al., 2002; Mavros et al., 2011). An increased psychological burden has been found to be associated with greater postoperative analgesic requirement (De Cosmo et al., 2008; Pan et al., 2006), poorer rehabilitation (Leeuw et al., 2007), and lack of engagement in different treatments (Shelby et al., 2012; Litt & Porto, 2013).

Although anxiety and depressive symptoms have unique features, e.g. sensorimotor hyperarousal in anxiety and anhedonia in depression (Clark & Watson, 1991), their comorbidity is high (Ball et al., 2002; Kircanski et al., 2016). The link between psychological factors and pain is acknowledged to be bidirectional; emotional reactivity and cognitive functions are known to affect pain experience and its persistence (Williams, 2014; Linton et al., 2011; Asmundson & Katz, 2009), and also a prolonged pain condition increases the risk for mood disorders and lowers the quality of life (Edwards et al., 2016; Williams, 2014; Linton et al., 2011; Asmundson & Katz, 2009).

2.4.1.1 Anxiety

Pain naturally consists of an element of fear since its ultimate purpose is to function as an alarm of a possible danger. Fear motivates the person to the defensive response of avoidance or escape. When the feeling of fear appears together with physiological, cognitive, and behavioral components, it forms an affective experience of anxiety (Fernandez, 2002). Fear together with experience of anxiety informs the individual of a vulnerability, and individual processing to cope
with anxious arousal varies markedly (Fernandez, 2002). Anxiety does not merely affect the physiological reaction to how pain is modulated (Voscopoulos & Lema, 2010), but also influences the cognitive processing of pain (Eccleston & Crombez, 1999). It seems that pain attracts more attention in anxious individuals (Eccleston & Crombez, 1999). Anxiety sensitivity is known to be associated with an interpretative and negative attentional bias, and this in part explains why anxious individuals evaluate pain in a more threatening and negative manner and report a more intense pain experience (Keogh & Cochrane, 2002). The results of neuroimaging studies have shown that anxiety and negative expectation of pain (nocebo) are close to each other also on a neural level (Kong et al., 2008). This has been addressed also in clinical studies in which highly anxious patients were shown to expect more pain after Cesarean section (Pan et al., 2013). In a study done with breast cancer patients, where in particular the origin of pain expectations was investigated, high trait anxiety and preoperative distress were associated with higher expectancy of pain (Schnur et al., 2007).

Evidence of the association between anxiety and persistent surgical pain is strong. In a review article including all surgery types, no negative associations were found (Theunissen et al., 2012). Although, studies reporting no association existed, the majority found that anxiety or pain catastrophizing were related to pain persistence (Theunissen et al., 2012). Measurement of anxiety varies widely between studies (Theunissen et al., 2012). Most studies have used measurements of general anxiety, but also pain-related anxiousness and pain catastrophizing have been of interest (Theunissen et al., 2012). A meta-analysis comparing different scales used to assess anxiety did not reveal significant differences in how well these scales predicted the risk of persistent postsurgical pain (Theunissen et al., 2012). Pain-related catastrophizing is continuously found to be a risk factor for higher acute or persistent pain experience (Khan et al., 2011; Quartana et al., 2009; Theunissen et al., 2012). This refers to a tendency to exaggerate and to ruminate on pain experience (ongoing or anticipated), and to anticipate pain in a more threatening and worrying way. Catastrophizing belongs to the anxiety spectrum symptoms and is associated with increased awareness of bodily sensations and heightened attention towards pain (Khan et al., 2011; Quartana et al., 2009).
2.4.1.2 Pain Expectation

Many different contexts of pain have revealed that the expectation of pain or its relief has an enormous impact on how the pain is experienced (Lariviére et al., 2002; Bingel et al., 2011; Atlas & Wager, 2012; Colloca & Benedetti, 2006; Petersen et al., 2014; Tracey, 2010; van Laarhoven et al., 2011). Pain expectation is an important component of the placebo effect, and neuroimaging studies have shown a solid neural basis for it and its involvement in descending pain modulation (Figure 3) (Apkarian et al., 2005; Atlas & Wager, 2012; Eippert et al., 2009; Koyama et al., 2005; Goffaux et al., 2007). Especially the prefrontal-limbic-brainstem interactions are involved in emotional and cognitive pain processing (Tracey, 2010). The placebo effect is shaped by a patient’s prior experiences (Colloca & Benedetti, 2006). Pain expectancy and placebo effects are concrete evidence of how psychological variables influence the pain experience. In a clinical study, lower pain values for an experimental test stimulus were reported in the group told to expect pain relief after the conditioned pain stimulus (Lariviére et al., 2002). Furthermore, the same study also showed a reduction in nociceptive-related somatosensory-evoked potentials in the group primed to expect an analgesic effect in a DNIC condition. Authors suggested that these findings prove the connection between brain structures involved in expectations and modulation of DNIC effects (van Wijk & Veldhuijzen, 2010). In another study in healthy subjects, the efficacy of opioid analgesics was dependent on the expectancy of its efficiency. When the participants were told that the given opioid infusion was stopped (but was actually still ongoing), its analgesic effect was abolished (Bingel et al., 2011). The predictive role of pain expectancy on acute postoperative pain reports has also been demonstrated in patients undergoing Cesarean section (Pan et al., 2013). Montgomery et al. (2010) found that higher expectation of pain predicted the first week of pain after breast cancer surgery. Not only negative expectations have found to be associate with poorer pain related outcomes, but also on the other way around, positive beliefs have found to be related with more positive treatment outcomes (Wertli et al., 2017). The close relationship between pain expectations, anxiety (Schnur et al., 2007; Pan et al., 2013), and hypervigilant behavior towards pain (Keogh & Cochrane, 2002) could partly explain the impact on individual pain sensitivity.
2.4.1.3 Depressive symptoms

Whereas pain is the most common physical reason to seek medical help, the predominant psychological symptom is depressive symptoms (Kroenke et al., 2009). Therefore, the high comorbidity of depressive symptoms and pain is understandable (Knaster, 2012; Kroenke, 2009). The relationship between depression and pain is known to be bidirectional (Edwards, 2016). It has been proposed that coexistence of pain and depression is in part due to underlying inflammatory mechanisms (Walker et al., 2013). Inflammation is a known nominator behind both, activating several pathways that can trigger either transition of acute to persistent pain or the development of depression (Walker et al., 2013). Negative affect is one important part of depressive symptomatology and known to modulate pain perception (Janssen, 2002). However, it also has been suggested that negative affect influences the reporting of pain (Aronson et al., 2006).

In a recent meta-analysis of pain perception in people with depression, a conclusive association between pain tolerance or threshold and depression was not found (Thompson et al., 2016). While an association between experimental pain and depression exists, it is complex. Depression seems to differently affect different modalities of pain, either increasing (ischemic stimulation) or decreasing (other modalities) the pain response (Thompson et al., 2016).

The influence of depression on pain may be indirect. Depressed individuals feel more disabled by their symptoms, and results of pain rehabilitation are often poorer (Edwards, 2016; Leeuw, 2007; Linton, 2011). Unfavorable health behavior, such as smoking and physical inactivity, as well as high BMI are also known to have an association with both depression and pain (Igna et al., 2008). Depression is often considered to be an outcome of persistent pain (Knaster, 2012). In a Finnish study done with tertiary pain clinic patients, the comorbidity of persistent pain and depression was 37%, and depression was found to be more a result of a chronic pain condition than to precede the pain (Knaster et al., 2012). Symptoms of depression and especially major depressive disorder (MDD) may also add to the risk of pain and postsurgical complications e.g. postoperative infections (Doering et al., 2007). Depressive symptoms, especially severe cases, have been shown to precede more severe postsurgical pain in several studies (Hinrichs-Rocker et al., 2009; Sobol-Kwapinska et al., 2016), also in a breast cancer cohort (Miaskowski et al., 2012). A study with Finnish cancer patients found that depression was associated also with breast cancer progression (Lehto et al.,...
Pain Sensitivity and Factors associated with the Pain Experience after Breast Cancer Treatments

The psychobiological mechanisms affecting cancer progression are suggested to be related to psychological stress (Kiecolt-Glaser & Glaser, 1999).

When depression has been studied in pain or in the context of breast cancer, usually the symptoms of depression have been evaluated. Few studies have used a diagnostic interview to clarify the severity of clinical depression or the presence of MDD. The three most frequently used scales are the Hospital Anxiety and Depression Scale (HADS) (Snaith & Zigmond, 1986), the Beck Depression Inventory (BDI) (Beck et al., 1961), and the Center for Epidemiological Studies Depression Scale (CES-D) (Radloff, 1977). HADS is found to provide the lowest scores relative to CES-D and BDI (Maass et al., 2015). This may reflect the role of physiological questions in the latter two questionnaires, which have questions overlapping with somatic symptoms caused by the disease and its treatment and may overestimate the symptoms of depression. PHQ-9 (Spitzer et al., 1999) is a depression questionnaire increasingly used to assess depression in particular in somatic conditions (Fisher et al., 2017). Although it has been shown that somatic questions affect the responses in the widely used BDI (Knaster et al., 2016; Morley et al., 2002), this is not necessarily a sign of overestimation of the severity of depression. In a Finnish study, the results of the diagnostic interview of chronic pain patients were comparable with the level of depression evaluated with BDI (Knaster et al., 2016). There is no clear consensus as to which scales should be used and how to manage the role of somatic symptom questions in the depression scales (Knaster et al., 2016; Maass et al., 2015).

2.4.1.4. Anger regulation

Compared with depression and anxiety, the study of anger regulation is a relatively new area in pain research. Even though the relationship between pain and anger inhibition has been introduced at least in theory in early psychoanalytical literature (Freud, 1917; Engel, 1959), the broader meaning of regulation strategy is newer. Anger can be seen as different from aggression. Anger is more of a cognitive and emotional reaction to a provoking situation, whereas aggression also includes the aim to cause harm and damage to other people or objects (Spielberger, 1999). Anger regulation, as emotion regulation in general, may be an automatic or controlled process (Spielberger, 1999; Gross, 1998). Regulation may be seen as a part of cognitive and behavioral efforts to cope with external or internal demands on a person and a way to maintain personal resources (Lazarus & Folkman, 1984).
The chosen strategies may have an effect on the way a person adapts to life after cancer and the extent of interference attributed to pain (Julkunen et al., 2009; Lehto et al., 2005; Bruehl et al., 2002; Bruehl et al., 2008; Ducro et al., 1995).

Two strategies of emotional regulation in general have been studied in more detail: emotional expression and suppression (Gross, 1998). Also the study between anger regulation and pain has focused on these strategies, anger expression and anger inhibition. Anger regulation strategies, how an individual usually behaves when feeling angry, have been thought to be quite stable traits (Linden et al., 2003; Spielberger, 1999). Anger inhibition reflects a disposition to suppress angry feelings, e.g. “I’m criticizing others in my mind”, whereas anger expression reflects a person’s way to express angry feelings outwards, e.g. “I may slam doors when angry” (Spielberger, 1999). The theory of anger regulation has been criticized as being an overly simplistic way to describe the variety of ways individuals may express or inhibit their anger (Linden, 2003). Also, it does not take into account the situational variety of anger regulation strategies (Linden, 2003; Burns, 2008). Individuals may react to one anger-arousing situation by shouting or losing their temper, but in another by keeping angry thoughts inside. Long follow-up studies are not available regarding how this behavior evolves with e.g. age. In addition, whether this behavior changes during dramatic life events, such as severe disease, is unknown.

Like mood factors, also anger regulation is thought to influence pain experience through physiological, affective, and cognitive mechanisms (Bruehl et al., 2003; Bruehl et al., 2008a; 2008 b; Bruehl et al., 2011; Burns et al., 2008; Greenwood et al., 2003; Trost et al., 2012). Anger regulation processes have been suggested to be potentially meaningful contributors to mental and also physical health, e.g. to the development of coronary disease and blood pressure (Burns et al., 2008; Gross, 1998; Igna et al., 2009; Julkunen et al., 2009; Krantz et al., 2006; Stanton et al., 2000), and thus, to the quality of life (Julkunen et al., 2009; Lehto et al., 2005). Not only the arousal of anger or aggression per se, but the manner in which anger is regulated is thought to be relevant to the pain experience (Bruehl et al., 2006; Burns et al., 2008).

The relation of anger and pain is not straightforward, and contradictory findings in both acute and chronic pain experience have been published (Bruehl et al., 2009; Bruehl et al., 2012; Materazzo et al., 2000; Nisenzon et al., 2014; Sayar et al., 2004). Bruehl et al. (2003) found higher anger expression to be linked to CRPS (Complex Regional Pain Syndrome) -related pain, but not to other types of upper extremity pain. In one study, anger inhibition was related to pain intensity in headache
patients (Nicholson et al., 2003), and in other study neither inhibition nor expression of anger was relevant to pain intensity (Materazzo, 2000). However, especially anger expression has been reported to be associated with higher or more unpleasant pain experience (Bruehl et al., 2002; Bruehl et al., 2008). Anger inhibition, by contrast, may have more of a mediating role in the pain experience through negative affect, depressive symptoms, and anxiety (Burns et al., 2008; Duckro et al., 1995; Nisenzon et al., 2014; Okifuji et al., 1999). Furthermore, it has been suggested that anger inhibition and expression are probably mediated through different pathways, and therefore, also differently overlap with pain, depression, and anxiety with respect to pain (Bruehl et al., 2003).

The explanations regarding the effects of anger expression on pain have mostly been physiological, e.g. increased muscle reactivity (Burns, 1997) or activation of the sympathetic nervous system (Bruehl et al., 2003). Also, anger expression has an impact on the immune system (Kiecolt-Glaser et al., 2002), and an influence on genetic polymorphisms has been suggested (Bruehl et al., 2008b). Bruehl et al. (2008a; 2008b) have also proposed that individuals with a higher tendency to express anger have a deficient endogenous opioid system. This mechanistic approach to evaluate anger regulation as a cause of biological variables is very different from the contextual explanation where the relationship between anger regulation and pain is perceived as more interactive. From a contextual perspective, anger regulation affects how a person copes with pain. As an example of the behavioral perspective, Duckro et al. (1995) suggest that anger mediated by depression influences pain-related disability, but not particularly the intensity of pain.

Some evidence has emerged that the role of anger regulation in pain experience is different between the genders. In a study done with chronic pain patients, a higher tendency to express anger was associated with worse rehabilitation outcomes in men, but not in women (Burns et al., 1998). Also opioid analgesia was weaker in women with high anger expression in an experimental pain situation, but this was not shown in men (Bruehl et al., 2007). One study evaluating the role of anger expression in postsurgical acute pain found a positive correlational association in men (Bruehl et al., 2006b). No studies have evaluated the effect of anger regulation on the intensity of acute or persistent pain in a breast cancer patient cohort. Most studies evaluating the role of anger regulation in pain experience have used the Spielberger State-Trait Anger Expression Inventory (STAXI). Consequently, Burns (2008) stated that the relationship between anger regulation and pain reflects more the quality of that specific scale rather than reflecting the whole truth about the construct of anger regulation.
2.5. PSYCHOLOGICAL FACTORS AND BREAST CANCER

Symptoms of depression and anxiety are well-recognized and natural reactions to the cancer diagnosis. Like breast cancer and pain, also symptoms of depression and anxiety are more common in females (Li & Graham, 2017; Markkula N. et al., 2016). A recent Finnish study (Kokkonen et al., 2017) found that the prevalence of depression in breast cancer patients (37%) was significantly higher than in the general population in Finland (from 4.9% to 9.3%) (Pirkola et al., 2005). A recent large review (Maass et al., 2015) evaluated the prevalence of depression and anxiety in a long follow-up among breast cancer survivors and reported 39.9% (range 9.4-66.1%) of women to have depressive symptoms and 27.2% (range 17.9-33.3%) to have anxiety. They concluded that the symptoms of depression usually increase at the first year after diagnosis, whereas anxiety remains stable. Symptoms of depression were also more common in breast cancer patients relative to healthy controls in an eight-year follow-up, whereas presence of anxiety did not differ between these groups in the follow-up (Maass et al., 2015). Both anxiety and depressive symptoms are at the highest during the first year of diagnosis (Begovic-Juhant et al., 2012; Zainal et al., 2013).

2.6. POSTOPERATIVE PAIN

2.6.1. ACUTE PAIN

Nociception alone is not sufficient to produce pain experience. However, nociception is essential for an individual’s survival since it is required for reflexive and protective autonomic responses. Acute pain is a warning signal for an individual that something is wrong in the body. The nociceptive reaction to pain is followed by a more conscious interpretation of pain. This has been shown also in functional brain imaging studies where the conscious experience of pain has emerged when neural input has been integrated to different cortical regions (Lee & Tracey, 2013). Postsurgical acute pain is physiologically different from other pain conditions, e.g. herpes zoster pain or fibromyalgia (Brennan, 2011), but also different psychologically. The onset of postsurgical pain is known and psychological factors, e.g. anxiety, surgical worry, and pain anticipation, are inevitably a part of the acute pain experience. Normally, surgically induced pain at rest resolves within a week, but the pain in movement often continues longer, even weeks (Brennan, 2011). Postsurgical pain is mostly due
to tissue injury that sets off a chain of inter-related events, the purpose of which is to fight infection, limit further damage, and initiate repair (Voscopoulos, 2010). Proinflammatory neurotransmitters cause both peripheral and central nerve sensitization and heighten pain awareness, aiming to limit further injury in the affected area. Multiple areas of the pain matrix are known to be activated in this complex process (Voscopoulos, 2010).

The intensity of severe acute postsurgical pain varies widely between individuals, but also between surgical procedures. Gerbershagen et al. (2013) listed in their large cohort study comprising 529 different surgical procedures that the highest acute pain intensity procedures were operations related to obstetrics, orthopedics, and general abdominal surgeries. Surgeries related to breast cancer were far from the highest acute pain risk procedures (ranks 160 and 166) (Gerbershagen et al., 2013).

Individual clinical factors associated with higher acute postsurgical pain are known to some extent. Ip et al. (2009) conducted the first systematic review about factors associated with acute postoperative pain, including all surgical procedures. They combined factors assessed in different studies in groups, and four main categories were found to predict acute postsurgical pain: age, psychological factors (especially anxiety), presence of other pain conditions, and surgical type. A more recent review (Sobol-Kwapinska et al., 2016) analyzing only psychological variables found that pain catastrophizing, higher expectation of pain, higher depression, and lower optimism were quite systematically associated with more intense acute postoperative pain.

2.6.1.1. Acute pain after breast cancer surgery

There are a limited number of previous studies assessing factors associated with acute pain after breast cancer surgery (Table 1) (Bruce et al., 2012; Katz et al., 2005; Rehberg et al., 2017). Comparison of these studies is difficult since the outcome pain variables differ, as well as the independent variables. The cut-off for clinically significant pain intensity after surgery has also varied (Rehberg et al., 2017; Katz et al., 2005). Furthermore, the outcome variable defining acute pain varies from hours (Rehberg et al., 2017) to days (Katz et al., 2005; Bruce et al., 2012) to up to one month after surgery (Katz et al., 2005). To minimize a measurement bias related to the moment of pain rating, it has been suggested that pain trajectories of the acute pain, consisting of both the
intensity and the direction of the pain path, would give a more precise picture of the nature of acute pain (Chapman et al., 2011).

Consistent factors predisposing to higher acute pain intensity and more altered sensations after breast cancer surgery are more invasive surgery type (Rehberg et al., 2017; Bruce et al., 2012; Katz et al., 2005) and psychological factors, mainly anxiety. Greater preoperative anxiety was a good predictor of more intense pain both immediately (24 h) (Rehberg et al., 2017) and at two and 30 days after surgery (Katz et al., 2005). Bruce et al. (2012) found a composite resilience variable consisting of positive attitude and low distress to predict lower pain intensity during the first week after breast cancer surgery. The role of pain expectancy is rarely assessed in breast cancer studies (Montgomery et al., 2010), but its predictive value for pain in other surgery types has been found consistently (Gramke et al., 2009; Logan & Rose, 2005; Pan et al., 2006; Pan et al., 2013; Sommer et al., 2010). As in other surgery types, also in breast cancer surgery other existing pain problems before the surgery (Bruce et al., 2012) and younger age (Rehberg et al., 2017; Katz et al., 2005) predict acute pain. Also, the association of more invasive axillary surgery with more intense acute pain is consistent (Rehberg et al., 2017; Bruce et al., 2012). Extensive surgery in the axilla may potentially damage the sensory intercostobrachial nerves, and if dissection of lymphatics is also needed, this can cause lymphedema (prevalence is approximately 6-20%) (DiSipio et al., 2013).
<table>
<thead>
<tr>
<th>Reference</th>
<th>Year of publication</th>
<th>Country</th>
<th>Number of patients</th>
<th>Psychological factors</th>
<th>Outcome</th>
<th>Prevalence of moderate to severe pain</th>
<th>Statistical method</th>
<th>Risk factors for pain</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACUTE PAIN</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Bruce et al.</td>
<td>2012</td>
<td>UK</td>
<td>338</td>
<td>HADS STAI state and trait (short form) PCS Surgical worry PANAS LOT (short form)</td>
<td>NRS≥4 Average pain (rest and movement) in the 1st postoperative week</td>
<td>At rest 40.8% At movement 50.4%</td>
<td>Logistic regression</td>
<td>Chronic preoperative pain Lower psychological “robustness” Axillary surgery Handling of the Intercostobrachial nerve</td>
</tr>
<tr>
<td>Rehberg et al.</td>
<td>2017</td>
<td>Switzerland</td>
<td>198</td>
<td>BDI PSQ STAI state and trait</td>
<td>Maximum NRS≥4 24 hours postoperatively</td>
<td>44.9%</td>
<td>Logistic regression</td>
<td>Higher PSQ score State anxiety Younger age Mastectomy Axillary surgery</td>
</tr>
<tr>
<td>Katz et al.</td>
<td>2005</td>
<td>USA</td>
<td>114</td>
<td>BDI STAI state and trait HDARS FACT-E Somatosensory-Amplification Scale Illness Behavior Questionnaire</td>
<td>NRS≥5 at day 2 to day 30</td>
<td>Day 2 54%</td>
<td>Logistic regression</td>
<td>Anxiety (day 2) Age (days 2-30) Marital status (days 2-30) Anxiety (days 2-30)</td>
</tr>
</tbody>
</table>
### Persistent Pain

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Country</th>
<th>Sample Size</th>
<th>Measure of Pain (State and Trait)</th>
<th>Time Post-treatment</th>
<th>Method of Analysis</th>
<th>Predictive Factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Miaskowski et al.</td>
<td>2012</td>
<td>USA</td>
<td>398</td>
<td>CES-D, STAI state and trait, GSDS, LFS, AFI, QOL-PV</td>
<td>6 months</td>
<td>*Pain subgroup comparison Analyses of variance Chi-square analyses</td>
<td>Younger age, Ethnicity, BMI high, Preoperative pain, ALND, Radiotherapy, Depression, Anxiety, Sleep disturbances</td>
</tr>
<tr>
<td>Bruce et al.</td>
<td>2014</td>
<td>UK</td>
<td>362</td>
<td>HADS, STAI state and trait (short form), PCS, PANAS, LOT (short form)</td>
<td>4 and 9 months</td>
<td>Logistic regression</td>
<td>ALND, Lower psychological “robustness”, Acute pain intensity</td>
</tr>
<tr>
<td>Andersen et al.</td>
<td>2015</td>
<td>Denmark</td>
<td>475</td>
<td>HADS, DT**, PCS**</td>
<td>1 year</td>
<td>Logistic regression</td>
<td>Age &lt;65 years, Breast-conserving surgery, ALND, Preoperative pain, Acute pain intensity, Signs of neuropathic pain at one week, Lower diastolic BP</td>
</tr>
</tbody>
</table>

**Table 1.** Prospective studies (n>100) of predictive factors of acute and persistent pain after breast cancer treatments.

Abbreviations: CES-D=Center of Epidemiologic Studies-Depression, STAI=Spielberger State-Trait Anxiety Inventory, GSDS=General Sleep Disturbance Scale, LFS=Lee Fatigue Scale, AFI=Attentional Function Index, QOL-PV=Quality of Life Scale-Patient Version, HADS=Hospital Anxiety and Depression Scale, PCS=Pain Catastrophizing Scale, PANAS=Positive and Negative Affect Scale, LOT=Life Orientation Test, ALND=Axillary Lymph Node Dissection, DT=Diestress Thermometer, Blood Pressure, PSQ=Pain Sensitivity Questionnaire, HDARS=Hamilton Depression and Anxiety Rating Scales, FACT-E=Functional Assessment of Cancer Treatment. *no multivariate analyses were done,**not included in regression analyses
2.6.2. TRANSITION FROM ACUTE TO PERSISTENT PAIN

The complex pathophysiological processes behind the transition from acute to persistent postsurgical pain are not fully understood. It has been suggested that in most cases postsurgical persistent pain shows signs of neuropathic pain in the acute phase (Chapman & Vierck, 2016; Katz & Seltzer, 2009). Tissue damage due to surgery sensitizes sensory endings by peripheral chemicals and causes inflammation at the surgical site. This causes a burst of afferent nociceptive signaling, contributing to the development of central sensitization. Infiltration of immune cells and increased glial cell activation observed in the dorsal horn of the spinal cord following peripheral tissue and nerve injury causes neuroinflammation, which plays a major role in the induction and also the maintenance of this central neuronal plasticity (Ji et al., 2014). Woolf and Salter (2000) have suggested that the remodeling of neuronal synaptic connections in the dorsal horn combined with pathological neuronal sprouting causes abnormal links between afferent fibers in differing modalities, e.g. touch and nociception. However, new studies suggest that the line between inflammatory pain and neuropathic pain is not that clear since inflammatory mediators exacerbate ectopia in afferent neurons (Bali et al., 2014). The changes in the descending pain modulation system, and the role of psychological factors in this process, may also have influence on why acute pain persists after treatments (Chapman & Vierck, 2016; Katz & Seltzer, 2009). A small study done with women operated on for breast cancer showed that women with persistent postoperative pain had enhanced temporal summation of mechanical pain and also deficient function in the DNIC test compared with pain-free patients (Edwards et al., 2013).

2.6.3. PERSISTENT PAIN

Pain experience is far from a linear relation from nociceptive input and conscious experience of pain. This is especially true when pain transits from acute to persistent. Long-lasting persistent pain does not have the same purpose as acute pain as a warning signal. The question of vulnerability to develop persistent pain has been asked already decades ago, and multidimensionality of the process is certain. Persistent pain due to different causes affects millions of people around the world (Murray and Lopez, 2013). Also, the burden of persistent postsurgical pain is high measured at both individual and economic levels (Macrae, 2008). It has been widely accepted that earlier life and pain
experiences (Afari et al., 2014; Brennstuhl et al., 2014), attributions of pain (Eccleston, 1999), present context (Carlino et al., 2014), cognitive and emotional variables (Edwards et al., 2016) all have an effect on the interpretation that forms an experience of pain. These are involved in both acute and persistent pain, but in persistent pain the role of psychological variables is even more emphasized.

2.6.3.1. How to study pain persistence

Pain persistence can be studied with a model where the actual time of pain onset can be addressed. Traditional research settings are studies of postsurgical pain, postherpetic neuralgia, and posttraumatic pain models (Radresa et al., 2014). Postsurgical pain is perhaps the most studied model since the cause of pain can be quite precisely controlled. A prospective research setting is reliable and free from the recall bias known to influence an individual’s retrospective report about the level of preoperative pain or mood related factors (Van den Bergh & Walentynowicz, 2016). In a retrospective research setting, there is a tendency to overestimate e.g. adverse symptoms (Van den Bergh & Walentynowicz, 2016). Pain persistence can be investigated also with twin studies (Markkula R. et al., 2009 and 2016). Especially the role of genetics in the pain persistence process can be studied in a situation where the environmental variables are the same between twin pairs, as mentioned earlier in the text. A cross-sectional cohort design is also common in evaluation of postoperative pain persistence (Gartner et al., 2009). The prevalence of persistent pain after breast cancer treatment has been distinctly higher in cohort studies (Bell et al., 2014; Gartner et al., 2009) than in prospective studies. This may be due to retrospective recall bias.

A very commonly cited theory on pain persistence is the fear-avoidance model (Vlaeyen & Linton, 2000). It is a cognitive-affective model that states that negative emotional and attentional processes in some individuals focus on the threat value of pain and pain-related stimuli, which may increase the intensity and perceived disability of pain. It was originally developed to explain the persistence of low-back pain, but the mechanism may be similar in postoperative pain persistence.
2.6.4. PERSISTENT POSTOPERATIVE PAIN

Persistent pain after surgical procedures has not been acknowledged in research until about 20 years ago (Crombie et al., 1998). Postoperative pain is considered persistent if it lasts beyond the average healing time. A more precise and frequently cited definition is by Macrae et al. (2001), according to which 1) the pain should have developed after a surgical procedure, 2) it should have lasted at least two months after the operation, 3) other causes for the pain should be excluded (e.g. chronic infection of ongoing malignancy), and 4) the possibility that the pain is continuing from a pre-existing problem should be explored and attempted to exclude (Macrae, 2001). More recent propositions by Werner at al. (2014) to refine the definition are the length (lasted 3-6 months after surgery) and that the pain should have been developed or increased or have different characteristics than before the surgery. Nevertheless, these definitions do not take into account the possible evolving nature of persistent pain. In a large study done with cardiac surgery patients the amount of reported pain decreased remarkably during a two-year follow-up (Choiniere et al., 2014). A cross-sectional study with breast cancer surgery patients found that the variation in the courses of pain between patients was high five to seven years after surgery (Mejdahl et al., 2013).

After breast cancer surgery, the duration of pain may be longer than two months since usually adjuvant treatments are not yet over. Persistent pain risk procedures, such as thoracic surgery, breast surgery, and groin hernia repair, have been shown to have a high prevalence of probable or definite neuropathic pain (Duale et al., 2014; Finnerup et al., 2016; Haroutiunian et al., 2013). As presented in Table 2, commonly identified risk factors for pain persistence are the same regardless of the surgical type. Pre-existing pain problem, intensity of acute pain, and psychological variables are the most commonly found factors associated with postoperative persistent pain (Perkins & Kehlet, 2000; VanDenKerkhof et al., 2013; Ip et al., 2009; Katz et al., 2009). Psychological risk factors for pain persistence have been compared in a study with knee arthroplasty and breast cancer and found to be the same: state anxiety and pain magnification related to catastrophizing were associated with pain regardless of the surgical procedure (Masselin-Dubois et al., 2013). Psychological variables often associated with persistent postsurgical pain include anxiety, catastrophizing, depression, psychological vulnerability, and stress (Hinrichs-Rocker et al., 2009; Khan et al., 2011).
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Psychological variables often associated with persistent postsurgical pain include anxiety, catastrophizing, depression, psychological vulnerability, and stress (Hinrichs-Rocker et al., 2009; Khan et al., 2011).

<table>
<thead>
<tr>
<th>Authors</th>
<th>Year</th>
<th>Type of surgery</th>
<th>Number of patients</th>
<th>Maximum follow-up time</th>
<th>Predictive factors for persistent pain</th>
</tr>
</thead>
<tbody>
<tr>
<td>Choiniere et al.</td>
<td>2014</td>
<td>Cardiac surgery</td>
<td>1247</td>
<td>2 years</td>
<td>Preoperative pain↑, Intensity of acute pain↑, Anxiety↑</td>
</tr>
<tr>
<td>Montes et al.</td>
<td>2015</td>
<td>Hernia repair, Hysterectomy, Thoracotomy</td>
<td>2929</td>
<td>2 years</td>
<td>Preoperative pain↑, Age↓, Physical health↓, Mental health↓</td>
</tr>
<tr>
<td>Duale et al.</td>
<td>2014</td>
<td>Multiple procedures</td>
<td>3112</td>
<td>6 months</td>
<td>Preoperative pain↑, Presence of neuropathic components of postoperative pain↑, Anxiety↑, Age↓, Negative life events↑, Quality of life↓</td>
</tr>
<tr>
<td>Hoofwijk et al.</td>
<td>2015</td>
<td>Multiple procedures</td>
<td>908</td>
<td>1 year</td>
<td>Surgery type↑, Preoperative pain↑, Preoperative analgesic use↑, Intensity of acute pain↑, Fear of surgery↑, Optimism↓, Quality of life↓</td>
</tr>
<tr>
<td>Fletcher et al.</td>
<td>2015</td>
<td>Multiple procedures</td>
<td>889</td>
<td>1 year</td>
<td>Preoperative pain↑, Acute pain intensity↑, Surgery type↑</td>
</tr>
</tbody>
</table>

Table 2. Factors associated with persistent postoperative pain across surgery types.

2.6.4.1. Persistent pain after breast cancer treatments

Although breast cancer surgery is not the greatest cause of acute postsurgical pain, it is known to be a high-risk surgery for the development of persistent pain (Cregg et al., 2013; Gerbershagen et al., 2014). Approximations of the prevalence of persistent pain after breast cancer surgery vary from 14% to 60% (Andersen & Kehlet, 2011; Andersen et al., 2015; Bruce et al., 2012; Miaskowski et al.,
2014; Wang et al., 2016). Higher prevalences are reported in cross-sectional studies (Andersen, 2011). Based on the current prevalence of breast cancer in Finland (Finnish Cancer Registry), around 700-3000 new patients each year will report persistent pain related to breast cancer treatments.

The reason for pain persistence after breast cancer surgery is multifactorial. In addition to surgery (Jung et al., 2003), breast cancer treatment usually includes adjuvant therapies that challenge physical recovery after the primary surgery. Persistent pain may be encountered with both radiotherapy and certain chemotherapy agents (Jung et al., 2005). The pathological mechanisms leading to pain persistence after breast cancer treatments are likely multiple, and the pain is considered to have both inflammatory and neuropathic components (Finnerup et al., 2016; Haroutianian et al., 2013; Jung et al., 2003; Jung et al., 2005). A large study comparing different surgery types found that breast cancer patients most commonly had neuropathic features in their persistent pain compared with other studied procedures (Duale et al., 2014). The pain has often been classified into intercostobrachial neuralgia, phantom breast pain, neuroma pain, and other nerve injury pain (Jung et al., 2003).

A recent review (Andersen & Kehlet, 2011) and meta-analysis (Wang et al., 2016) performed to verify known risk factors for pain persistence following breast cancer surgery concluded that the comparison of different studies is in part difficult since the definition of the painful area (e.g. breast only or entire upper body), the cut-off for the intensity of pain regarded as moderate or severe, and the definition of the duration of pain have wide variation between studies. In addition, most of the studies have cross-sectional and retrospective designs with causality of findings remaining unanswered. Furthermore, some studies with prospective design are performed with insufficient sample sizes (n<100), which enables the reliable use of multivariate statistical methods. Nevertheless, Wang et al. (2016) concluded in their meta-analysis that younger age, radiotherapy, more invasive surgery (ALND), preoperative pain, and greater acute pain were the most systematic and high-quality predictors for persistence of pain at 12-month follow-up.

Previous knowledge on well-powered prospective studies is presented in Table 1. Risk factors associated with pain after breast cancer surgery are in part the same as for other types of surgery. The severity of cancer produces variation between surgeries within patients.
2.6.4.2. Psychological factors and pain persistence after breast cancer treatments

Psychological factors may play a large role in recovery and in the process of pain persistence since the cause of surgery is malignant and possibly life-threatening. The attribution that a patient assigns to bodily sensation after a malignant disease is known to be different from a benign disease. A recent study found that presence of symptoms of depression and anxiety was quite common (44.5%) at six months after breast cancer surgery (Gold et al., 2016). The relevance of psychological variables to pain persistence after breast cancer surgery has been controversial between studies, and most studies have not included preoperative psychological assessment. A cross-sectional study comparing patients with and without pain at an average of four years from surgery found that depressive symptoms, anxiety, catastrophizing, and somatization were elevated in women with persistent pain. Even though the research setting does not allow determination of the causality of symptoms, this highlights the importance of psychological factors in the pain experience after breast cancer surgery (Schreiber et al., 2013). Andersen et al. (2015) evaluated previously known psychological risk factors for pain persistence. Unfortunately, they performed mostly univariate group comparisons between persistent and non-persistent groups. Patients with pain (NRS ≥4) at one year after the surgery reported significantly more anxiety, depression, and distress preoperatively, but surprisingly not catastrophizing. Only preoperative anxiety was included in the final analyses and found to be an insignificant predictor. The collinearity of the psychological scales used is a common problem when models are built. Bruce et al. (2014) have taken this into account in their study by forming a new aggregated variable with factor analysis. They found that this new variable consisting of high optimism and low psychological distress predicted lower pain after surgery.

2.7 PREDICTION AND PREVENTION OF PERSISTENT PAIN

2.7.1 PREDICTION

Some risk factors for higher acute and persistent post-treatment pain after breast cancer have been recognized (Andersen & Kehlet, 2011; Andersen et al., 2015; Bruce et al., 2012; Miaskowski et al., 2014; Wang et al., 2016; Rehberg et al., 2017; Katz et al., 2005; Bruce et al., 2012). Remaining to be elucidated, however, are the relative importance of a single risk factor and how to identify patients at high risk for persistent pain in different interventions. The lack of assessment tools for identifying
Psychological factors may play a large role in recovery and in the process of pain persistence since the cause of surgery is malignant and possibly life-threatening. The attribution that a patient assigns to bodily sensation after a malignant disease is known to be different from a benign disease. A recent study found that presence of symptoms of depression and anxiety was quite common (44.5%) at six months after breast cancer surgery (Gold et al., 2016). The relevance of psychological variables to pain persistence after breast cancer surgery has been controversial between studies, and most studies have not included preoperative psychological assessment. A cross-sectional study comparing patients with and without pain at an average of four years from surgery found that depressive symptoms, anxiety, catastrophizing, and somatization were elevated in women with persistent pain. Even though the research setting does not allow determination of the causality of symptoms, this highlights the importance of psychological factors in the pain experience after breast cancer surgery (Schreiber et al., 2013). Andersen et al. (2015) evaluated previously known psychological risk factors for pain persistence. Unfortunately, they performed mostly univariate group comparisons between persistent and non-persistent groups. Patients with pain (NRS ≥ 4) at one year after the surgery reported significantly more anxiety, depression, and distress preoperatively, but surprisingly not catastrophizing. Only preoperative anxiety was included in the final analyses and found to be an insignificant predictor. The collinearity of the psychological scales used is a common problem when models are built. Bruce et al. (2014) have taken this into account in their study by forming a new aggregated variable with factor analysis. They found that this new variable consisting of high optimism and low psychological distress predicted lower pain after surgery.

2.7 PREDICTION AND PREVENTION

Like most medications, also the proposed analgesic interventions to prevent postsurgical persistent pain (Kalso et al., 1996; Yarnitsky et al., 2012) may have adverse effects, highlighting the importance of identifying high-risk patients for these interventions. There are also studies of preventive psychological interventions for postoperative pain (Ziehm et al., 2017) and even a recent review focusing solely on breast cancer patients (Johannsen et al., 2013). The effectiveness of these interventions in preventing pain is controversial (Weinrib et al., 2017; Ziehm et al., 2017; Johannsen et al., 2013), and the types of interventions used vary widely. Better recognition of the importance of different factors in persistent pain will allow more targeted psychological interventions to be developed (Weinrib et al., 2017). For instance, for some individuals the best approach to manage pain and/or cancer-related anxiety could be the use of relaxation-based interventions, whereas others will benefit from patient education or supportive therapy (Johannsen et al., 2013).
3. AIMS OF THE STUDY

The aim was to examine factors associated with pain experience in a female breast cancer cohort. Specific aims were to identify factors explaining higher experimental pain sensitivity and factors predicting both higher acute and persistent breast cancer treatment-related pain intensity. Of particular interest were clinically feasible factors associated with acute and persistent pain experience.

Specific aims were as follows:

1. To describe experimental pain sensitivity and to examine clinical factors associated with both experimental and clinical postoperative acute pain and analgesic use.
2. To identify clinical factors associated with acute pain intensity and its course during the first postoperative week and to identify clinical factors associated with persistent post-treatment pain.
3. To identify the role of depressive symptoms, anxiety, and anger regulation in pain experience at different follow-up time points in this patient cohort.
4. To develop an easy-to-use clinical tool to identify women at the highest risk for pain persistence.
4. SUBJECTS AND METHODS

4.1 STUDY DESIGN AND PARTICIPANTS

The whole cohort of this prospective study included 1000 patients. These patients were recruited from the Breast Surgery Unit of Helsinki University Hospital and were operated on between August 2006 and December 2010. Women who were fluent in the Finnish language, were aged 18-75 years, and had a histologically proven newly diagnosed, unilateral, invasive breast cancer (T1-4 N0-3 M0) met the inclusion criteria and were invited to participate in the study. Exclusion criteria were metastasized cancer (other than axillary lymph nodes), clinically significant liver or kidney failure, previous breast cancer surgery on the same side, BMI >35 (from the patient number 100 on), immediate reconstruction at the primary surgery, alcoholism, contraindications for use of oxycodone, and severe psychiatric disease (e.g. schizophrenia). Prior to enrolment, the study protocol was disclosed to the subjects. The informed consent was explained carefully to the patients, and a written informed consent was obtained from all subjects by either a research nurse or a physician. The recruitment process, exclusion criteria for different sub-studies, and the number of patients in different sub-studies are presented in a flow-chart (Figure 4).
4.2 DATA COLLECTION

The study protocol and follow-up times for different variables are outlined briefly in Table 3. More detailed information of the variables included in different sub-studies is provided in the original publications (Studies I-VI, Methods). The data was collected with paper questionnaires and entered to the SPSS-files by two research nurses. The data was examined by the researchers to find potential errors in the data entry. This was done by checking minimum and maximum values and possible odd numbers.
### Pain Sensitivity and Factors associated with the Pain Experience after Breast Cancer Treatments

<table>
<thead>
<tr>
<th>Study</th>
<th>Protocol and Methods</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study I</td>
<td>Pain in the area of surgery (NRS)</td>
</tr>
<tr>
<td>Study II</td>
<td>Pain in the area of surgery (NRS)</td>
</tr>
<tr>
<td>Study III</td>
<td>Pain in the area of surgery (NRS)</td>
</tr>
<tr>
<td>Study IV and V</td>
<td>Pain in the area of surgery (NRS)</td>
</tr>
<tr>
<td>Study VI</td>
<td>Pain in the area of surgery (NRS)</td>
</tr>
</tbody>
</table>

- Preoperative: Anesthesia protocol
- Perioperative: Type of surgery in the breast (mastectomy or breast conserving surgery), Type of surgery in the axilla (sentinel node biopsy or axillary clearance)
- Postoperative: Pain related questions, Pain related variables: Pain at rest (NRS), Pain during movement (NRS), oxycodone consumption, use of patient controlled analgesia (PCA) during 24h

- Demographic factors: Medical and medication history
- Psychological questionnaires: BDI, STAI, STAXI
- Pain related questions: Other chronic pain, Pain in the area of surgery (NRS), Expectation of post-operative pain
- Experimental heat and cold pain tests

| Table 3. Study protocol and methods. |
4.2.1. DEMOGRAPHIC DATA

Preoperative clinical assessments included data on age, height, and weight, from which the Body Mass Index (BMI) was calculated. Other data comprised smoking habits (never, yes, stopped), use of alcohol (no, <6, 6-11, >11, >40 doses per week), drug abuse, and medical and medication history, e.g. number of previous operations, number of previous cancer, presence of other disease, use of medication. Presence of chronic pain (e.g. migraine, fibromyalgia) was also asked.

4.2.2. PAIN-RELATED ASSESSMENTS

**Numerical Rating Scale (NRS)**

Most of the pain variables preoperatively and in the follow-up times were assessed using an 11-point Numerical Rating Scale (NRS). This scale ranges from 0 to 10, where zero means “no pain” and ten means “the worst possible pain one could imagine”. This is a common method to assess pain in both clinical and research settings, and it has shown good validity when measuring pain intensity in various age groups (Gagliese et al., 2005).

**Pain in the area of surgery (Studies I-VI)**

Preoperatively, the patients were asked to assess pain during the past week in the area of surgery and to assess the amount of pain they expected to have postoperatively. Immediately after the surgery, patients were asked about the intensity of pain during motion at five minutes from waking. Every day during the first postoperative week and at all follow-up points, patients similarly evaluated the pain intensity in the area of surgery (Table 3). The area of surgery included the breast, the axilla, and the upper arm (Studies I, II, V, VI) and in Studies III and IV also the lower arm and the hand and fingers. The highest rating (NRS 0-10) of pain in any of these areas was used as an indication of the intensity of pain.

**Experimental pain (Studies I, II, and VI)**

Patients were tested 1-3 days prior to the surgery for experimental thermal heat and cold pressure pain. Thermal heat pain was assessed using the TSA-II NeuroSensory Analyzer. A temperature of 43°C and 48°C was applied, once each, for 5 seconds on the antebrachium contralateral to the side of surgery. Cold pressure test was measured by immersing the hand contralateral to the side of surgery in a cold water bath (2-4°C) (JULABO) for as long as the patient can tolerate the test, but for
a maximum of 90 seconds (Picture 1). Pain intensity and unpleasantness were asked using NRS (0-10) every 15 seconds and at the end of the test. Time to withdrawal (seconds) and pain intensity (NRS 0-10) and unpleasantness (NRS 0-10) at withdrawal were measured.

![Picture 1. Cold pressure test.](image)

**Oxycodone consumption (Studies I, II, VI)**

Immediate acute pain was measured with different oxycodone consumption measures. After surgery, subjects were administered intravenous (IV) oxycodone for pain relief. Patients were initially titrated with oxycodone by the research nurse until adequate pain relief was obtained (NRS 0-3). The quantity of oxycodone required was recorded and used as a proxy for acute pain intensity (Studies I, II, and VI). The time until the patient needed a new dose of oxycodone for pain was recorded. The total amount of oxycodone consumed over 20 hours after the surgery using a Patient-Controlled Analgesia (PCA) device was recorded. NRS measurements of pain intensity and pain unpleasantness were recorded (Study I).
4.2.3. TREATMENT

Anesthesia
An anesthesia protocol was developed in collaboration with the treating anesthesiologists who were either members of the research team or who were supervised by members of the research team. Patients were premedicated with diazepam 10 mg and paracetamol (acetaminophen) 1 g. In the operation theatre, IV infusion of remifentanil (0.2 µg/kg/min) was started. The induction of anesthesia was achieved with propofol 2-3 mg/kg IV. Tracheal intubation was facilitated with rocuronium and further boluses were given adjusted to clinical needs. The mechanical ventilation was adjusted to achieve normocapnia with a mixture of oxygen and nitrous oxide. Remifentanil (short-acting opioid) infusion was used at a rate of 0.05-0.25 µg/kg/min to keep the systolic blood pressure at the pre-anesthesia level. During closure of the skin, the infusion of remifentanil was stopped and a 0.07 mg/kg dose of oxycodone was given. A blood specimen for DNA isolation and banking was drawn during anesthesia to avoid unnecessary injections.

Surgery and oncological treatment
The breast surgeries that the women underwent were either modified radical mastectomy (MRM) or breast-conserving surgery (BCS). Axillary surgery included either sentinel node biopsy (SNB) or axillary lymph node dissection (ALND) or both. There was a consistent surgical approach and the surgeons kept careful records of all surgeries. For statistical analyses (Studies II, IV, V, VI), type of surgery in the axilla was combined to be categorical SNB alone or ALND with or without SNB. In Studies I and III, the surgery type was divided into four categories: BCS with SNB, BCS with axillary evacuation, mastectomy with SNB, or mastectomy with axillary evacuation.

Oncological adjuvant treatment consisted of radiotherapy, chemotherapy (taxanes, antracyclines, metotrexat, herceptin), and endocrine therapy (antiestrogens, aromatase inhibitors, LHRH agonists, or combinations) according to local clinical guidelines (Goldhirsch et al., 2007).

Genetic analyses (Study VI)
The Autopure LS automated DNA purification instrument was used to extract DNA from peripheral blood (Gentra Systems, Inc., Minneapolis, MN, USA). The SNPs were genotyped using the Sequenom MassARRAY system and the iPLEX Gold Single Base Extension chemistry (Sequenom, San Diego, CA, USA) in a multiplex format (Jurinke et al., 2001). To confirm the accuracy of the genotyping results both duplicate Centre d’Etude du Polymorphisme Humain control and water control samples were
included in each DNA plate. Phenotypic information was blind when genotyping was performed. Genotypes \textit{OPRM1} rs1799971 (A118G) and \textit{COMT} rs4680 (Val158Met) were analyzed in Study VI.

4.2.4. PSYCHOLOGICAL QUESTIONNAIRES

**Depressive symptoms (Studies I-VI)**

The Beck Depression Inventory (BDI) (Beck et al., 1961) was used to measure depressive symptoms. The BDI is a 21-item self-report questionnaire to assess such depressive symptoms as pessimistic thoughts, irritability, guilt, and lowered mood. A person responds on a four-point scale from 0 (not at all) to 3 (very much) about how well a statement describes her. A sum score of all items is calculated to indicate the level of depressive symptoms, higher scores indicating higher depressive symptoms. Sum scores range from 0 to 63. Cut-off scores for clinical evaluation of the severity of depressive symptoms are as follows: 0-9 no symptoms, 10-18 mild symptoms, 19-29 moderate symptoms, and 30-63 severe symptoms (Beck et al., 1961). Cronbach’s $\alpha$ coefficient for BDI in this cohort was 0.89. BDI has been validated, also in Finnish (Steer et al., 1999; Varjonen et al., 1997), and it is widely used in Finnish cohorts (Knaster et al., 2016; Kokkonen et al., 2017; Markkula R. et al., 2016).

**Anxiety (Studies I-VI)**

State and trait anxiety was measured by using the State-Trait Anxiety Inventory (STAI) (Spielberger et al., 1983). The STAI is a 40-item scale that evaluates the intensity of both state (20 items) and trait anxiety (20 items). State anxiety assesses how a person is feeling at a specific time, e.g. “I am tense”, “I feel safe”, and trait anxiety assesses relatively stable reactions in threatening situations e.g. “I worry too much over something that really does not matter” and “I’m stable as a person”. A person responds on a five-point scale ranging from 0 (not at all) to 4 (very much). A sum score of all items indicates the level of state or trait anxiety. The scores range from 20 to 80, higher scores indicating a higher level of state or trait anxiety. Cut-off scores for evaluating the severity of anxiety are 20-40 no-low, 41-60 moderate, and 61-80 severe anxiety (Spielberger et al., 1983). Cronbach’s $\alpha$ for STAI state and trait were 0.95 and 0.91, respectively. STAI measures symptoms of general anxiety and is not a pain-specific questionnaire. STAI has also been previously used in breast cancer cohorts to evaluate the level of anxiety (Tasmuth et al., 1996a; 1996b; Bruce et al., 2012 and 2014; Rehberg et al., 2017; Katz et al., 2005; Miaskowski et al., 2012).
Anger regulation (Study VI)

The Anger Expression Inventory, revised version (STAXI-2) was used to evaluate the way that individuals typically regulate their anger. Anger regulation is often divided into two strategies: anger expression (anger-out, angry feelings are expressed in physically or verbally aggressive behavior) and anger inhibition (anger-in, angry feelings are suppressed, i.e. not expressed verbally or physically) (Spielberger, 1999). Questions assessing anger-out include statements like: “I lose my temper” and “I may slam doors and throw things” and for assessing anger-in: “I try not to show my anger” and “I’m criticizing others in my mind”. STAXI-2 is a commonly used scale to assess anger regulation in somatic diseases, also in pain studies (Burns et al., 2008; Duckro et al., 1995; Estlander et al., 2008; Julkunen et al., 2009; Lehto et al., 2005). Both sub-scales comprise 8 items and a person responds on a four-point scale ranging from 0 (not at all) to 3 (completely true) about how well each claim describes typical behavior when angry. A sum score is calculated for both subscales and it can vary between 0 and 24, with a higher number indicating a greater tendency to either inhibit or express anger. Cronbach’s α was 0.77 for anger-in and 0.74 for anger-out.

4.3. STATISTICAL ANALYSES

The data were analyzed using SPSS software (versions 19.0.0.1 and 22.0 for Windows, SPSS Inc., Chicago, IL, USA), the R statistical package (versions 2.14.2 and 3.2.2), pROC package (version 1.8) (Robin et al., 2011), and Python 2.7.11 module Statsmodels (version 0.6.1). Studies I, II, and IV-VI were performed using traditional statistical methods. In Study III, multivariate analyses were performed using the Bayesian method (Carlin & Louis, 1996). Tests of normality were conducted using the Kolmogorov-Smirnov test and by estimating skewness and kurtosis. Descriptive data were presented as means (standard deviations, SDs), medians (ranges), and numbers (percentage) when appropriate. Comparisons between different study groups were performed using either parametric or non-parametric tests depending on variable distributions. Student’s t-test and Pearson’s correlational coefficient for normally distributed data and Mann-Whitney U-test, Kruskall-Wallis, and Spearman’s correlational coefficient for non-parametric data. Chi-square test was used for analyzing differences between categorical variables. The p-value correction was performed by using the Bonferroni-correction. To estimate the reliability (internal consistency) of the psychological questionnaires (BDI, STAI and STAXI-2) Cronbach’s α coefficients were calculated. There were singular missing items in
psychological questionnaires that were imputed by replacing the missing item with the mean value of the other items the person had answered. If a patient had ≥20% missing items, the questionnaire was removed from the analyses. The amount of missing items in the questionnaires was low, usually there was only one missing item per person and approximately 1-3% of the patients had missing values per questionnaire. Singular missing values were imputed by the mean value of the answered items. This was done to be able to include as many participants as possible to the final data. The number of imputed items was small and therefore not likely to add the risk of the Type I or II error. Type I error occurs when the null hypothesis is true but falsely rejected, and the Type II error when the false null hypothesis is not rejected. The outcome variable “The amount of oxycodone needed for the first state of satisfactory pain relief” (Study VI) underwent a logarithm transformation to achieve more normal distribution.

To describe acute pain during the first postoperative week (Study II), the pain trajectories were formed by fitting a regression line across the pain measures of the seven postoperative days using an ordinary least-squares fit. The trajectories include two features, the intensity of pain on the hypothetical day zero assessment point (the intercept) and the change in pain intensity with time (the slope). Figure 5 gives an example with five different patients of how the linear line was fitted through the exact values during the first week, also showing how different slopes were formed.

Figure 5. Trajectories of five individuals’ pain resolution over the first postoperative week.
Three groups according to the direction of the slope were formed. Individual slope values with 50% confidence intervals (CI) were calculated and slopes with CI crossing value zero were defined as flat slopes, whereas entirely positive CIs were considered increasing slopes and entirely negative CI were defined as decreasing slopes.

In Studies I, II, and IV-VI, multivariate analysis was performed using traditional statistical methods: linear regression (I, II, VI) ordinal logistic regression (IV), and stepwise binary logistic regression (V). Based on the results of the binary regression analyses (Study V), prediction models for pain persistence were developed at different time points (preoperative, intraoperative, 1st postoperative day, and 7th postoperative day models) and validated in two separate breast cancer patient cohorts. The performance of the prediction models was assessed by the area under the receiver-operating characteristic curves (AUC-ROC). The sensitivity and specificity rates were calculated for each of the models. These are statistical measures evaluating the goodness of the classification test. Sensitivity refers to the proportion of positive findings that are correctly identified as positive (a patient with pain correctly identified as having pain). Specificity refers to the proportion of negative findings that are correctly identified as negative (a patient with no pain correctly identified as having no pain). In Study III, the Bayesian method was used to determine those variables that best explained clinically significant pain at six months (Carlin & Louis, 1996; Pelkonen et al., 2012). First, preoperatively collected data and surgery- and adjuvant treatment-related data were analyzed separately. Then these were combined. The sum variables were produced through logarithmic transformation of the Bayesian values (Kurki and Kataja, 1996). Finally, a multifactorial risk index was constructed and a tool comprising six factors was chosen.

General linear model (GLM) repeated-measures analysis was used to assess the associations between anger regulation and mood in the three-year follow-up (Study VI).
4.4. ETHICAL ASPECTS

The research protocol was approved by the Coordinating Ethics Committee of the Helsinki University Hospital (136/E0/2006) and the Ethics Committee of the Department of Surgery (Dnro 148/E6/05) of the Hospital District of Helsinki and Uusimaa (HUS). All subjects were fully informed of study procedures, potential risks, and their right to withdraw from the study at any time. All reasonable precautions were taken (including coding of specimens and clinical data files) to prevent loss of confidentiality. Genetic data were not revealed to the patients. If a patient reported high intensity of pain, she was contacted by the research nurse who then consulted the research team. When needed, the patient was referred to the pain clinic for management.
5. RESULTS

5.1. CHARACTERISTICS OF PATIENTS

The mean age of the whole cohort of 1000 women was 57 years (SD 9.3), ranging from 28 to 75 years. The average BMI was 25.4 (SD 4.3), ranging from 16 to 42.8. Almost one-fourth of the patients, 24% (n=240), reported a chronic pain condition (e.g. musculoskeletal pain, migraine, fibromyalgia) preoperatively. The majority of the women had never smoked regularly (59.1%), 22.8% had stopped smoking, and 16.7% were still smoking every day and 1.4% periodically. No alcohol use was reported by 17.4%, less than 6 doses per week by 64.4%, 6-11 doses per week by 13.2%, and >11 doses per week by 5% of the women. The type of breast surgery was resection in 62.5% (n=625) and mastectomy in 22.7% (n=375). Of the patients, 56% (n=560) had only sentinel node biopsy in the axilla, whereas 44% had axillary clearance. At 6 months after the primary surgery, there were 48 women who had had a second surgery, and axillary clearance was performed on a total of 486 patients (48.6%). At 5 years after surgery, the survival rate of the patients was 96.2% (new data). At 12, 24, and 36 months after the surgery there was no statistically significant difference between the responders and non-responders regarding the baseline depressive symptoms, anxiety or anger regulation variables. However, the non-responders were more often smokers (p=0.002, p=0.007, p=0.016, respectively), and had higher numbers of metastatic lymph nodes (p=0.011, p=0.001, p=0.005, respectively). Non-responders at 12 and 36 months were younger at baseline than responders (p=0.026 and p=0.041). These differences are unlikely to cause significant bias, as the response rate was so high.
5.2 PAIN

Reports of pain in the area of surgery at different time points are presented in Table 4.

<table>
<thead>
<tr>
<th></th>
<th>Preoperative</th>
<th>6 months</th>
<th>12 months</th>
<th>24 months</th>
<th>36 months</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>%</td>
<td>n</td>
<td>%</td>
<td>n</td>
</tr>
<tr>
<td>NRS 0-3</td>
<td>928</td>
<td>92.8</td>
<td>756</td>
<td>87.4</td>
<td>744</td>
</tr>
<tr>
<td>NRS 4-10</td>
<td>72</td>
<td>7.2</td>
<td>109</td>
<td>12.6</td>
<td>116</td>
</tr>
<tr>
<td>Total</td>
<td>1000</td>
<td>865</td>
<td>860</td>
<td>770</td>
<td>709</td>
</tr>
</tbody>
</table>

Table 4. Number of patients reporting no to low pain (NRS 0-3) or moderate to severe pain (NRS 4-10) in the area of surgery preoperatively and after the surgery.

5.2.1. ACUTE PAIN

5.2.1.1. Experimental pain (Studies I, II, VI)

The patients varied widely in the sensitivity to both experimental heat and cold pain, and the tolerance of cold pain. There was a correlation between heat and cold experimental pain (cold withdrawal time and heat pain intensity, $r=-0.32$); the shorter the time to withdrawal in the cold water test, the higher the reported heat pain intensity. In the cold pressure test, there were 117 patients (13%) who kept their hand in the cold water for less than 15 s, and approximately one-quarter (24%) of the patients tolerated the cold water for the maximum of 90 s. The average time tolerated was $46.4 \pm 29.5$ s. Experimental pain sensitivity was only weakly correlated with the acute pain measures: total oxycodone consumption (experimental heat pain 48°C, $r=0.10$; and cold pressure test maximum time tolerated, $r=-0.11$) and pain during motion at 5 min from waking (cold pressure test maximum time tolerated, $r=-0.08$; and heat pain 48°C, $r=0.13$) (Study I). The patients who reported a higher expectation of postoperative pain (NRS 7-10 vs. NRS 0-3) were more sensitive to heat pain at 48°C ($p<0.001$) and kept their hand in the cold bath for a shorter time ($p=0.001$) (Study II).

Of the studied variables (Study I), state anxiety had the strongest effect on experimental pain sensitivity (heat pain 48°C $\beta=0.02$, $p=0.012$; cold pressure test maximum time tolerated $\beta=-0.43$, $p=<0.001$, and cold pain intensity (15 s) $\beta=0.032$, $p=0.002$). Preoperative chronic pain condition was associated with shorter toleration of cold pain ($\beta=-6.68$, $p=0.034$), higher heat 48°C pain ($\beta=0.69$, $p=0.001$), and higher cold pain (15s sensitivity ($\beta=0.62$, $p=0.048$). Number of previous operations
was also associated with the intensity of experimental pain (heat pain 48°C $\beta=0.137$, $p=0.018$). Women reporting higher anger inhibition (anger-in) reported higher heat pain sensitivity compared with their low anger-in peers (mean 3.16 vs. 3.80, $t=-2.17$, $p=.031$, $d=-0.27$). This univariate association was not seen in the linear regression analyses after controlling for anxiety and depressive symptoms (Study VI).

As new data for this thesis (previously unpublished results), correlations between experimental pain variables and acute pain trajectories were calculated (Table 5). There was a significant, but weak correlation between the first week pain intensity (the intercept) and the studied experimental measures. As new data, experimental pain sensitivity was compared between persistent pain groups at one year after the surgery (NRS 0-3 vs. NRS 4-10). Patients in a pain group (NRS 4-10) reported significantly more intense heat pain (mean 3.4 vs. 4.1, $t=-3.03$, $p=0.003$, $d=-0.21$). No differences in cold pain tolerance or pain at 15 s were found.

<table>
<thead>
<tr>
<th>First week acute pain trajectory slope</th>
<th>Heat pain 48c (NRS 0-10)</th>
<th>Cold pressure pain intensity at 15 s (NRS 0-10)</th>
<th>Cold pressure total time tolerated (s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>First week acute pain trajectory intercept (NRS 0-10)</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>First week acute pain trajectory intercept (NRS 0-10)</td>
<td>.17**</td>
<td>.12**</td>
<td>-.10*</td>
</tr>
<tr>
<td>n=557</td>
<td>n=499</td>
<td>n=563</td>
<td></td>
</tr>
</tbody>
</table>

**Correlation is significant at the 0.01 level * Correlation is significant at the 0.05 level (2-tailed). Available data from the study II were included in this analysis.

**Table 5.** Correlations between the first week pain trajectories and experimental pain sensitivity.

5.2.1.2. Clinical perioperative pain (Studies I, II, VI)

The type of surgery in the axilla was relevant to the intensity of immediate pain measures. Patients who underwent more invasive axillary clearance surgery needed significantly more oxycodone during 20 h after surgery than patients with sentinel node biopsy ($p=<0.001$). The total use of oxycodone at 20 h (mg/kg) was associated with younger age ($\beta=-0.005$, $p<0.001$), lower BMI ($\beta=-0.005$, $p<0.001$), previous chronic pain condition ($\beta=0.048$, $p=0.001$), presence of preoperative pain in the breast to be operated ($\beta=0.039$, $p=0.004$), and higher state anxiety ($\beta=0.002$, $p=0.003$). These variables explained approximately 16% of the total variance ($r^2=0.158$) in oxycodone consumption.
Younger patients needed more oxycodone to achieve satisfactory pain relief for the first time after the surgery ($\beta=0.128$, $p<0.001$) and reported more pain during motion before the 1st dose of oxycodone ($\beta=-0.028$, $p<0.001$). Women with elevated anger expression (anger-out) needed significantly more oxycodone to achieve satisfactory pain relief for the first time after surgery (log-transformed mean -1.62 vs. -1.49, $t=-3.02$, $p=0.003$, $d=-0.33$) than women reporting low levels of anger-out. This univariate finding was not significant in the hierarchical regression analyses after controlling for age (Study VI).

5.2.1.3. Pain during the first postoperative week (Study II)

More than five out of six patients (84.4%) expected postoperative pain to be moderate to severe (Study II). Figure 6 shows the proportions of patients with different expectations of postoperative pain (low pain 0-3, moderate pain 4-6, and severe pain 7-10) that actually had pain $\geq 4$ preoperatively or during the first postoperative week.

![Figure 6. Distributions of different pain expectation groups of women reporting pain NRS $\geq 4$ preoperatively and during the first postoperative week.](image)

Figure 7 displays the courses and intensities of the first postoperative week in the entire cohort of 1000 women. There is a negative correlation between the intercepts and the slopes; the greater the
initial pain, the faster it resolves during the first post-operative week. Three groups were identified based on the direction of the slope. The proportion of patients whose pain remained quite stable over the first week (flat slope) was 31.1%. In 19% of patients, pain increased over the week (positive slope), and in 49.7% pain decreased over the week (negative slope).

**Figure 7.** Association between intensity (the intercept) and resolution (the slope) of pain during the first postoperative week.

The initial pain intensity and its resolution during the first postoperative week was modeled by using the pain trajectories. The factors that explained one-fourth ($r^2=0.25$) of the initial intensity of the pain during the first week (the intercept) were the type of axillary surgery ($\text{SNB } \beta=-0.39, p=0.03$), preoperative pain in the area of surgery ($\beta=0.17, p=0.01$), psychological distress (anxiety and depressive symptoms) ($\beta=0.24, p=0.01$), expectation of postoperative pain ($\beta=0.16, p<0.001$), and the amount of oxycodone needed for the first state of adequate analgesia ($\beta=3.88, p<0.001$). A more negative slope (faster pain resolution) was explained mostly by those factors that explained high initial pain intensity: expectation of pain ($\beta=-0.02, p=0.02$), the amount of oxycodone needed for the first state of adequate analgesia ($\beta=0.44, p=0.01$), and high BMI ($\beta=-0.01, p<0.001$). The variance of the slope was explained by these factors only modestly ($r^2=0.04$).
5.2.2. PERSISTENT PAIN (Studies II-VI)

5.2.2.1. Persistent pain at six months

In a subgroup of the whole cohort (first 489 patients), at six months after surgery 87.1% of the patients reported no or low pain intensity (NRS 0-3), and clinically significant pain (NRS 4-10) was reported by 12.9% (n=63) of the patients (Study III). This analysis also included the worst pain in the lower arm, joints, and fingers. Table 4 shows the percentages of different pain intensities in the area of surgery (the breast, the axilla and the upper arm) at all time points of the study with all available data. In order to create a clinically useful prediction tool, we chose six factors that best explained persistent pain at six months. These factors were chronic preoperative pain (OR 2.99; CI 1.76-5.08; p<0.001), number of previous operations ≥4 (OR 2.91; CI 1.62-5.25; p<0.001), preoperative pain in the area of surgery ≥4 (OR 2.90; CI 1.32-6.39; p<0.01), BMI ≥31 (OR 3.38; CI 1.83-6.24; p<0.001), previous smoking (OR 2.41; CI 1.41-4.17; p<0.01), and age ≥70 years (OR 2.01; CI 0.84-4.78; p=NS). Sum score for estimation of the risk of developing moderate or severe persistent pain in the operated area was created by weighting the factors in the model based on their relative contribution to the risk. The chosen cut-off limit (20) identifies 81% (sensitivity) of those who will develop persistent pain, but 56% (specificity) will be false-positive assumptions.

5.2.2.2. Persistent pain at one year

As the data were re-analyzed for this dissertation summary, an unfortunate error in the data analysis of Study IV was found. Instead of the preoperatively acquired scores for psychological factors, depressive symptoms (BDI), and State and Trait Anxiety Questionnaires (STAI), the questionnaire scores from the 12-month follow-up were used. The erratum was made to the journal (JAMA) and the corrected values of all variables are presented here. Risk factors for persistent pain at 12 months after surgery were assessed (Study IV) with all available data (n=860). Table 4 shows the distribution of reported clinically significant pain. Factors that were significantly associated with higher pain intensity as an ordinal variable (NRS 0-10) were mainly either treatment-related variables: type of axillary surgery (clearance) (OR 0.38 CI 0.28-0.52; p<0.001) received chemo- (OR 1.48 CI 1.10-2.01; p=0.01) and radiotherapy (OR 0.52 CI 0.39-0.69; p<0.001), or pain-related variables: chronic preoperative pain (OR 0.67 CI 0.50-0.89; p=0.006) and preoperative pain in the area of surgery (OR 1.47 CI 1.35-1.60; p<0.001). From psychological variables, higher trait anxiety was associated with higher pain intensity (OR 1.02 CI 1.01-1.04). In the reanalysis of the data, the only change was that
depressive symptoms was replaced by trait anxiety. Depressive symptoms at 12 months after surgery were associated with higher pain experience at that time (12 months) (OR 1.04 CI 1.00-1.08; p=0.003).

In the second prediction tool study (Study V), all available data at the one-year follow-up were analyzed and the outcome variable was pain at 12 months categorized as no or low pain (NRS 0-3) or moderate to severe pain (NRS 4-10). Four different stepwise logistic regression analyses were conducted with factors collected at different time-points (pre- and perioperatively, first and seventh postoperative days). From the preoperative factors, preoperative pain in the area of surgery was associated with pain intensity at 12 months (OR 1.39 CI 1.24-1.56; p<0.001). When perioperative factors were added to the model, also BMI ≥31 (OR 1.86 CI 1.06-3.24; p=0.030), and axillary clearance (OR 2.19 CI 1.44-3.34; p=0.002) were significant predictors of pain intensity. The intensity of acute postoperative pain on the first (OR 1.11 CI 1.02-1.21; p=0.017) and seventh postoperative days (OR 1.17 CI 1.05-1.29; p=0.003) was also associated with higher pain intensity and added to subsequent models. All of the factors predicting persistent pain in the previous models remained in the subsequent model, except the 1st day acute pain intensity, which was replaced by the intensity of pain on the 7th day in the last model. Odd ratios remained quite stable throughout the models.

Based on the proportion of patients having persistent pain, the risk estimates in the different datasets on the seventh postoperative day were calculated for three different levels (<20% low risk, 20-30% moderate risk, and >30% high risk). The prediction models for the four different time-points were validated by applying the regression coefficients into the independent datasets from Denmark and Scotland. ROC-AUC values for the seventh day model were for the Finnish cohort 0.704 (0.64-0.755), for the Danish cohort 0.739 (0.666-0.812), and for the Scottish cohort 0.740 (0.646-0.834). The sensitivity of the seventh postoperative day model at the 20% risk level was 32.8% in the Danish cohort and 47.4% in the Scottish cohort, and the specificities were 94.4% and 82.4%, respectively. At the 30% risk level, the sensitivity was 12.1% for the Danish cohort and 26.3% for the Scottish cohort, and the corresponding specificities were 97.3% and 93.9%. Based on the results of the prediction models a web-based risk calculator was then developed (Figure 8). The web address for the developed predictive tool is http://www.hus.fi/breastsurgery/predictivemodel.
Figure 8. An example of how the web-based pain prediction calculator works. The information of a hypothetical patient was input and the calculator shows the risk percentages for different follow-up points.

5.3. PSYCHOLOGICAL FACTORS

The variability between patients in all psychological variables were high throughout the follow-up period. Table 6 shows the distributions of depressive symptoms (BDI) and state (STAI state) and trait (STAI trait) anxiety variables at different time-points. All variables are higher preoperatively, and the mean values remain quite stable from the one-year to the three-year follow-up.
Table 6. Descriptive statistics of the mood scale sum scores in the three-year follow-up.

Anxiety

Anxiety was the most consistent psychological variable predicting higher pain experience. State anxiety predicted experimental pain sensitivity, both modalities (heat pain 48°C $\beta=0.02$, $p=0.012$; cold pressure test maximum time tolerated $\beta=-0.43$, $p<0.001$, and cold pain intensity (15 s) $\beta=0.032$, $p=0.002$) and analgesic consumption ($\beta=0.002$, $p=0.003$). Higher level of trait anxiety added a risk for persistent pain at the one-year follow-up (OR 1.02 CI 1.01-1.04)

Depressive symptoms and anger regulation

Depressive symptoms and both state ($r=0.72$; $p<0.001$) and trait ($r=0.68$; $p<0.001$) anxiety were highly correlated with each other. Also, state and trait anxiety correlated with each other ($r=0.65$; $p<0.001$). Expectation of postoperative pain was associated with mood factors. Women expecting severe postoperative pain (NRS 7-10) compared to those expecting no or low pain (NRS 0-3) reported preoperatively more depressive symptoms (MD 5, IQR 9 vs. MD 9 IQR 10, $p<0.001$) and both state (MD 35 IQR12 vs. MD 43 IQR 17; $p<0.001$) and trait anxiety (MD 34.5 IQR 12 vs. MD 38 IQR14; $p=0.010$). Women reporting high levels of anger-out also expected to have more postoperative pain (mean 4.90 vs. 5.76, t=-2.72, $p=.007$, $d=-0.40$).

Anger regulation and pain

Anger regulation had a modest association with different pain variables. Anger inhibition (anger-in) and anger expression (anger-out) were categorized in extremes (1SD +- from the mean) to
determine differences between low and high pain intensity groups. Women reporting high anger-in scored higher for experimental heat pain intensity (mean 3.16 vs. 3.80, \( t=-2.17, p=0.031, d=-0.27 \)). High levels of anger-out were associated with higher pain expectations of postoperative pain (mean 4.90 vs. 5.76, \( t=-2.72, p=0.007, d=-0.40 \)), and the need for a greater amount of oxycodone to achieve satisfactory pain relief for the first time after surgery (log-transformed mean -1.62 vs. -1.49, \( t=-3.02, p=0.003, d=-0.33 \)). Linear regression analyses revealed an association between anger-in and heat pain intensity only until it was controlled for mood. Anger-out was associated with a higher need for oxycodone and expectation of postoperative acute pain after controlling for mood factors in multivariate analysis, but controlling for age attenuated the association to non-significance.

Anger-in was associated with mood factors. Results indicate that the tendency to inhibit anger is associated with mood factors, especially with depressive symptoms (adjusted means 5.9 vs. 11.6, \( p<0.001, \eta^2=0.108 \)). Patients with high anger-in reported significantly more depressive symptoms at all measured time-points than patients in the low anger-in group (adjusted \( p<0.001 \)).

Table 7 presents the results of a cross-tabulation of low to high anxiety (STAI state and trait) and depressive symptoms (BDI) groups from questionnaires acquired preoperatively and at one year postoperatively. Anxiety is defined as low when the sum score of STAI state and trait is 20-39, and high when the sum score is over 40. Depressive symptoms are defined as low when the BDI sum score is \( \leq 18 \) and high when it is \( \geq 19 \).

<table>
<thead>
<tr>
<th>PREOPERATIVE MOOD</th>
<th>ONE YEAR AFTER SURGERY</th>
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<tbody>
<tr>
<td></td>
<td>Low</td>
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<tr>
<td>Anxiety state</td>
<td>Low</td>
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<tr>
<td></td>
<td>High</td>
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<tr>
<td>Anxiety trait</td>
<td>Low</td>
</tr>
<tr>
<td></td>
<td>High</td>
</tr>
<tr>
<td>Depressive symptoms</td>
<td>Low</td>
</tr>
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<td></td>
<td>High</td>
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</tbody>
</table>

Table 7. Proportions of individuals experiencing low or high symptoms of anxiety and depression preoperatively and at the one-year follow-up.
Anger regulation and genetics

In Study VI, genotype association analyses were performed with anger regulation variables (anger-in and anger-out) and two genotypes were selected, OPRM1 c.118A>G genotype and COMT c.158G>A (Val158Met). In that study cohort, 595 patients (62.4%) had the A/A genotype of OPRM1 c.118A>G genotype, 316 patients (33.2%) had the A/G genotype, and 35 patients (3.7%) were homozygous, G/G, for the variant allele. No significant association between OPRM1 c.118A>G genotype and anger regulation was found. Also, the formed interaction term OPRM1 c.118A>G genotype X anger-out was not significantly associated with the amount of oxycodone needed for satisfactory pain relief for the first time after surgery.

The genotype COMT c.158G>A (Val158Met) and anger-out ($\beta$=.496, $p$=.004) were significantly associated. In women with the A/A genotype (= Met/Met) (n=271) the mean value of anger-out was one digit lower (8.2) than in women having the G/G genotype (9.2) (n=193). A summary of factors associated with pain-related outcomes is presented in Table 8.

<table>
<thead>
<tr>
<th>Experimental pain</th>
<th>Oxycodone consumption</th>
<th>Acute pain (1st week)</th>
<th>6 months</th>
<th>1 year</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Demographic</strong></td>
<td>Number of previous operations Smoking (previous)</td>
<td>Age (younger) BMI (lower)</td>
<td>Age (older) Obesity (BMI&gt;31) Previous operations ≥4 Smoking (previous)</td>
<td>Obesity (BMI&gt;31)</td>
</tr>
<tr>
<td><strong>Psychological factors</strong></td>
<td>State anxiety</td>
<td>State anxiety Distress (depressive symptoms and anxiety) Expectation of postoperative pain</td>
<td>Trait anxiety</td>
<td></td>
</tr>
<tr>
<td><strong>Pain factors</strong></td>
<td>Chronic pain Preoperative pain</td>
<td>Chronic pain consumption Preoperative pain</td>
<td>Chronic pain Preoperative pain</td>
<td>Preoperative pain Acute pain (1st and 7th day)</td>
</tr>
<tr>
<td><strong>Type of surgery</strong></td>
<td>Axillary clearance</td>
<td>Axillary clearance</td>
<td>Axillary clearance</td>
<td></td>
</tr>
<tr>
<td><strong>Adjuvant treatments</strong></td>
<td></td>
<td></td>
<td>Radiotherapy Chemotherapy</td>
<td></td>
</tr>
</tbody>
</table>

Table 8. Conclusion of factors associated with pain measures.
6. DISCUSSION

6.1. MAIN FINDINGS

The pain experience constitutes a variety of factors also in breast cancer patients, and the range of pain sensitivity between individuals is high. Pain sensitivity is not sufficient to explain the complex experience of post-treatment pain. Of the women treated for breast cancer, 13.5% had developed clinically significant persistent pain at the one-year follow-up. Since approximately 5000 women are operated on for breast cancer every year, this means that around 675 new women per year in Finland are at risk of suffering from persistent pain at one year postoperatively. The survival rate at five years after surgery was very high (96.2%), highlighting the importance of prevention and management of treatment-related adverse effects.

The best predictors of pain of any kind, i.e. experimental, acute clinical, or persistent pain, were found to be quite similar and can be divided into three categories. Pain (other chronic pain condition, pain in the area of surgery, or the intensity of acute pain), more invasive surgery (axillary clearance), and psychological distress (mainly anxiety) were found to be consistent predictors of heightened pain experience. In addition to these, pain expectation and higher need of oxycodone for obtaining satisfactory pain relief after surgery were associated with higher first postoperative week pain intensity. Obesity was associated with persistent pain at six months and one year after surgery. Number of previous operations and smoking cessation were associated with persistent pain at six months. The adjuvant treatments of radiotherapy and chemotherapy added to the risk for persistent pain at one year.

Screening tools for preoperative and acute-phase use for identifying women at risk for persistent pain at six months and one year after breast surgery were developed. The one-year prediction tool was also validated in two other prospective patient cohorts. With preoperative information, the sensitivity and specificity for 30% risk of persistent pain were 11.2% and 97.5%, respectively. And, when information about the acute pain intensity was added to the model, the corresponding proportions were 16.5% and 95.0%.

The average levels of psychological burden, depressive symptoms, anxiety, and heightened anger expression or inhibition were surprisingly low. However, there was a group of women whose distress remained quite stable during the first year. Depressive symptoms were higher at one year in women with persistent pain. Anger regulation had only a modest independent association with
pain in this patient cohort. However, anger inhibition was associated with higher depressive symptoms throughout the three-year follow-up period.

Figure 9. Summary of the main results and predictors of acute and persistent pain after breast cancer treatments. The most consistent predictors appear in boldface.

6.2. RESULTS IN RELATION TO PREVIOUS STUDIES

6.2.1. EXPERIMENTAL AND PERIOPERATIVE PAIN SENSITIVITY

The overall variability in experimental pain sensitivity between women was high, and this finding is consistent with earlier studies (Kim et al., 2004; Nielsen et al., 2009; Mogil et al., 1999b; Edwards, 2005). There was a group of women in the experimental cold pressure test whose pain reports plateaued approximately halfway through the cold pressure experiment. This may reflect differences in the central pain processing and descending pain modulatory systems such that more pain-tolerant individuals have more efficient endogenous inhibitory systems that became activated in the experimental acute pain setting (Yarnitsky et al., 2008). A very significant difference in cold
intensity tolerated the cold pain test almost twice as long as those who expected much pain. It could be hypothesized that individuals are quite aware of how sensitive they are to pain stimulus. On the other hand, these individuals may represent a hypervigilant reaction group towards pain, imagined or actual, and therefore, the pain is experienced as more intense (Eccleston & Crombez, 1999). It has been shown in healthy participants that interfering with a negative expectation of pain has enabled the participants to diminish the pain ratings in experimental cold pain tests (Brown et al., 2008). Another interesting finding was that there was only a moderate correlation between the two studied experimental pain modalities (heat and cold). This is a consistent finding with earlier studies, suggesting that experimental pain sensitivity in not a single entity, and the modality of pain must be taken into account (Granot, 2009; Nielsen et al., 2009).

Contradictory results regarding the predictive value of experimental pain sensitivity for clinical pain outcomes have been reported (Kim et al., 2004). Either no associations (Kim et al., 2004) or associations only with a specific pain modality (Abrishami et al., 2011; Johansen et al., 2014; Granot, 2009) have been found. The association between experimental pain variables and acute postoperative clinical pain was modest in our study. Rehberg et al. (2017) found in a study with breast cancer patients that higher pain intensity in a preoperative experimental hot water test was associated with higher pain intensity during the 48 hour postoperative period. We did not include experimental pain measures in the acute or persistent clinical pain models since the purpose was to find clinically feasible predictive factors. However, when univariate associations were tested for this thesis, there was a weak association between acute pain intensity and experimental pain (both modalities, but greater for heat pain) and a small association with heat pain intensity and persistent pain at one year. This needs to be further examined, but the results are consistent with earlier studies that modality of pain is an important factor when predicting clinical pain (Abrishami et al., 2011). This also needs to be controlled for other possible covariates (Lariviere et al., 2002), e.g. other previous pain conditions (Johansen et al., 2014), mood (Starr et al., 2010; Strulov et al., 2007), and age (Lautenbacher et al., 2017).

Some contradictory previous findings have been presented regarding the association between experimental pain sensitivity and persistent postsurgical pain (Granot, 2009). But there are no studies done with breast cancer patients. A large study of factors predictive for persistent postoperative pain found that lower cold pain tolerance was associated with persistent postsurgical pain (Johansen et al., 2014). However, this result became non-significant when other chronic pains were controlled. The impact of previous chronic pain on experimental pain sensitivity was also seen in our study. Presence of chronic pain was associated with higher experimental pain sensitivity (both
modalities). Previous chronic pain of any kind and preoperative pain in the area to be operated was associated also with higher need for oxycodone in the 20 hours after surgery. These findings together with the results that the higher number of previous operations was also associated with experimental pain (heat) sensitivity and with pain at six months postoperatively suggest that repeated injuries may enhance central sensitization. It may also reflect interpersonal differences in pain vulnerability (Denk et al., 2014). There may be differences in genetics, brain structures, and pain modulation that lead to higher pain sensitivity (Denk et al., 2014). In the present study, clinical factors tested explained only 16% of the perioperative pain and approximately 5% of tested experimental pain sensitivity. This suggests that there are a large number of factors affecting pain sensitivity in addition to clinically measurable factors.

Anxiety was the most important predictor of experimental pain sensitivity in this study. This finding was independent of the modality or measure. Also, previous studies have reported that more anxious individuals, especially women, report more experimental pain (Pan et al., 2008; Starr et al., 2010; Thompson et al., 2008; Strulov et al., 2007). We found also high pain expectations to be associated with higher experimental pain sensitivity. Amount of emotional appraisal related to pain varies widely between individuals (Buckelew et al., 1992; Hadjistavropoulos & Craig, 1994). Furthermore, it has been suggested that anxiety directs one’s attention to pain-related information (Keogh & Cochrane, 2002). It is possible that those patients whose automatic emotional reaction to pain was smaller tolerated more pain and did not report it as being as intense as patients who were more anxious about the situation. Anxiety and pain expectations can have an effect on descending pain modulation (Bingel et al., 2012), and they could also explain the associations found in this study. The differences found in pain tolerance (endogenous pain modulatory systems) could be in part explained by these differences between patients.

6.2.2 FACTORS ASSOCIATED WITH POST-TREATMENT PAIN

The factors associated with acute and persistent pain were quite similar. Preoperative pain of any kind, psychological distress (especially anxiety), and axillary clearance were consistent predictors. Higher BMI, greater number of previous operations, previous smoking, and received adjuvant treatments also added to the risk for pain persistence.
6.2.2.1. Previous pain conditions

The phenomenon that pain predicts pain is a consistent finding in the risk of postoperative pain outcomes (VanDenKerkhof et al., 2013; Ip et al., 2009; Katz et al., 2009). Higher need for oxycodone in the acute phase, preoperative pain in the operative area, other chronic pain conditions, and higher postoperative acute pain intensity plausibly share a common background, explaining why they have an effect on postoperative pain. Differences in the effectiveness of individual endogenous analgesia systems may explain some of the differences in postoperative pain (Yarnitsky et al., 2008). In addition, although self-reports of pain (NRS) have been found to be reliable measures and quite consistent with brain imaging findings of the activity of brain areas when in pain (Coghill et al., 2003), our finding that preoperative pain predicted both acute and persistent pain may represent individual differences in pain reporting. The reports of pain of some patients may consistently be higher than in others. However, since pain is such a subjective experience and there is no objective way to measure it, the subjective report of the intensity of pain provided by the patient is the most important information when evaluating pain. The pain-related predictors that were identified here may additionally have some unique features predisposing to more pain after breast cancer treatments.

6.2.2.1.1. Preoperative pain in the area of surgery

The most consistently found risk factor for all measured pain outcomes was the presence of preoperative pain in the area of surgery. Pain during the first postoperative week and persistent pain at six months and at one year after surgery were found to be predicted by more intense preoperative pain in the area of surgery. Preoperative pain has been identified as a predictive factor in other surgery types as well (Ip et al., 2009; Gerbershagen et al., 2011; Gramke et al., 2009; Hoofwijk et al., 2015; Sommer et al., 2010), and also in breast cancer cohorts (Andersen et al., 2015; Miaskowski et al., 2012). The explanation for why preoperative pain in the operative area predicts postsurgical outcomes is partly unclear and is likely multifactorial. It has been hypothesized that in breast cancer patients preoperative pain can be related to regional inflammation caused by the tumor (Cabodi & Taverna, 2010). Also, differences in cytokine genes have been proposed to explain the association (McCann et al., 2012). However, preoperative pain in the area that is known to have a malignant tumor may also reflect a psychological component of the pain experience in that area. Pain holds a natural threat value (Eccleston & Crombez, 1999; Vlaeyen & Linton, 2000), and preoperative pain may reflect the heightened worry and fear due to this known threat. We did not
study factors explaining preoperative pain per se, but those women who had more preoperative pain also expected higher postoperative pain and were younger. Preoperative pain may be partially explained by this heightened awareness towards sensations in the cancer-diagnosed breast and reveal a hypervigilant reaction towards pain (Eccleston & Crombez, 1999). Kynanou et al. (2013) found in their study that women with preoperative breast pain reported more depressive symptoms than their peers without pain. Surprisingly, they did not differ in levels of anxiety (Kyranou et al., 2013). Preoperative pain is clinically a very easy factor to screen and should not be overlooked.

6.2.2.1.2. Acute postoperative pain
It is important to acknowledge that all persistent pain is initially acute. Factors explaining acute pain intensity in this study included preoperative pain in the operative area, higher need for oxycodone, higher psychological distress, and higher pain expectation. Moreover, the intensity of postoperative acute pain on the first and seventh day predicted persistent pain at one year. As the results of this and previous studies emphasize, acute pain is an important component in the transition from acute to persistent pain (Chapman & Vierck, 2016; Hoofwijk et al., 2015; Flecher et al., 2015; Perkins & Kehlet, 2000), also after breast cancer surgery (Andersen et al. 2015, Bruce et al., 2014; Andersen & Kehlet, 2011). The acute pain trajectories have shown that an unfavorable pain path increases the risk for pain persistence in other surgery types (Althaus et al., 2014). In this study, approximately half of the patients (49.7%) showed decreasing pain resolution over the first week and almost one-fifth (19%) of the patients were discharged with pain that was increasing over the week. The proportion of unfavorable pain paths was slightly higher than in previous studies including different surgery types (Althaus et al., 2014; Chapman et al., 2011). Associated factors for adverse pain paths warrant further research in breast cancer patients. In a study by Althaus et al. (2014), unfavorable acute pain resolution was predicted by depression and anxiety, whereas weaker pain resolution in the acute phase predicted persistent postoperative pain. The authors hypothesized a link between psychosocial vulnerability and pain persistence.

The role of acute pain in pain persistence process is most likely a continuum for findings that preoperative pain of any kind predicts worse pain outcome. The link between these two pain measures is possibly pain sensitivity (Johansen, 2014) and the function of descending pain inhibition (Yarnitsky et al., 2008). Insufficient treatment of postoperative acute pain may in some individuals lead to malfunctions of central pain processing, and thus, to sensitization (Katz et al., 2009). This highlights the fact that some women should be followed carefully after discharge from hospital
throughout the acute phase and pain should be treated adequately. Gerbershagen et al. (2013) discussed in their large cohort study that high acute pain ratings are related not only to the severity or diversity of tissue trauma, but also to healthcare professionals’ estimates of how painful different operations are and how well the acute pain phase is treated. Therefore, identification of patients at the highest risk for severe acute postoperative pain is essential. Surgeries related to breast cancer are not ranked within the highest acute pain risk procedures (Gerbershagen et al., 2013), nevertheless, because the long-term adverse consequences are considerable, extra attention should be paid to these patients.

6.2.2.1.3. Presence of other chronic pain conditions
About one-quarter (24%) of patients reported a preoperative chronic pain condition. Chronic preoperative pain of any kind has been shown to correlate with persistent pain after various surgical procedures (Johansen et al., 2012). The mechanism for this is unclear and likely multifactorial. Chronic preoperative pain may be due to a chronic disease, e.g. fibromyalgia, which is known to have a high co-occurrence with other pain conditions (Markkula R. et al., 2016). A previous pain condition may have sensitized the central pain modulatory system, predisposing to persistent pain after tissue injury. Since pain and psychological factors are known to be bi-directionally related (Janssen, 2002), it is difficult to rule out the possibility that pain symptoms before the operation would have had an effect on mood symptoms or vice versa. A prolonged pain condition may weaken psychological flexibility and affect an individual’s recovery from surgery and how pain is experienced.

6.2.2.3. Axillary surgery
Axillary clearance is a well-established risk factor for both acute and persistent pain after breast cancer surgery (Wang et al., 2016; Katz et al., 2005; Andersen & Kehlet, 2011; Andersen et al., 2015). This may be explained by the more extensive surgery in the axilla, with potential injury to the sensory intercostobrachial nerve, and by the dissection of lymphatic vessels of the arm, potentially causing lymphedema (Andersen et al., 2015; Jung et al., 2003 and 2005). However, according to the results of this study axillary clearance was not associated with a more negative pain resolution over the first week. Thus, even though the intensity of acute pain initially is higher, it is not significantly associated with slower recovery during the first week. However, the impact of axillary surgery
remains important for pain persistence at the one-year follow-up. The variables that were analyzed varied slightly between the follow-up studies (III-V). The variable of the type of surgery was formed differently in the first six-month follow-up study (III), which may affect the result that axillary surgery did not explain pain at six months.

6.2.2.4. Adjuvant treatments

In addition to surgery, adjuvant treatments are a further challenge for recovery from breast cancer. We found that both radiotherapy and chemotherapy increased the risk for pain in the area of surgery at the one-year follow-up. A large meta-analysis by Wang et al. (2016) found a strong association between radiotherapy and risk for pain persistence after breast cancer surgery. Radiotherapy is generally given to all patients with breast-conserving surgery and to patients at high risk for recurrence after mastectomy. Neuropathic pain is a known complication of radiotherapy for breast cancer (Cross & Glantz, 2003; Meric et al., 2002), and may contribute to persistent pain. The brachial plexus, in particular, is vulnerable to radiation and is at risk when the supraclavicular fossa is included in the radiation field in patients with increased risk of locoregional recurrence (Aebi et al., 2011; Recht et al., 2001). Adjuvant chemotherapy is given when the risk of recurrence is high. The chemotherapy agents currently in use differ in their side effect spectrum, and especially the taxane group of drugs is likely to cause neuropathic pain (Song et al., 2017). Administration of chemotherapy showed an association with persisting post-treatment pain in this study. Adjuvant chemotherapy is not a frequently found risk factor for persistent pain. However, a few retrospective studies have reported chemotherapy to be associated with persistent pain after breast cancer treatments (Gartner et al., 2009; Sheridan et al., 2012).

6.2.2.5. Body Mass Index (BMI)

The association between pain persistence and high BMI was not linear. However, obesity (BMI >31) was found to be a risk factor for more severe pain. This has also been previously reported in other surgery types (Johansen et al., 2014). Higher BMI has been associated with the development of lymphedema after breast cancer surgery, through which it may have an effect also on pain persistence (Helyer et al., 2010). Obesity may also render the axillary dissection more difficult to perform. Obesity has been suggested to be related to a proinflammatory mechanism, which has
been reported to increase general pain sensitivity (Shi et al., 2010). In a large cohort study, high BMI was associated with a higher risk of infections after hip arthroplasty (Bozic et al., 2012).

6.2.2.6. Age

Age has been shown to be associated with pain sensitivity (Lautenbacher et al., 2017). In many studies, younger age has been found to predict higher postoperative pain (Duale et al., 2014; Montes et al., 2015; Ip et al., 2009). Previous studies with breast cancer patients have described younger age to be a risk factor for higher pain experience, both acute (Katz et al., 2005; Rehberg et al., 2017) and persistent (Wang et al., 2016; Miaskowski et al., 2012; Andersen et al., 2015). Age was not a consistent predictor for pain in the present study. However, in accord with previous studies oxycodone consumption was higher in younger patients during the 20-hour postoperative period. This may reflect the pharmacokinetics of oxycodone. It has been reported that oxycodone clearance slows down with older age (Saari et al., 2012). However, our finding may also reflect pain sensitivity in younger patients. Lautenbacher et al. (2017) concluded in their systematic review that pain sensitivity seems to decrease with age, even though pain tolerance does not. We also found that older age (>65 years) increased risk for higher pain at six months after the surgery. A putative mechanism behind increased pain in the elderly could be the deterioration of diffuse noxious inhibitory control (DNIC) with age (van Wijk & Veldhuijzen, 2010). Lariviere et al. (2002) found in their study that DNIC begins to diminish already in middle age, which may explain some of the variance between reported persistent pain and advancing age. The explanation for why younger age was not a constant predictor of pain in the present cohort is unclear. Younger age was associated with a variety of psychological factors in our study, e.g. higher pain expectations, state anxiety, depressive symptoms, lower anger inhibition, and higher anger expression. When age was examined as the only independent variable, it was associated also with many pain variables. Younger patients expected significantly more postoperative pain and reported more preoperative pain in the area of surgery. Hence, one could argue that the meaning of age is represented in those factors that were found to explain pain outcomes.

6.2.2.7. Gender

One explanation for the high prevalence of persistent pain after breast cancer treatment compared with many other procedures could be female gender (Bartley & Fillingim, 2013). As Gerbershagen
et al. (2014) pointed out in their large cohort study, female gender has been shown to be a risk factor for acute pain in all surgery types. However, breast cancer surgery is not a high-risk procedure for acute pain (Gerberschagen et al., 2013). Initial acute pain may by more adequately treated after breast cancer surgery if it is attributed to be a more painful procedure (Alqudah et al., 2010; Wandner et al., 2010). Also, the malignant nature of the cause of the surgery may add to this attribution.

Since differences between males and females have been shown both in experiencing pain and in responses to treatment, it is important to conduct research that is gender-specific. Results of the present study may, therefore, not be generalized to both sexes. Gender may also explain the differences between the results of the present study and those of Bruehl et al. (2008) regarding the association of OPRM1 and anger-out interaction in acute pain. Moreover, gender may be an important moderating factor when genetics are studied (Mogil, 2012b), and should be acknowledged in statistical analyses.

6.2.2.2. Role of psychological factors in postoperative pain

High variability existed between patients on reports of depressive symptoms and anxiety. A subgroup of patients reported high levels of symptoms during the follow-up period. It seems that women who reported higher anxiety or depressive symptoms preoperatively were likely to report those symptoms also later on. On the other hand, women with low levels of anxiety or depressive symptoms were likely to stay that way. There may be some vulnerability for heightened mood reactions in some patients after diagnosis, and they also have difficulties in “returning to normal”.

6.2.2.2.1. Pain expectations

Higher pain expectation was found to predict higher acute pain intensity. This finding is in line with a study done with women about to have a Cesarean section (Pan et al., 2013). However, Rehberg et al. (2017) found only a univariate association in a breast cancer cohort. In our study, for those women who expected high pain, the pain also resolved slightly faster during the first week. However, the clinical significance of this weak statistical association warrants further investigation. Depressive symptoms, anxiety, and younger age were found to explain higher expectations of pain. Anger expression did not have an independent contribution. These results are in line with previous
findings that pain expectations are associated with mood factors, especially anxiety (Pan et al., 2013; Schnur et al., 2007; Keogh & Cochrane, 2002).

6.2.2.2. Anxiety
The presence of anxiety was an important predictor of experimental pain sensitivity, perioperative analgesic consumption, and acute and persistent clinical pain. The contribution of anxiety to the pain experience has been reported also earlier in breast cancer studies (Bruce et al., 2014; Miaskowski et al., 2012), although studies without an association also exist (Andersen et al., 2015). Interestingly, in the present study higher state anxiety was associated with acute pain and trait anxiety in persistent pain.

These results are understandable in light of the definition of these anxiety positions. State anxiety is characterized by nervousness, tension, and apprehension in a given moment and by arousal and activation of the autonomic nervous system. Trait anxiety, on the other hand, is defined as a relatively stable disposition to perceive stressful situations as threatening and to feel discomfort, stress, and worry (Spielberger, 1983). The arousal of the autonomous nervous system in state anxiety is relevant also for the pain experience (Voscopoulos & Lema, 2010). Also, rumination behavior, stress, and fearful thoughts related to trait anxiety are known to predispose to pain persistence (Eccleston & Crombez, 1999; Edwards et al., 2016; Chapman & Vierck, 2016).

The explanation for why anxiety predisposes to pain is most definitely multifactorial. State and trait anxiety are highly correlated and share naturally common features with respect to pain, e.g. hypervigilant behavior (Spielberger, 1983). A high correlation was also seen in the present study. Vulnerability to anxious reactions (trait anxiety) also has an effect on the strength of the state anxiety reaction. This may be a key element in how anxiety influences the acute pain experience. An anxious reaction after breast cancer diagnosis is a normal reaction to a stressful situation, and the finding that all evaluated mood factors were higher preoperatively is understandable and is supported by earlier research (Begovic-Juhant et al., 2012; Zainal et al., 2013). One could argue that the “normal” anxious reaction to cancer is not sufficient to heighten the pain experience, but that a broader susceptibility to anxiety must be present. A study by Starr et al. (2010) reported an result in healthy participants where a small rise in anxiety was associated with higher experimental pain tolerance, and it was hypothesized to be a sign of a boost of an individual’s own descending pain modulation caused by anxiety. None of the participants in that study had clinically significant depression or anxiety. This is in line with our findings that anxiety may work differently in individuals
with a proneness to anxious reactions. This finding may be even more pronounced in breast cancer patients since anxiety is a common reaction to cancer and includes also more cognitive and affective attribution of the cause of pain. Fear of recurrence of cancer may direct attention more to pain sensations in the operated area in cancer patients compared with nonmalignant surgeries.

Preoperative psychological factors explained rather modestly pain persistence at the one-year follow-up. One explanation for this could be that psychological symptoms are already included in factors related to pain sensitivity, and therefore, these stronger predictors of pain already cover some of the shared variance. The consistent predictor, preoperative pain in the area of surgery, may for example be a more acceptable way to express fear and worry about the upcoming surgery and cancer than reporting anxious feelings. It may also in part represent anxiety sensitivity, as argued earlier. Anxiety sensitivity is defined as heightened fear and concentration on bodily sensations (Esteve & Camacho, 2008). We did not study anxiety sensitivity as such, but trait anxiety is known to be closely related to it (Reiss, 1997). Some researchers argue that these two, anxiety sensitivity and trait anxiety, highly overlap and represent the same construct (Lilienfeld et al., 1993).

In the screening tool studies (III, V), anxiety and depressive symptoms were divided into diagnostic categories and did not predict persistent pain. The usage of diagnostic categories loses some information compared with using continuous variables (Goldberg, 2000). Also, psychological symptoms, mood or cognitive, are not categories, but rather dimensions. This means that the cut-offs for the presence of depression or anxiety predefine who has or does not have such symptoms. A person who scores slightly lower in e.g. a questionnaire of depressive symptoms is defined as “not having depressive symptoms” when the score stays above the cut-off point. When we want to explore the relationship between pain experience and psychological factors, the dimensional approach is more sensitive in determining how these are associated (Goldberg, 2000). This was proven in this study where trait anxiety predicted persistent pain as a continuous variable, but not when it was divided into diagnostic categories. The categorization of depressive symptoms and anxiety, however, was done for two reasons in the screening tool studies. First, the tools were designed for clinical use where information of the cut-off point for increased risk is needed. The other reason was that we wanted to validate the second diagnostic tool in two different datasets, and the use of different questionnaires between studies made the exact comparison difficult. Therefore, the compromise was to use diagnostic categories of depressive symptoms and anxiety.
6.2.2.2.3. Depressive symptoms
Depressive symptoms were not an independent predictor of pain in this study. However, for the predictors for acute pain trajectories, depressive symptoms were combined with reported anxiety to form a variable to represent overall psychological burden (distress). That aggregated factor was a good predictor of acute pain intensity. The covariation of psychological symptoms is high (Ball et al., 2002; Kircanski et al., 2016), but this is rarely acknowledged in breast cancer pain studies (Andersen et al., 2015; Katz et al., 2005; Rehberg et al., 2017).

We found that higher depressive symptoms at one year were associated with pain experience at that time. Women with higher pain reported more depressive symptoms. It should be emphasized that depressive symptoms preoperatively measured did not have predictive value for pain persistence. However, depressive symptoms were more of an outcome of pain. Previous studies support this conclusion that depressive symptoms follow rather than precede pain (Knaster et al., 2012; Schreiber et al., 2013), and, more importantly, their concomitant presence makes the treatment of both more difficult (Edwards et al., 2016; Gureje, 2008). This finding underlines the importance of prospective studies so that we may better explain the causalities between mood factors and pain.

In conclusion, anxiety seems to be a better predictor of pain, whereas depressive symptoms manifest when the pain has become persistent. Depressive symptoms related to the interference and threat that pain evokes are understandable and normal reactions (Morley, 2008). Negative affect and loss of energy, signature features for depression, have an influence on how a person can handle different stress factors in her life such as ongoing pain.

Symptoms of depression and anxiety are common in breast cancer survivors (Maass et al., 2015), and depressive symptoms are reported to develop during the first year after breast cancer diagnosis (Maass et al., 2015). Lowered mood has an influence on a variety of health-related factors and quality of life (Champion et al., 2014; Lehto et al., 2005; Kokkonen et al., 2017). A recent study reported that a combination of depressive symptoms and anxiety was quite common at six months after breast cancer surgery (Gold et al., 2016), and it was associated with several negative outcomes such as lower performance status, greater difficulty dealing with disease and treatment, and less perceived support from others. These women also had lower physical and psychological quality of life, and increased fears of recurrence. Furthermore, female gender and presence of anxiety are known risk factors for the development of depression (Markkula N et al., 2016). Both of these factors
were present in this study, and they were also significant for the pain experience. Some studies suggest that negative emotions may have an unfavorable effect even on cancer survival (Hjerl et al., 2003; Lehto et al., 2006).

6.2.2.2.4. Anger regulation
It is commonly acknowledged that cognitive and emotional processes, such as anxiety, depression, and pain expectation, affect pain, but it is not known whether the manner in which a person usually expresses her anger is meaningful to the pain experience in a breast cancer cohort. The results of this study imply that anger regulation is more meaningful to mood than to pain outcome in breast cancer patients. This is the first study done to evaluate anger regulation and both experimental and post-treatment pain in women with breast cancer. A previous study examining postoperative pain in male patients found higher anger expression to predict higher pain intensity (Bruehl et al., 2006). Contradictory findings between anger regulation and other types of pain have also been reported (Bruehl et al., 2009; Bruehl et al., 2012; Materazzo et al., 2000; Nisenzon et al., 2014; Sayar et al., 2004).

A variety of factors have been suggested to be meaningful in how anger regulation affects pain. Gender (Bruehl et al., 2007; Burns et al., 1998), modality of pain (Bruehl et al., 2003; Sayar et al., 2004), and mood (Knaster et al., 2008; Burns et al., 2008; Materazzo et al., 2008) are possible mediating factors. Anger regulation is considered a rather stable behavioral trait. However, long follow-up studies describing how this trait evolves over the lifetime or during dramatic life experiences, like cancer, are not available. Age is rarely controlled in studies of pain and anger regulation, and in this study age was found to be an important predictor for how anger is associated with pain. The result that the association between higher anger expression and higher analgesic requirement and higher pain expectation was non-significant after controlling for age indicates that age indeed is an important mediator between anger regulation and pain. Anger expression outward was more common in younger patients, whereas inhibition of anger was associated with older age. This is also reported in the theory of anger regulation (Spielberger, 1999). This could indicate that anger regulation changes with lifetime experiences. Reporting of anger regulation may be biased due to social expectations. This may also explain some differences between patient groups and age.

Our finding that anger regulation has only a marginal independent effect on pain experience does not rule out the possibility that it may mediate how e.g. mood factors affect pain, and especially coping with pain. Ongoing depression is potentially a risk for more perceived pain and disability in
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breast cancer patients (Bruce et al., 2014; Miaskowski et al., 2012). Results of this study suggest a close relationship between ongoing depression and emotional suppression (anger inhibition) in the three-year follow-up. Anger inhibition and depressive mood are plausibly parts of the same mood and behavior constellation, negative affect (Burns et al., 2008; Materrazzo et al., 2008). Future research is needed to clarify whether also the tendency to expect higher postoperative pain is part of this constellation. Expression of negative emotions has been shown to be beneficial for the quality of life of breast cancer patients (Lieberman & Goldstein, 2006), whereas anger inhibition was found to be associated with less perceived spousal support in cancer patients (Julkunen et al., 2009). Lack of partner support and increased depressive symptoms may therefore have a major influence on how well a person adjusts to her life with treated or ongoing breast cancer and how well she can manage fearful thoughts and rumination about the recurrence of cancer.

6.2.2.2.5. Anger regulation and OPRM1 rs1799971 (A118G) and COMT rs4680 (Val158Met) genotypes

Like previous studies (Bruehl et al., 2006; Bruehl et al., 2008), we found no significant direct associations between OPRM1 rs1799971 genotype and anger expression or anger inhibition. Our study did identify a statistically significant association between COMT rs4680 (Val158Met) and anger expression. The reports of anger expression increased with the number of G allele carriers. This COMT gene variant has earlier been associated with a history of suicidal attempt (Baud et al., 2007; Rujescu et al., 2003) and aggressive behavior (Jones et al., 2001). Previous studies assessing the associations between anger regulation and COMT (Val158Met) have produced conflicting results (Baud et al., 2007; Rujescu et al., 2003). This is a preliminary finding and needs to be further investigated. However, it seems that the association of the COMT G/G genotype and anger-out is stronger in certain patient groups (suicide attempters) (Baud et al., 2007) and that it modulates the influence of environmental factors (Perraud et al., 2010). It has been suggested that COMT Val carriers may be more vulnerable to epigenetic changes (Perraud et al., 2010). Therefore, early life stressors may influence emotional regulation and the chosen survival strategy in stressful life-situations, including pain and cancer.
6.2.3. PAIN PREDICTION TOOL

Upon identifying the risk factors for pain, the next step is to devise an easy method to reliably screen women likely to develop a persistent pain condition after breast cancer surgery. This is important in order to find ways to prevent postoperative pain. Here, two different screening tools were developed. In the first, preliminary prediction tool study (Study III), the follow-up period was six months and the independent variables were slightly different compared with the second model (Study V). In the second study, four different models were developed, and the variables available after the first week were included in the final model. As the screening tool was developed further, a consistently shown risk factor, the intensity of acute pain, was included in the model. This second tool was validated in two different datasets. Therefore, only variables common to all datasets were chosen for the analyses. Two variables that were important in the preliminary six-month prediction tool, i.e. previous smoking and number of previous operations, were left out for this reason. Some compromises, concerning e.g. psychological variables, were also necessary to make the data more concordant. However, the risk factors for persistent pain were replicated in all datasets: preoperative pain in the operated area, acute pain intensity, ALND, and obesity. This is the first study that has validated the developed risk tool.

Development of a diagnostic tool is always a trade-off between sensitivity and specificity. To find as many patients as possible who will probably develop persistent pain, the tool needs to be sensitive. On the other hand, high sensitivity comes at the cost of low specificity; i.e. among the selected women is a subgroup not at risk for persistent pain (false-negatives). The selection of the criteria is based on the needs of the diagnostic tool. If the intervention is psychological or a more intense follow-up after breast cancer surgery, sensitivity is more relevant than specificity. However, if the intervention is e.g. preventive medication, specificity should be as high as possible so that the medication with possible side effects is not targeted to women who do not actually need it. In this study, the model was aimed to be as specific as possible. The developed tool finds with a high certainty (>90%) those women who are at high risk.

A false-positive prediction may cause anxiety and fear, focusing the patient’s attention on the surgical area. In the worst case scenario, it may work as a self-fulfilling prophecy, as we know that expectancy of specific symptoms may sensitize to the development of pain (Atlas & Wager, 2012; Tracey, 2010; Colloca & Benedetti, 2006). Although, this prediction model does not find all women at heightened risk (low sensitivity), only few will have false-positive risk estimation.
Persistent pain after breast cancer treatments may in part arise from a different process than in other surgeries. Therefore, the developed screening tool may not work universally for all surgery types, although it definitely includes some of the components that are risk factors for pain persistence more broadly.

6.3. STUDY LIMITATIONS

6.3.1. Questionnaires

Measuring psychological constructs is difficult and no matter how well designed a questionnaire is there is always the possibility of misunderstanding and bias. The psychological questionnaires (BDI, STAI, and STAXI-II) that were used in this study have not been validated in cancer patients in Finnish cohorts. However, they have been widely used and found to be reliable and valid scales to measure these psychological constructs. Their specificity in cancer patients remains unknown. In this study, trait anxiety was reported to be higher preoperatively than in the follow-ups, even though it should measure a quite stable behavioral trait. This may suggest that scales designed to measure mood in a healthy population may perform differently in cancer patients. There is no gold standard regarding measurements to use in this specific group of patients. However, a study with advanced cancer patients showed good validity and reliability of measuring depressive symptoms with BDI (Warmenhoven et al., 2012). No such study exists with a sufficient number of patients for the STAI scale.

Also, the well-recognized problem of covariation between the scales used brings up the question if significant predictors of pain persistence dropped out from the models because of this problem. Covariation between other studied variables, e.g. cancer severity index, surgery type, and adjuvant treatment, is an unavoidable problem. A strength of this study may also be viewed as a limitation; we used a wide range of questionnaires to evaluate both pain and psychological variables. It may be exhaustive for a patient to fill in long questionnaires, which in turn may have an effect on how reliable the answers are. However, the questionnaires of pain-related catastrophizing or surgical worry may have brought more information about risk factors for heightened pain experience in this cohort.

Despite good validity in measuring pain intensity with NRS, it is not an objective measure of pain and may be sensitive to reporting biases. Cancer patients may either over- or underestimate their
pain ratings regarding the attribution of the cause of pain (Smith et al., 1998). Measuring pain is always a patient’s subjective evaluation of how interfering or severe the pain is. This subjective rating includes the person’s life history of pain, expectations of pain, and the context in which the pain is measured (Carlino et al., 2014). This was seen also in this study. Pain expectation influenced the reporting of pain.

6.3.2. Study protocol

Patients were very intensively attended to by our research nurse pre- and postoperatively. Patients had the possibility to contact the research nurse if they had problems with pain or recovery. This may have brought an extra sense of security and may have influenced mood and hypothetically also pain ratings positively.

6.3.3. Statistical analyses

Statistical significance is not the same as clinical significance. Statistical risk represents the odds of a risk occurring. However, the reality in a patient’s life is far more complex and unpredictable. In a study, we cannot control all possible factors that explain, for example, pain persistence. In a paradoxical way, the most reliable statistical model is one where the independent factors are reduced to a minimum. Risk models are often built to contain factors hypothesized to be the most likely to explain dependent factors. The results thus reflect the factors we have tested, and we most likely test factors that have previously shown a predictive tendency. Therefore, new statistical approaches are needed to uncover new predictive factors. For example, the big data analyses (Gerbershagen et al., 2014) from a large dataset may also yield new perspectives in research of breast cancer cohorts.

As seen also in this study, the statistical approach applied affects to some extent the results. The use of categorical versus continuous variables as a dependent variable has an effect, as discussed earlier. Also, the choice of the regression model may affect the results. The widely used binary regression model loses some information about the outcome variable. The cut-off limits for risk versus no-risk groups are often clinically attributed. For example, a cut-off line for clinically significant pain is often NRS ≥ 4 (Gerbershagen et al., 2011), but in some individuals NRS 3 may have a significant impact on everyday activities and mood. Therefore, the linear regression model may,
in some cases, be more sensitive in detecting the dimensional variability of the studied variables. Both statistical approaches are correct, but the reader needs to be aware of the differences between the methods.

6.4. STRENGTHS OF THE STUDY

The most important strength of this study is the large number of participants, allowing the use of multivariate analyses in a reliable way. Other strengths are the carefully described perioperative and acute postoperative phases and the great number of studied variables and pain and psychological symptoms. The wide range of pain-related variables, experimental, pre- and perioperative, and follow-up information, and evaluation of the core of mood factors from the same individuals give a good picture of these phenomena in this patient cohort. Another noteworthy strength is the prospective study design, which allows the study of causalities. Most studies done with breast cancer patient cohorts are cross-sectional in nature. The prediction tool that was developed is easy to use in clinical practice and offers a simple way to select women for future preventive studies. Validation of the prediction tool in two different prospective datasets gives it reliability.
7. CLINICAL IMPLICATIONS AND FUTURE PERSPECTIVES

The most clinically relevant result of this study was the developed and validated screening instrument. Furthermore, the risk factors identified for higher acute pain are important to recognize, and intervention should occur most optimally in the preoperative phase or in the acute pain phase. This is important for several reasons. Minimizing the suffering of individuals is paramount. Another reason is that heightened acute pain is a good predictor of pain persistence. A further concern is treating the pain caused by surgery as well as possible before adjuvant treatments begin approximately one month postoperatively.

Depressive symptoms and anxiety remained fairly stable “traits” in some individuals in the follow-up. The significance of this finding in the pain process warrants further investigations. Perhaps, instead of only measuring mood factors preoperatively as a predictive factor, a more meaningful way to elucidate their role in the process of pain becoming persistent would be to follow the change of mood factors over time at least through adjuvant therapies. The finding that anger inhibition combined with depression remains stable in a long follow-up suggests this as a possible target for psychotherapeutic intervention.

Pain expectation explained one part of the difference in pain sensitivity and acute pain intensity. The role of higher expectation of pain, representing possibly placebo and nocebo effect, is an important finding for clinical practice. Pain expectation is easy to screen, and by identifying patients with higher expectations, it is possible to determine its source and to intervene in the expectations. In addition, healthcare professionals should not enhance these expectations when preparing patients for surgery. Information about effective medication and the average intensity of acute postoperative pain after breast cancer surgery is recommended, and sufficient, for most patients. However, the close relationship between anxiety and pain expectation suggests that some patients would benefit from psychological consultation. Anxious women, with preoperative pain and high expectations of postoperative pain could be a target for intervention. Psychological interventions could include, for example, training to acknowledge the habit of negative thinking, expectations, and biased attention towards pain. Future research is needed to see if managing these risk factors for higher pain experience could lower the risk of their mediating role in the path of pain persistence and potential development of depression.

The mood scales used in this study were time-consuming to fill in and were not specifically designed for this patient group, and therefore, may not have been selective enough in this cohort.
Psychometric research of different scales is a very important target for future studies. Selection of the best and most targeted questions of all scales used could more specifically find those psychological dimensions that are important for pain experience and its persistence in this patient group. Different psychological factors, e.g. catastrophizing and surgical fear, should also be included in the models. The fear of recurrence may bring its own challenge in this group of patients and may have an effect on the descending modulation of pain through anxiety, fear, and negative expectations.

There is still much that we do not know about the pain experience and its persistence in women treated for breast cancer. The experimental pain tests revealed groups of high and low pain-tolerant individuals. Closer study of the underlying factors related to the hypothesized more efficient endogenous descending pain mechanisms could bring new knowledge about pain modulation in this cohort and, more importantly, how this is related to the risk of pain persistence. However, this study gives good perspectives for designing new research in this field. Therefore, the developed risk tool should be used in future studies to find new predictive factors. Prospective studies with longer follow-up periods are needed to see how pain and the factors associated with persistence plausibly evolve. We now know that breast cancer and pain related to its treatments are risks for lowered mood. The next step would be to clarify how trajectories of mood changes after breast cancer surgery impact on pain in post-treatment years.

We focused on risk factors in this study. Future studies should also focus more on those factors that are protective of pain persistence, in other words, to determine a balance between vulnerability and resilience factors. After all, the majority of women after breast cancer treatments do not develop any pain condition. The information of the protective factors behind a favorable pain path may also help those women who are at risk of developing a pain condition. Many women will have all the risk factors and still will not develop persistent pain. It is therefore important to be aware that studies merely describe the statistical risk for pain. However, an individual patient is far more complex to predict.
8. CONCLUSIONS

Conclusions to study aims:

1. Experimental pain sensitivity varied widely between women undergoing surgery for breast cancer. The modality of experimental pain seems to be important when examining the association between experimental pain and clinical factors. Higher level of state anxiety and previous pain condition were significant variables explaining both experimental pain sensitivity (regardless of modality) and postoperative analgesic consumption. Younger patients were more sensitive to postoperative pain measured by the amount of required analgesics. However, age did not explain the variety in experimental pain sensitivity.

2. Risk factors for higher pain experience, both acute and persistent, in breast cancer patients were identified and found to be quite similar. More invasive surgery, presence of preoperative pain (other chronic pain or pain in operative area), and mood, especially heightened anxiety, were the most consistent predictors of pain experience. Expectation of higher postoperative acute pain predicts higher acute pain intensity. Obesity and received adjuvant therapies were associated with persistent pain. Also the intensity of acute pain predicted higher pain intensity at one year. The meaning of previous pain in pain experience after breast cancer treatment is an important clinical observation since chronic pain due to several reasons is common, especially in females. Pain tolerance or threshold from experimental pain is not enough to explain the complex process of either acute or persistent postoperative pain.

3. Psychological symptoms, anxiety, depressive symptoms, and pain expectation are linked to the pain experience in women with breast cancer. State anxiety seems to be particularly relevant to heightened acute pain experience and analgesic use, whereas trait anxiety is meaningful for pain persistence. Anxiety variables are highly correlated, which leads to the conclusion that overall proneness to anxiety is important for heightened pain experience. Depression, however, did not have an independent predictive value for heightened pain experience, although it was more common at one year in women with persistent pain. The contribution of anger regulation to the pain experience was modest in this patient group. However, anger inhibition is closely associated with depressive symptoms and is therefore important to recognize. The presence of anxiety is
important to screen because it is associated with pain sensitivity and more intense pain experience. Depression most likely persists in individuals with difficulties in expressing negative emotions such as anger.

4. Clinically feasible predictive tools to screen women at risk for persistent pain were developed. The prediction tool with a one-year follow-up and with all available women was validated in two separate cohorts. The absence of psychological factors in risk models does not mean that they are not relevant to pain.

Better knowledge of singular risk factors will help us to understand why some patients are more vulnerable to pain persistence than others. The developed models explained only a portion of the persistent pain, highlighting the importance of continuous research in this field. New treatments to prevent the progression of the undesirable pain path from preoperative through acute to persistent should be studied. Future research should elucidate why when many/all of the risk factors are found in some women, the risk is actualized in only a portion.
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This journey has taken me through all the emotions studied here, from state anxiety to more prominent trait anxiety, through a more sophisticated way to express anger (In) to open rage (Out). Fortunately, the resilient part of me protected me from depression. What a great adventure!

Sincerely,

Reetta
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