THE RELATIONSHIP BETWEEN MENOPAUSAL STATUS AND PAIN AFTER BREAST CANCER SURGERY

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ABSTRACT

Women often undergo surgery as treatment for breast cancer, which results in moderate-to-severe acute postoperative pain (APOP), and in some patients transitions into chronic pain. Given that pain is influenced by a multitude of biopsychosocial factors, it is important to continue identifying those which affect individual postoperative pain (POP) experiences. This study examines the relationship between menopausal status and breast cancer surgery (BCS) pain. Women were divided into groups by menopausal status, and examined on four pain outcomes: prevalence, intensity, quality, and impact on quality of life (QoL) one week and six months postoperatively. Using chi-square tests and ANCOVAs, it was found that PRE-M women were more likely to exhibit persistent pain, but LP-M women had a higher prevalence of neuropathic-type pain and worse long-term mental health outcomes. Our results support the biopsychosocial model of pain, and highlight menopausal status as an important factor when considering pain management strategies.

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ABBREVIATIONS

Abbreviation	Meaning
ALND	Axillary Lymph Node Dissection
APOP	Acute Postoperative Pain
BCS	Breast Cancer Surgery
BPI	Brief Pain Inventory
CCI	Charlson Comorbidity Index
CES-D	Centre for Epidemiologic Studies – Depression Scale
CNS	Central Nervous System
CPOP	Chronic Postoperative Pain
HRQoL	Health-Related Quality of Life
IASP	International Association for the Study of Pain
EP-M	Early Postmenopause
GABA	Gamma-Aminobutyric Acid
LP-M	Late Postmenopause
NRS-M	Numeric Rating Scale - Movement
NRS-R	Numeric Rating Scale - Rest
NWC	Number of Words Chosen
NSAIDs	Nonsteroidal Anti-inflammatory Drugs
OVX	Ovariectomized
PCS	Pain Catastrophizing Scale
PRE-M	Premenopause
PERI-M	Perimenopause
POP	Postoperative Pain
RA	Research Assistant
SF-12	Medical Outcome Study (Short Form)
SF-MPQ	McGill Pain Questionnaire (Short Form)
SF-NPQ	Neuropathic Pain Questionnaire (Short Form)
STAI-S	State-Trait Anxiety Inventory – State Subscale
STAI-T	State-Trait Anxiety Inventory – Trait Subscale
SLNB	Sentinel Lymph Node Biopsy
SOMC	Short Orientation-Memory-Concentration
QoL	Quality of Life

INTRODUCTION

Breast cancer is the most common cancer affecting Canadian women, with an estimated prevalence of 1 in 8[1]. The current five-year survival rate is 87%, and mortality has been on a steady decline over the past forty years[1]. Surgery, the first line of treatment, results in APOP in 15-60% of patients[2,3]. Poorly controlled APOP is associated with increased morbidity, functional and QoL impairment, delayed recovery time, prolonged duration of opioid use, and development of chronic postoperative pain (CPOP)[4]. The increasing survival rate means more women are living longer with the negative effects of BCS. Thus, further research into factors that contribute to persistent POP and associated negative outcomes is necessary.

Breast Cancer Surgery

Most women diagnosed with breast cancer undergo either a lumpectomy or mastectomy[1], which may include sentinel lymph node biopsy (SLNB) or axillary lymph node dissection (ALND)[1]. Lumpectomy is a breast-conserving surgery, resecting only the tumour and a small margin of healthy tissue, whereas mastectomy removes the entire breast[1]. In SLNB, the first lymph node is removed with the tumour and if cancer is present, patients will often undergo ALND, which removes 10-30 lymph nodes in the axilla region, to determine the extent of metastasis and attempt to stop disease progression. The recommended surgery depends on breast size, tumour size and location, spread to the lymph nodes, and risk of recurrence[1]. BCS is associated with moderate-to-severe APOP in the ipsilateral shoulder, arm, and hand[5]. Up to half of patients will transition into CPOP[6], namely pain persisting for ≥3 months following surgical healing[7].

Pain: Definition and Theories

As defined by 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"[8]. Nociceptive pain results from activation of peripheral sensory neurons by an intense mechanical, chemical, or thermal stimuli[9], and is usually described as throbbing, aching, or pressure-like[10]. It is short in duration and fades as the peripheral driving force is removed[9]. Inflammatory pain is the heightened pain sensitivity that occurs due to release of sensitizing inflammatory mediators in response to tissue injury, but usually resolves once the wound has healed. However, if the source of inflammation persists, so will the associated pain[9]. Finally, pain can also be neuropathic in origin[11] – caused by a lesion or disease of the somatosensory nervous system[12] – and is typically described as lancinating, shooting, stabbing, or electric-like[10]. A key aspect of neuropathic pain is the combination of sensory loss with paradoxical hypersensitivity to produce spontaneous sensations[9]. Features that are associated with neuropathic pain are allodynia – pain from a stimulus that does not normally cause pain, and hyperalgesia – increased pain from a stimulus that normally causes pain[9,13].

Prior to the acceptance of the current model of pain processing, the prevailing view involved a signal relay that conveyed peripheral noxious stimuli to the central nervous system (CNS)[14]. That is, the pain pathway was regarded as a series of anatomical connections, linking sensory input generated in the periphery with the spinal cord, brain stem, thalamus, and cortex, resulting in conscious awareness of painful sensations[14]. In 1965, Melzack and Wall proposed the Gate Control Theory, postulating that transmitted impulses from the periphery are, in fact, integrated with other afferent neurons, interneurons, and descending modulatory signals at the dorsal horn of the spinal cord[15]. The balance between facilitatory and inhibitory impulses will

determine if the gate at the dorsal horn will be "open" or "closed", dictating whether the signal will be propagated to higher regions of the CNS[15,16]. The Gate Control Theory continues to be the most widely accepted model of pain, but has since been refined to posit that pain is a multidimensional experience generated by a complex neural network in the brain – the neuromatrix[17,18]. The neuromatrix encompasses visual and auditory inputs, cognitive and emotional contributions (cultural learning, personality, etc.), as well as the body's stress-regulatory systems[18]. This expansion in our understanding of pain as being influenced by a multitude of innate and environmental factors, gave rise to the biopsychosocial model[19]. It explains individual variability in the pain experience through dynamic interaction among biological, psychological, and social factors, which create, perpetuate and may even worsen clinical presentations[20]. People experience pain uniquely, and a range of factors can interact to modulate report of symptoms and disability[20]. The biopsychosocial model is now widely accepted; however, the range of factors that may contribute to pain remains to be fully established.

Pain Following Breast Cancer Surgery

Tissue damage triggers a cascade of immune, endocrine, and nervous system responses, which result in activation of nociceptors, inflammation, and in some cases nerve injury[9,21]. Many patients experience pain aggravated by movement, touch, breathing, coughing, and even gastrointestinal motility[9]. The damaged cells release endogenous mediators that activate nociceptors[22] and can lead to sensitization[23,24]. Peripheral sensitization is defined as a reduced activation threshold in peripheral nociceptors and increased frequency of stimulus-evoked action potentials[10]. This hypersensitivity reduces the intensity of the stimulus needed to induce pain, but

once the source of mediators subsided with healing, so does this form of hyperexcitability[9]. Tissue injury in the periphery can also induce changes in the CNS that contribute to increased sensitivity[14]. Central sensitization is first induced by the constant action potentials evoked by noxious peripheral stimuli (such as during POP) and the subsequent synaptic activity generated in the dorsal horn[9,25]. After tissue injury, there is an alteration in sensory neurons and spinal cord gene transcription that amplifies the release and action of excitatory transmitters and reduces inhibitory transmitters. This leads to responsiveness of neurons to normally innocuous or insufficient inputs[26], and the spread of sensitivity well beyond the peripheral site of injury[9,27]. Importantly, prolonged sensitization is associated with permanent neuropathological changes that may contribute to extended recovery time[28] and the development of chronic postoperative pain (CPOP)[29]. Many patients generally respond well to opiates and nonsteroidal anti-inflammatory drugs (NSAIDs), such as COX inhibitors, and will recover uneventfully. A subset of patients will exhibit a continuous inflammatory response, and for some, neuropathic-type pain can becomes resistant to analgesics due to the absence of an apparent noxious stimuli or inflammation[9].

APOP after BCS differs in intensity between patients, ranging from minimal to severe[30]. Research in anesthesia and pain management indicates that although opioids are the mainstay of systemic treatment for moderate-to-severe POP, doses of opioids producing complete relief of resting pain actually have relatively little effect on movement-evoked pain[31]. Furthermore, it is equally important to distinguish between resting and movement-evoked POP in terms of their physiological effects. While assessment of the intensity of APOP at rest is important for making the patient comfortable, adequate relief of dynamic pain during movement, deep breathing, and coughing is important for reducing risks of cardiopulmonary and thromboembolic complications[31]. This study measured both pain at rest and with movement. It is also important to

assess the sensory qualities of pain, because describing it solely in terms of intensity does not adequately convey the depth of the experience. Understanding the quality of a patient's pain can help identify treatments that are effective for certain types of pain independent of pain severity[32]. The Short-Form McGill Pain Questionnaire (SF-MPQ) is a multidimensional measure that assesses sensory and affective qualities of pain. In this study, the most commonly chosen descriptive words and the number of words chosen (NWC) to describe pain (derived from the measure) were used to quantify the sensory qualities of pain within the given population. Neuropathic pain in the acute postoperative period occurs simultaneously with nociceptive pain[33], but few studies distinguish between them despite different etiologies and management strategies. The Short-Form Neuropathic Pain Questionnaire (SF-NPQ) was administered after surgery to assess specifically for neuropathic symptoms.

Acute pain usually resolves as damaged tissues heal, but its persistence is an established risk factor for CPOP[30], which affects up to 50% of BCS patients[6]. The convention established by the International Association for the Study of Pain (IASP) is that pain can be considered chronic when it has persisted beyond normal healing time, with 3 months being considered an appropriate division point between acute and chronic pain[11]. Persistent pain after BCS can occur for a number of reasons including tumor recurrence, complications of radiotherapy, chemotherapy[11], ongoing inflammation, or neuropathy[9]. CPOP often leads to physical and psychosocial sequelae that affects survivors' QoL[34]. QoL represents subjective evaluations of oneself, one's social and material world, and reflects the extent to which s/he is satisfied with them. It is an intersection of physical, mental, and social wellbeing[35]. Breast cancer mortality rates have been declining since the mid-1980s[1], which means that many women will survive the disease. However, women with CPOP report impaired work[36], life enjoyment, less energy[34] and

poor physical and psychological health[35]. Many have significant limitations in arm function including decreased strength and range of motion[37]. Using multidimensional assessments of depression and anxiety, two of the most commonly reported psychological issues for cancer patients[38], as well as questionnaires about health-related quality of life (HRQoL) we examined the impact of chronic pain on women's experience after BCS.

Risk Factors for Postoperative Pain

Variability in APOP and CPOP after BCS, may be attributed to the biopsychosocial or surgery-related characteristics of each woman. Younger age[39], comorbidities[40] and extent of ALND[12] have been shown to predict APOP, which is associated with the development of CPOP[41]. In research, emphasis is often placed on established chronic pain, rather than early cues of its development[39]. Surgical factors that have been linked to an increased likelihood of developing CPOP are longer duration of surgery[42,43], type of stitches[44], and intraoperative nerve damage[45,46]. Moreover, evidence also points to several psychological predictors including higher preoperative depression[30] and anxiety[43], introverted personality[39], catastrophizing (a tendency to magnify or exaggerate the threat value of various circumstances, including pain sensations)[47] as well as fear of surgery, among others[39]. One of the most consistent factors associated with the development of acute and CPOP is concurrent or past pain[39,41,48–51], but the prevalence of preoperative pain in the breast cancer population is low[40].

Consistent with the biopsychosocial model of pain, Jung et al.[11] note associations among several risk factors for APOP and CPOP after BCS. They recommend examining whether each variable is an independent risk factor or if the development of pain can be explained by its relationship with other demographic, clinical, and psychosocial variables. A large number of

studies show that sex differences exist in the human and animal pain experience[52–60,64–66], and gonadal hormones have often been suggested to have an effect. However, given that pain is a biopsychosocial construct, it may be important to consider hormones simultaneously with other factors. Menopausal status has not been studied extensively in relation to POP, but may be an important variable to consider in women's experience after BCS.

Sex Differences in Clinical Pain

Epidemiological research consistently demonstrates differences in pain prevalence, frequency, and severity between the sexes[52]. The population prevalence of several common pain conditions including fibromyalgia, migraine, irritable bowel syndrome, temporomandibular disorders, and interstitial cystitis[53] is greater in women than men[54]. Furthermore, acute head, facial, abdominal, and musculoskeletal pain are more frequent in women[55]. Women also report more chronic widespread pain[56] as well as pain-related disability than men do, and are more likely to consult physicians for it[55]. Several investigators examining patients seeking care for chronic pain, report greater severity among women[57–60], while others have found no such differences[61–63]. Sex differences in pain severity have also been studied in relation to post-procedural or postoperative pain. Results from these studies have been inconsistent and conflicting, with some finding greater severity among women[64–66], others greater severity among men[67], and still others reporting no sex differences[68]. However, the general trend is towards greater acute post-procedural pain in women[52]. Given that the severity of APOP is an established risk factor for persistent POP, transition to chronicity has also been suggested to be more prevalent in women[39].

A variety of organizational and activational mechanisms have been proposed to account for these sex differences, and likely produce an interaction of biological, psychological and

social factors[52]. There is evidence suggesting sex differences in the cortical regions involved in pain processing[42-46], in the endogenous opioid system[74], and genotype[75,76]. For example, animal studies suggest that early (neonatal) exposure to testosterone may be necessary for the development of the adult male phenotype – less sensitivity to noxious stimuli – for mechanical, thermal, and stress-induced stimulation[77–80], but not for inflammatory nociception[81]. Moreover, women have more comorbid mood and physical disorders than men that are likely to affect pain treatment and outcomes[82]. Psychosocial mechanisms may also contribute to sex-related differences in pain. For example, pain coping strategies have been found to differ between men and women. While men often use behavioural distraction or problem-solving to manage pain, women tend to use social support, positive self-statements, emotion-focused techniques, and cognitive reinterpretation[53,83,84]. Sociocultural beliefs about femininity and masculinity have been examined in relation to pain, and it has been suggested that gender role expectations influence pain expression, tolerance and ratings of experimental pain (heat, pressure, chemical irritants, etc.)[85,86]. The most frequently proposed explanation for sex-related differences in pain involves the contribution of female gonadal hormones (estrogen and progesterone), as testosterone appears to be generally anti-nociceptive[52,87].

Female Gonadal Hormones and Pain

Estrogen and progesterone are two of the female gonadal hormones, mainly produced by the ovaries[88]. They fluctuate on a cyclic basis during a woman's reproductive years[55]. Pain transmission involves peripheral as well as CNS events, where gonadal hormones have been suggested to play a role[55]. By extension, it has been proposed that pain sensitivity changes with different phases of the menstrual cycle due to different hormonal milieu[55]. This relationship is usually studied using experimental pain stimuli and may depend on the stimulation method[55].

Consistent with gate control theory, estrogen and progesterone may be involved in nociception at multiple levels (diagram 1)[87], exerting both pro-nociceptive and anti-nociceptive effects under different circumstances[89].

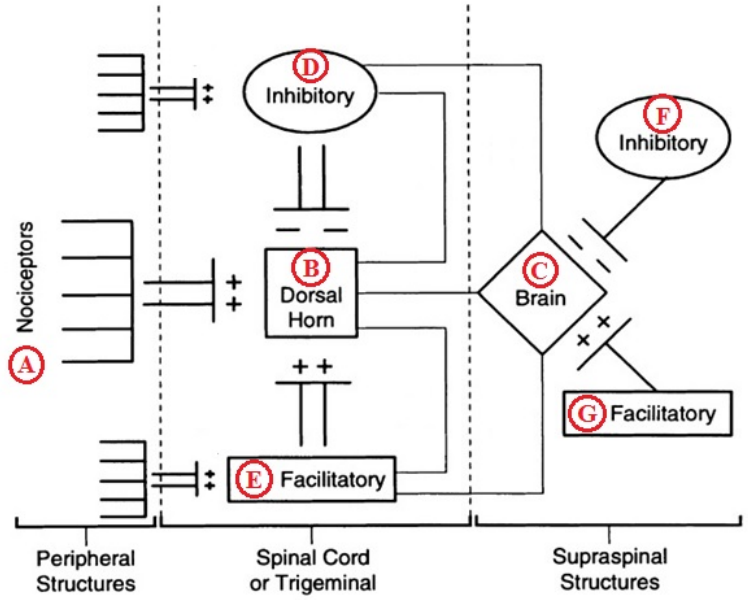


Diagram 1
Schematic illustration of ascending and descending pathways involved in pain transmission and potential sites for hormonal modulation (adapted from Fillingim and Ness, 2000).

Firstly, they can affect nociception at the primary afferent input level. (A) For example, progesterone has long been suggested to elicit anesthetic activity and decrease nerve conduction[90]. (B) Estrogen has been demonstrated to acutely upregulate and chronically downregulate levels of trkA (Nerve Growth Factor receptor; binding of the two leads to nerve sensitization) in the dorsal root ganglion neurons[91]; thereby (D) inhibiting or (E) facilitating pain transmission at the spinal cord level. Similar interactions occur in higher order neurons such as those found in the basal forebrain[87]. Estrogen also increases levels of neuromodulators involved in spinal nociceptive processing like GABA[92], glutamate and serotonin[55]. (C, F, G) In addition to their effects on primary afferents, gonadal hormones influence multiple CNS pathways involved in pain transmission. Estrogen and progesterone have been shown to provide feedback modulation of luteinizing hormone levels[93], and LH in turn desensitizes (F) brain opioid

receptors[87]. Smith et al. demonstrated a negative correlation between circulating estradiol and μ-opioid receptor binding in the hypothalamus and amygdala[94].

Any gonadal hormone influence on pain processing likely results from actions at multiple peripheral and CNS loci[87], where the net effect on pain depends on the additive effects of their pronociceptive and antinociceptive effects[55]. However, the biological mechanisms of these effects are beyond the scope of this study. Research suggests that women are more sensitive to clinical and experimental pain than men[52,54,64,82,87-88], and many studies support an effect of gonadal hormones[55,78,87-89]. However, there is no consistent evidence regarding the pattern and direction of this relationship[95], or a consensus as to which menstrual stage, if any, is associated with the greatest sensitivity[89].

Menopausal Status

Research is not yet conclusive, and sometimes even contradictory, with regards to the involvement of estrogen and progesterone in pain perception but continues to suggest an interaction of many biopsychosocial factors that affect pain sensitivity. In women, there is growing evidence suggesting an evolution in the characteristics of clinical pain in response to different hormonal states, and specifically menopausal status changes[96]. Therefore, menopausal status may be an important factor to examine in studying the variability in women's pain experience after BCS.

Chronological age has in the past been used as a proxy for menopausal status[97]. Morabia and Flandre found that in the absence of sufficient menstrual history, using a cutoff age of 50 to classify women as postmenopausal offers the highest accuracy or the lowest false positivity[98] and depending on the purpose of a study, an age-based definition may be sufficient and could save

time and resources in data collection[97]. However, in many epidemiologic studies of breast cancer, menopausal status is either a key main effect, covariate, or stratification factor and differences in definitions raise questions about the comparability of findings based on those classifications[97]. Cycling women undergoing breast cancer treatment such as chemotherapy may experience temporary amenorrhea or early menopause as a result of the toxicity to the ovaries[99]. Among other factors, these side effects vary according to a woman's age at the time of treatment[100,101]. Moreover, it has been shown that QoL (unrelated to pain) in postmenopausal women is worse than in women of the same age who are still regularly menstruating[102], suggesting age is not an adequate proxy of menopausal status and may therefore have an independent influence on pain responses. In order to remain consistent with current recommendations, the present study uses a more appropriate, menses-based definition.

Consistent with World Health Organization recommendations[103] as well as the Stages of Reproductive Aging Workshop[104], this study identifies four distinct menopausal status categories. Premenopause (PRE-M) is characterized by regular gonadal hormone cycling on a monthly basis, and in North American women usually lasts from 12.7 to 45.1 years of age[105,106]. Perimenopause (PERI-M) is a transition stage, for which the age of onset is between 39-51 years and on average lasts about 5 years[106]. It is marked by changes in the pattern of menstrual cycles and appearance of symptoms such as hot flashes, breast tenderness, vaginal dryness, and sleep disturbances[106]. Finally, the absence of menses over a 12 month period indicates transition into menopause, and in Canadian women is usually reached by age 52, but can occur naturally between the ages of 42 and 56[97]. It is a permanent cessation of estrogen and progesterone production by the ovaries which eliminates fluctuations[107]. If a woman has reached menopause within the last 1-5 years, she is in early postmenopause (EP-M), while if it has been over five

years, she is in late postmenopause (LP-M). The postmenopausal period can encompass up to a third of a woman's life, yet the distinction between the early and late stages of the postmenopause are rarely considered in research[119], either due to methodological issues surrounding collection of data, or because differences between these two groups are not a key point of interest. However, continued changes in estradiol and follicle stimulating hormone (FSH)[119] may influence sleep, mood, and cognition, all of which have been shown to vary with time since menopause[120–122]. In addition, vasomotor symptoms are the most frequent and prominent menopausal symptoms specifically during the early phase of postmenopause[104] while clinical problems such as bone alterations are more common during LP-M[120]. The biopsychosocial nature of this study calls for the differentiation between these phases, and we have thus separated the women accordingly. The transition from reproductive to menopausal status is primarily a hormonal event, but it is accompanied by various physiological and psychological changes[103].

Menopausal Status and Pain

There have been several studies looking at menopausal status and its relationship to pain, using human and animal models of experimental and clinical pain. Three pain models have been used to assess pain reactivity in animal studies: mechanical stimuli (e.g. heat/electric shock) to model acute pain, chemicals (e.g. capsaicin, formalin) to create a persistent inflammatory response, and peripheral nerve damage to induce neuropathic pain[55]. Acute pain models measure a threshold response, such as latency to tail flick, whereas inflammatory models use behavioural responses such as lip rubbing. In addition, all three models have used neurophysiological markers as outcome measures[55].

Ovariectomy (OVX), the surgical removal of one or both ovaries, is used to model

menopause in rodents[55]. Research demonstrates higher sensitivity to nociceptive stimuli in OVX female rodents compared to their intact counterparts, but there are also studies reporting the opposite or no effect at all[89], which may be dependent on the type and application site of noxious stimulation[55]. For example, researchers have noted increased pain responses in low estrogen milieu during the formalin test but not during electrical stimuli[108]. Studies measuring inflammation rather than pain after adjuvant administration also demonstrate that estrogen decreases indices of inflammation and immunoreactivity in OVX rats[89]. This implies that estrogen may reduce the inflammatory component of the pain response. However, when peripheral neuropathy was induced by chronic alcohol consumption, hyperalgesia only developed in gonadally intact and estrogen-replaced female rats but not in the OVX ones[109]. These studies suggest that estradiol may attenuate the immediate pain of inflammation, while possibly worsening its long-term trajectory, leading to greater hyperalgesia and allodynia[89]. It has also been reported that greater behavioural responses are observed when a pain stimulus is applied to the lip than the hind paws of OVX mice, suggesting cephalic pain may be more responsive than non-cephalic to changes in ovarian hormones[55].

Cross-species generalizations must be made with caution for several reasons. Firstly, rodents' reproductive cycles differs considerably from humans[110]. The analog to the human menstrual cycle in rats is the estrous cycle, which is significantly shorter in length (4-5 days, as opposed to the human average of 28 days). In addition, in contrast to humans, both of the rats' ovaries show similar changes through their cycle, and both ovulate simultaneously[110]. Most animal studies examine nociception either during steady-state estrogen exposure or at a single time point after injection, yet fluctuations appear to be more relevant than absolute levels for some types of pain[89]. Also, OVX studies usually include young healthy animals, which may not

be comparable to the human menopausal woman, given age, previous pain and surgical experiences[111]. Therefore, translation from animal models to human models regarding pain and aging requires great caution[112].

Human research on the relationship between menopausal status and pain is most often conducted regarding a few common chronic conditions[113]. Clinical pain in women has been shown to differ with changes in reproductive function in characteristics such as prevalence, intensity, frequency, and location[96]. For example, after menopause, the prevalence of migraines, temporomandibular joint disorders, and other cephalic[55] as well as orofacial pains[53] decreases, while that of fibromyalgia, rheumatoid arthritis, and osteoarthritis increases[89,96]. However, postmenopausal women using Hormone Replacement Therapy (HRT) for unwanted symptoms associated with the transition, sometimes see a worsening in conditions common to pre-menopause[53].

Few studies have examined the effect of menopausal status on POP. One found the severity of POP after cystocele and rectocele repair surgery (tightening of tissue around bladder and rectum) was higher among premenopausal women than postmenopausal women[114]. Another study examined POP outcomes after transvaginal mesh (used to treat urinary incontinence) removal, replacement, or revision. This surgery is commonly performed on women who experience complications such as pelvic and bladder pain following the original procedure. Menopausal status did not predict pain improvement in this study[115].

Importantly, the incidence of breast cancer is highest in mid-life[116], which coincides with the transition to menopause. The associated biological and psychological changes that occur at this time may impact women's experience after BCS. Thus, menopausal status is an important factor to consider in evaluating POP. However, research on the relationship between menopausal

status and pain has primarily focused on chronic pain disorders, very few have examined POP, and none have approached this relationship from a biopsychosocial perspective. This is the first study to compare women with different menopausal statuses on a range of biopsychosocial predictors of POP as well as pain outcomes of BCS at 1 week and 6 months after surgery.

OBJECTIVE

The objective of this exploratory study was to examine the relationship between menopausal status and POP one week and six months after BCS using a biopsychosocial approach. The groups – PRE-M, PERI-M, EP-M, and LP-M – were compared on four pain outcomes: (1) prevalence; (2) intensity; (3) quality; and (4) impact on QoL.

METHODS

Patient Recruitment

This study is part of a larger, ongoing longitudinal study of POP after BCS (Canadian Cancer Society Research Institute Grant no. 18367). Ethics approval was obtained from the University Health Network (UHN) and York University (#2012-129).

Inclusion and Exclusion Criteria: Women scheduled for unilateral/bilateral lumpectomy or mastectomy were approached at Toronto General Hospital and Princess Margaret Cancer Centre. All patients were ≥18 years old, able to read and write English sufficiently to provide informed consent and complete the questionnaires, and Class 1-3 on the American Society of Anesthesiologists Physical Status Classification System (ASA 1: healthy person, ASA 2: mild systemic disease; ASA 3: severe systemic disease)[117]. Patients with a variety of breast cancer diagnoses (stage 0-4) were recruited including ductal carcinoma *in situ*, invasive ductal carcinoma and invasive lobular carcinoma. Those scheduled for prophylactic surgery were also

included. The following patients were excluded: significant CNS, respiratory, cardiac, hepatic, renal or endocrine dysfunction and/or any significant associated sequelae; cognitive impairment or documented diagnosis of a DSM-IV Axis 1 disorder; contraindication to opioids or acetaminophen; documented substance abuse or dependence within 1 year; pregnant or breastfeeding within 6 months; regularly menstruating women who have used exogenous hormones (oral contraceptives, hormonal intrauterine devices, hormone replacement therapy) within 3 months; immunization within 30 days; blood donation within 60 days; acute/infectious illness, allergic reactions of any severity, herbal supplements, physical injuries or dental work within 2 weeks.

Sample: 647 patients were approached at Toronto General Hospital and Princess Margaret Cancer Centre (Figure 1) and 297 provided informed consent. The most common reasons for refusal were lack of interest, lack of time, and participants' place of residence being too far from the hospital for continuous follow-up. Nine patients were excluded due to: surgery location change (n = 1), postponement of the surgery date (n = 3), surgery cancellation (n = 3), and participants' involvement in other studies (n = 2). Out of the remaining 287 participants, 18 withdrew at or before their preoperative assessment, and stated reasons such as feeling too overwhelmed (n = 8) or too busy (n = 5) to continue; there were also four participants whom the RA could not reach. 270 patients were scheduled to be assessed again after surgery, but 13 dropped out before the 1 week follow-up due to unforeseen health complications that met the exclusion criteria (n = 1), being too sick to continue participation (n = 7), or not responding to RA phone calls and emails (n = 5). The present analysis only included patients with complete baseline data (n = 232).

Procedure

Pre-Admission Assessment. Patients were recruited from the survivorship class at PMCC and from the preadmission clinic at TGH. All patients approached were documented, and reasons for exclusion were recorded. A research assistant (RA) obtained informed consent and administered the Short Orientation-Memory-Concentration (SOMC) Test to verify that patients are cognitively intact. Patients with scores suggesting cognitive impairment (>10 errors) were withdrawn. Eligible patients were then asked to provide demographic information, their pain history and POP expectations, and details about their menstrual cycle (e.g. date of onset of last menses, usual length of cycle, regularity). Patients also completed several measures of pain and its impact (physical functioning and psychosocial factors), which can be found in Appendix A of this document. The Numeric Rating Scale at rest and with movement (NRS-R and NRS-M), Short Form – McGill Pain Questionnaire (SF-MPQ) and the Short Form – Neuropathic Pain Questionnaire (SF-NPQ) were completed on-site, while the Brief Pain Questionnaire (BPI), Centre for Epidemiologic Studies – Depression Scale (CES-D), Pain Catastrophizing Scale (PCS), State-Trait Anxiety Inventory (STAI), and Medical Outcome Study Short-Form 12 (SF-12) were given as a take-home package and returned on the day of surgery. After the assessment, the RA completed the Charlson Comorbidity Index (CCI) and a chart review for additional health-related information (diagnosis, stage of cancer).

Post-Operative Follow-Up. Follow-ups occurred at 1 week ± 1 day and 6 months ± 2 weeks after surgery. Information about the surgery including type, complications, whether the surgery was prophylactic or treatment-related, intraoperative and post-operative medications and information on any adverse events (e.g., surgical wound infection, excessive swelling) was obtained from the patient's chart. Each follow-up assessment began with the SOMC, and any

patients scoring below the normal range (>10 errors) were withdrawn. The RA again collected demographic information and recorded any new sensations, treatments and interventions, including repeated surgery and use of analgesics. Menstrual cycle changes (e.g., length, regularity) were also recorded. Patients were given the NRS-R, NRS-M, SF-MPQ, SF-NPQ, BPI, CES-D, STAI-S (state anxiety only), and SF-12 to complete at home and asked to return the package in the mail. The RA completed the CCI again through chart review.

Data Analysis

The participants were divided into four menopausal status groups prior to surgery: PRE-M, PERI-, EP-M, and LP-M. Descriptive statistics were calculated for all variables, including anthropometric variables, at each time point: baseline, 1 week, and 6 months post-surgery. All statistical analyses were conducted on IMB SPSS Statistical Software 24.0. Means and standard deviations were reported for normally distributed continuous variables; medians were reported for non-normally distributed variables; and frequencies were reported for categorical variables.

Missing Data: Data were screened for missing values and outliers. The distribution of missing data was assessed using Little's Missing Completely at Random test[148]. The multiple imputations technique[149–151] using five iterations to correct the missingness was considered. However, the chosen statistical software does not support pooling of individual iteration results for the subsequent statistical analyses of the study. As such, for values that were found to be missing "completely at random" or "missing at random", a single imputation method using the Expectation Maximization was employed[152]. Patients completed 11 questionnaires at each timepoint. Of the 232 patients, 65 (28.02%) had at least one postoperative questionnaire missing (PRE-M = 14; PERI-M = 14; EP-M = 17; LP-M = 20). 44 patients did not complete the 6-month follow-up and had every questionnaire missing for this timepoint (PRE-M = 11; PERI-M = 10;

EP-M = 12; LP-M = 11); rates did not statistically differ between menopausal status groups (p = 0.08). The other 21 patients had between 1 and 10 missing questionnaires. The questionnaire with the most missing values was the BPI with 6 missing values at 1 week (all LP-M) and 5 missing values at 6 months (PRE-M = 1; PERI-M = 1; EP-M = 1; LP-M = 2). Little's MCAR Test was conducted and revealed that the data were "missing at random" (p = 1.00), thus, the values were imputed using the Expectation Maximization technique.

Continuous variables that were not normally distributed were transformed using a logarithmic transformation with an added constant of 1 to account for zero values[153–155]. Baseline differences between the menopausal status groups including sociodemographic, clinical, psychological and surgery-related factors were assessed. Significant findings indicated differences among the groups before the surgery; age and comorbidities were thus entered as covariates in all ANCOVAs. Chi-Square Tests of Independence does not account for inclusion of covariates. For outcome analyses that failed to meet the assumption of sphericity, the Greenhouse-Geisser correction was used to correct for the violation. Analysis was done using ANOVAs for continuous variables (with a Bonferroni post-hoc) and Chi-Square for categorical variables. Because the Chi-Square test does not specify which combination of categories contributes to statistical significance, the Standardized Residual Method (SRM)[156] was used as post-hoc. Namely, the standardized residual for each cell was used to identify discrepancies between observed and expected values that were larger than expected by chance. SPSS converts the standardized residuals of each cell into individual p-values, which are then compared against an adjusted alpha level according to the number of cells to determine significance. Prevalence of pain was a 2x4 chi-square analysis, (α=0.05/8=0.006), while persistence was a 4x4 and the adjusted alpha level was α=0.05/16=0.003. This post-hoc method was employed for all

statistically significant chi-square tests. Pain was evaluated using four outcomes: (1) prevalence, (2) intensity, (3) quality, and (4) impact on QoL.

(1) Prevalence of Pain (at rest and with movement) was evaluated 1 week and 6 months after surgery using the NRS-R and NRS-M, where scores ≥1 indicated presence of pain[40]. In addition, persistence was analyzed by comparing the patients' prevalence reports at the 1 week and 6 months follow-ups. Participants who had no pain (NRS=0) at both time points were categorized as "no pain", those who reported pain at 1 week but not 6 months were categorized as "improved", some indicated they were in pain at both time points and were labelled as "persistent", and those who only presented with pain at the 6 month follow-up, but not at 1 week, were labelled as "developed". Group differences in pain prevalence at each time point as well as persistence were evaluated using the Chi-Square Test of Independence (with SRM post-hoc).

(2) Pain intensity was first evaluated at 1 week and 6 months using the NRS-R and NRS-M, including the mean score as well as the level of pain [categories: no pain (NRS=0), mild (NRS=1-3), moderate (NRS=4-6), or severe (NRS=7-10)][6]. Moreover, SF-MPQ sensory, affective, total scores and NWC were examined. Group differences on these measures were tested using chi-square test for the NRS categories (adjusted $\alpha=0.05/16=0.003$), and repeated measures ANCOVA for the continuous variables. A Bonferroni correction was adopted due to multiple comparisons where the significant p-value was adjusted to a more stringent value, reducing the likelihood of Type I error.

(3) Quality of pain was evaluated at 1 week and 6 months after surgery on the SF-MPQ using Chi-Square Test of Independence for the most commonly chosen words and an ANCOVA for NWC. Furthermore, a dummy variable was created to identify change in the presence of neuropathic qualities in POP. Women whose pain exhibited neuropathic characteristics at 1 week

but not 6 months were labelled "improved", those who did not exhibit them at 1 week but did at 6 months were labeled "developed", patients who had it at both time points were labeled "persistent neuropathic pain", and lastly, those who did not present with them at all were labelled "none". A Chi-Square Test of Independence was conducted to determine the proportion of each group reaching threshold for neuropathic pain (SF-NPQ).

(4) The impact of pain on QoL was examined preoperatively, 1 week and 6 months after surgery. The patients were divided into those that developed chronic pain (scored ≥1 on either the NRS-R or NRS-M at 6 months) and those who did not. Impact was examined on five domains: pain interference with daily life (BPI-I), depressive symptomatology (CES-D), state anxiety (STAI-S), physical HRQoL (SF-12 PCS) and mental HRQoL (SF-12 MCS). Score differences were analyzed using three-way repeated measures ANCOVA with time as the repeated factor, and presence of chronic pain and menopausal status as the between subject factors. Significant interactions were further investigated using the Bonferroni post-hoc method. Additionally, a chi-square test was conducted only on women who developed chronic pain, to determine the proportion of each menopausal status group reaching threshold for clinically relevant depressive symptomatology (CES-D≥16).

MEASURES

Menopausal Status

Women were asked about the regularity of their menstrual cycles and to recall the date of the onset of their last menses. Menopausal status was categorized into four groups before surgery based on past research [102,118], the World Health Organization recommendations[103], as well as the Stages of Reproductive Aging Workshop[104]. PRE-M is regular menses in the last 3 months;

PERI-M is irregular menses within the last 12 months; EP-M is 1-5 years since last menstruation; and LP-M is 5+ years since last menstruation.

Pain Measures

Numeric Rating Scale at rest (NRS-R) and *with movement (NRS-M)* are 11-point numeric rating scales, with horizontal lines numbered from 0 to 10 with the endpoints labeled "no pain" and "worst possible pain"[125]. For NRS-R, patients chose the number that corresponds to their present pain intensity. For NRS-M, patients were asked to sit up and take two deep breaths before rating their pain. Both scales have good reliability and validity in cancer patients[126] and across the adult lifespan in surgical patients[127].

The *Short Form McGill Pain Questionnaire (SF-MPQ)* is a multidimensional measure that assesses sensory and affective qualities of pain[128]. Patients rate 11 sensory and 4 affective pain descriptors on a scale (0 = none, 1 = mild, 2 = moderate, 3 = severe). The derived pain scores include: sum of the item scores, which can be divided into sensory and affective subscales, NWC, as well as their profile. This measure has been shown to be valid and reliable in cancer patients[129] and POP[130].

The *Neuropathic Pain Questionnaire-Short Form (SF-NPQ)*[131] is a 3-item questionnaire, which allows for the differentiation between neuropathic and non-neuropathic pain. On a scale of 0-100, patients are asked to rank the intensity of three symptoms: tingling, numbness and pain due to touch. A discriminant function score is then calculated and used in determining whether the patient meets the cut-off for neuropathic pain. The SF-NPQ has been validated and is reliable for use in various types of chronic pain[132].

The *Brief Pain Inventory (BPI)*[133] is a 11-item questionnaire with two subscales. It measures pain severity and interference with physical, emotional, and social domains. The pain severity scores were not used in this study. The pain interference score is an arithmetic mean of seven sub-items that are rated from 0 (does not interfere) to 10 (completely interferes). This measure has been validated for use in the breast cancer patient population[134] and for patients with chronic postoperative pain[135].

Physical Function

The *Charlson Comorbidity Index (CCI)*[136] generates a weighted score based on 16 comorbid conditions – AIDS, cerebrovascular disease, chronic pulmonary disease, congestive heart failure, connective tissue disease, dementia, hemiplegia, leukemia, malignant lymphoma, myocardial infarction, peripheral vascular disease, ulcer disease, diabetes mellitus, liver disease, renal disease, and malignant solid tumour. An RA examined the patient's medical chart to obtain this information. This is a widely-used measure which has been validated for use in older cancer patients[137] as well as clinical research in other populations[138].

The *Medical Outcome Study Short-Form 12 (SF-12)*[139] is a widely used 12-item generic measure of functional status, including physical and mental health. Scores on each subscale range from 0 to 100, with higher scores indicating better QoL[139]. It has good reliability and validity in breast cancer patients and older populations[140,141].

Psychosocial Function

The Short Orientation-Memory-Concentration Test (SOMC)[123] is a test of memory and concentration and was used to assess patients' cognitive impairment both prior to surgery and

subsequent follow-ups. It is free of cultural bias and has been shown to be both valid and reliable across age groups[124].

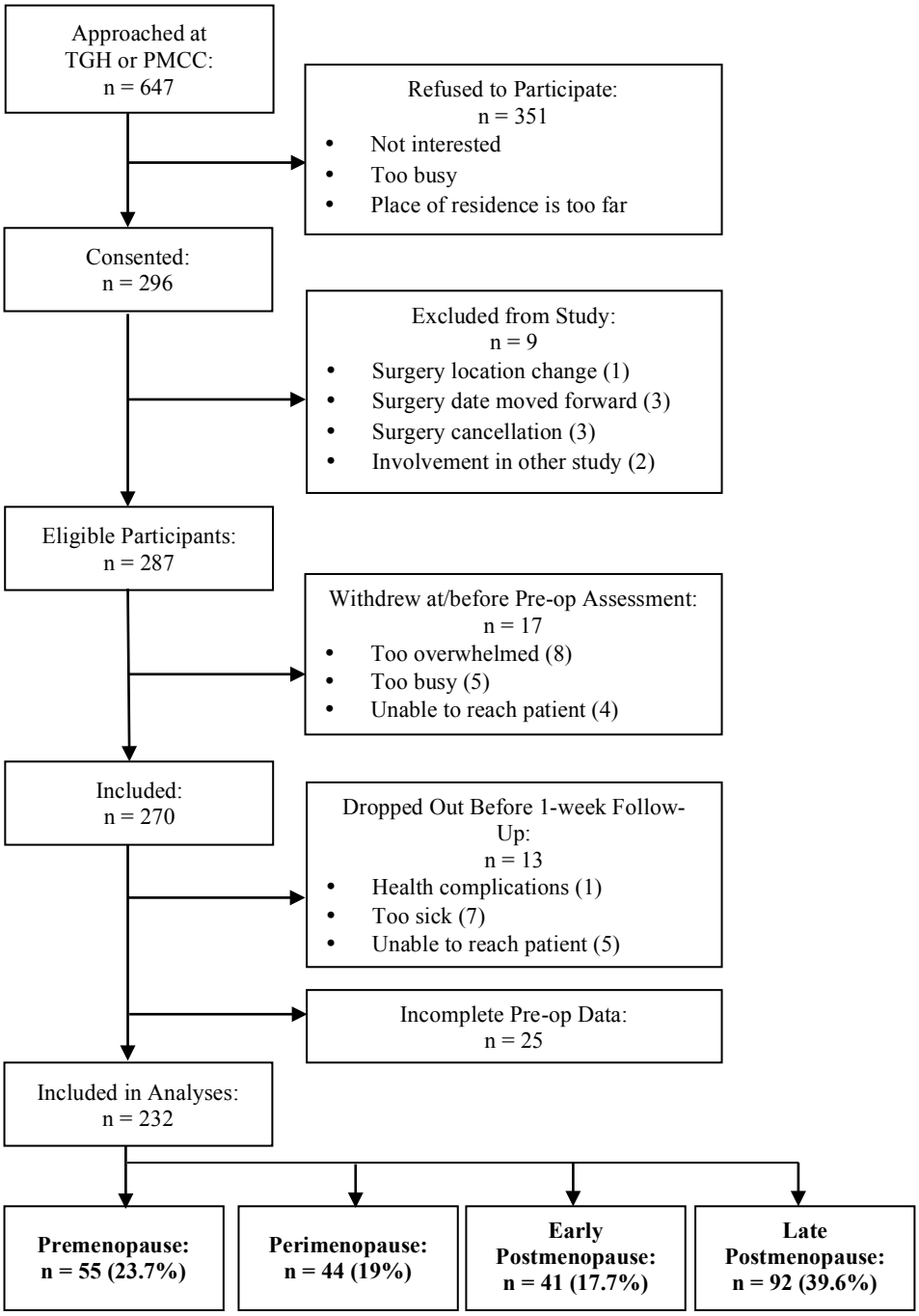
The *Centre for Epidemiologic Studies – Depression Scale (CES-D)*[142] is a 20-item measure of current depressive symptoms and their frequency over the last week. Response options for each item range from 0 to 3 (0 = Rarely or None of the Time, 1 = Some or Little of the Time, 2 = Moderately or Much of the time, 3 = Most or Almost All the Time). Scores range from 0 to 60, with high scores indicating greater depressive symptoms[142]. This scale has been validated for clinical research use with cancer patients[143] and older adults[144].

The *Pain Catastrophizing Scale (PCS)*[47] is a 13-item questionnaire with subscales measuring rumination, magnification, and helplessness as they relate to pain and its management. The score ranges from 0 to 52. Higher scores represent greater catastrophizing[47]. It has good reliability and validity in adult populations[145].

The State-Trait Anxiety Inventory (STAI)[146] measures the intensity of feelings of anxiety using two subscales. STAI-S has 20 items, which assess anxiety in response to specific states. The STAI-T measures trait anxiety, which is a general tendency towards anxious feelings, also using 20 items. Each item is given a weighted score of 1 to 4. A high rating indicates the presence of a high level of anxiety for ten STAI-S items and eleven STAI-T items. For the remaining ten STAI-S items and nine STAI-T items, a high rating indicates the absence of anxiety. The scoring weights for the anxiety-absent items are reversed (responses marked 1, 2, 3, or 4 are scored 4, 3, 2, or 1, respectively). The scoring weights are reversed for STAI-S items 1, 2, 5, 8, 10, 11, 15, 16, 19, 20 and STAI-T items 21, 23, 26, 27, 30, 33, 34, 36, 39. Scores for both subscales range from 20 to 80, where higher total scores represent higher levels of anxiety[146]. The questionnaire has been validated for use in BCS patients[147].

RESULTS

Figure 1. CONSORT diagram of participants



THG = Toronto General Hospital; PMCC = Princess Margaret Cancer Centre

Table 1. Demographic Characteristics and Preoperative Factors

	Total (n=232)	PRE-M (n = 55)	PERI-M (n =44)	EP-M (n = 41)	LP-M (n = 92)	P-Value
Sociodemographic Factors						
Age	52.63 ± 11.16	42.09 ± 7.14	46.34 ± 6.02	52.05 ± 6.70	62.18 ± 8.38 **α**	**<0.001**
Marital Status						0.05
Married	169 (72.8)	42 (76.4)	36 (81.8)	34 (82.9)	57 (62)	
Single	27 (11.6)	8 (14.5)	3 (6.8)	5 (12.2)	11 (12)	
Separated/Divorced	25 (10.8)	4 (7.2)	4 (9.0)	2 (4.9)	15 (16.3)	
Widowed	11 (4.7)	1 (1.8)	1 (2.3)	0 (0)	9 (9.8)	
Religion						0.12
Christian	110 (47.4)	33 (60)	23 (52.3)	17 (41.5)	37 (40.2)	
Jewish	24 (10.3)	1 (1.8)	3 (6.8)	4 (9.8)	16 (17.4)	
Muslim	8 (3.4)	2 (3.6)	1 (2.3)	1 (2.4)	4 (4.3)	
Other	20 (8.6)	2 (3.6)	3 (6.8)	7 (17.1)	8 (8.7)	
None	70 (30.2)	17 (30.9)	14 (31.8)	12 (29.3)	27 (29.3)	
Level of Education						0.17
High School or less	24 (10.3)	5 (9.1)	5 (11.4)	3 (7.3)	11 (12)	
Community College	52 (22.4)	8 (14.5)	16 (36.4)	6 (14.6)	22 (23.9)	
Bachelor's Degree	109 (47)	26 (47.3)	18 (40.9)	24 (58.5)	41 (44.6)	
Graduate Degree	47 (20.3)	16 (29.1)	5 (11.4)	8 (19.5)	18 (19.6)	
Clinical Factors						
BMI	26.34 ± 4.92	24.83 ± 4.77	25.83 ± 4.87	27.58 ± 4.56	26.95 ± 4.99	0.06
CCI	2.48 ± 1.62	1.71 ± 0.98	1.82 ± 1.60	1.90 ± 1.34	3.51 ± 1.51 *	**<0.001**
Pain Factors						
Chronic Pain History	53 (22.3)	11 (20)	9 (20.5)	7 (17.1)	26 (28.3)	0.44
Present Pain						
At Rest	0.66 ± 1.37	0.36 ± 1.02	0.91 ± 1.71	0.81 ± 1.31	0.64 ± 1.37	0.27
With Movement	1.07 ± 1.93	0.48 ± 1.26	1.35 ± 2.21	1.15 ± 1.93	1.15 ± 2.07	0.12
Psychological Factors						
Pain Catastrophizing (PCS)	14.55 ± 9.62	14.75 ± 9.72	16.38 ± 10.25	14.07 ± 9.91	13.77 ± 9.17	0.57
Rumination	6.33 ± 4.09	6.37 ± 3.74	7.59 ± 4.57	5.79 ± 3.99	5.94 ± 4.02	0.11
Magnification	2.62 ± 2.25	2.76 ± 2.47	2.52 ± 2.37	2.84 ± 2.02	2.50 ± 2.17	0.66
Helplessness	5.67 ± 4.37	5.40 ± 4.33	6.21 ± 4.59	5.75 ± 4.76	5.55 ± 4.16	0.89
Anxiety						
State Anxiety (STAI-S)	42.18 ± 12.93	44.85 ± 12.70	41.42 ± 11.17	43.44 ± 11.67	40.38 ± 14.19	0.62
Trait Anxiety (STAI-T)	36.06 ± 11.11	37.16 ± 10.39	38.10 ± 10.58	35.77 ± 11.09	34.55 ± 11.70	0.83
Depression (CES-D)	15.82 ± 11.50	17.56 ± 10.02	13.47 ± 8.36	13.33 ± 9.79	17.01 ± 13.87	0.06
Pain Expectations						
Immediately after surgery	5.64 ± 3.31	5.80 ± 3.08	5.67 ± 3.41	6.52 ± 2.61	5.15 ± 3.62	0.17
After taking pain medication	2.03 ± 1.95	2.13 ± 2.17	2.46 ± 2.05	2.34 ± 1.93	1.63 ± 1.70	0.07
One week after surgery	2.94 ± 2.23	3.34 ± 2.15	3.25 ± 2.54	3.52 ± 2.30	2.29 ± 1.95 *	**0.004**
Surgery Related Factors						
Indication						
Prophylactic	56 (24.1)	6 (10.9)	16 (36.4)	18 (43.9)	16 (17.4)	
Breast Cancer	176 (75.9)	49 (89.1)	28 (63.6)	23 (56.1)	76 (82.6)	
*Diagnosis**						0.14
Ductal Carcinoma In Situ	19 (10.8)	9 (18.4)	3 (10.7)	2 (8.7)	5 (6.6)	
Invasive Ductal Carcinoma	135 (76.7)	35 (71.4)	21 (75)	18 (78.3)	61 (80.3)	
Invasive Lobular Carcinoma	14 (8)	4 (8.2)	3 (10.7)	2 (8.7)	5 (6.6)	
Other	8 (4.5)	1 (2.0)	1 (3.6)	1 (4.3)	5 (6.6)	
*Breast Cancer Stage**						**0.01**
Stage 0	13 (7.4)	7 (14.3)	2 (7.1)	2 (8.7)	2 (2.6)	
Stage 1	89 (50.6)	21 (42.9)	12 (42.9)	10 (43.5)	46 (60.5)	
Stage 2	53 (30.1)	17 (34.7)	8 (28.6)	5 (21.7)	23 (30.2)	
Stage 3 or 4	21 (11.9)	4 (8.2)	6 (21.4)	6 (26.1)	5 (6.6)	
Procedure						0.12
Left Lumpectomy	45 (19.4)	14 (25.5)	7 (15.9)	8 (19.5)	16 (17.4)	
Right Lumpectomy	53 (22.8)	14 (25.5)	4 (9.1)	6 (14.6)	29 (31.5)	
Left Mastectomy	37 (15.9)	5 (9.1)	10 (22.7)	6 (14.6)	16 (17.4)	
Right Mastectomy	35 (15.1)	6 (10.9)	6 (13.6)	11 (26.8)	12 (13.0)	
Bilateral Lumpectomy	4 (1.7)	2 (3.6)	1 (2.3)	0 (0)	1 (1.1)	
Bilateral Mastectomy	58 (25)	14 (25.5)	16 (36.4)	10 (24.4)	18 (19.6)	
Length of Surgery (min)	776.6 ± 298.6	816.16 ± 342.25	776.61 ± 265.11	697.56 ± 328.78	815.97 ± 267.06	0.16

Values are means ± SD or frequency (%).
PRE-M = premenopause; PERI-M = perimenopause; EP-M = early postmenopause; LP-M = late postmenopause.
* = Significant difference from all menopausal status groups; α = Significant difference from PRE-M

Preoperative and Perioperative Factors

Sociodemographic and Clinical Characteristics. The participants' clinical and sociodemographic characteristics are described in Table 1. Age was statistically significant between PRE-M and LP-M, the youngest and oldest groups ($p<0.001$) but consistent with BCS populations[157]. Across the groups, most of the women were married ($n_{PRE\text{-}M} = 42$, 76.4%; $n_{PERI\text{-}M} = 36$, 81.8%; $n_{EP\text{-}M} = 34$, 82.9%; $n_{LP\text{-}M} = 57$, 62%), although there were a significantly higher number of widows in the LP-M group ($p = 0.02$). There was no statistically significant difference among the groups on religion ($p = 0.12$) or level of education ($p = 0.17$). The body mass index (BMI) of EP-M women was significantly higher than that of PRE-M ($p = 0.02$), while comorbidity (CCI) scores were significantly higher in LP-M compared to all other groups ($p<0.001$). Since BMI[158] and comorbidities[159] are influenced by age, ANOVAs were re-run controlling for age to isolate the effect of menopausal status. While BMI was no longer statistically significant ($p = 0.06$), comorbidities remained significant among groups. As such, age and comorbidities were included as covariates in all relevant analyses. There were no statistically significant differences in history of chronic pain ($p = 0.44$), present pain at rest ($p = 0.27$) or with movement ($p = 0.13$).

Psychological Factors: There were no significant differences between the menopausal status groups on baseline pain catastrophizing ($p = 0.57$) and state ($p = 0.62$) or trait anxiety ($p = 0.84$). With regards to depressive symptomatology (CES-D), there were no significant differences between the menopausal status groups on total score ($p = 0.06$) or in the proportion of women reaching cutoff for clinically relevant depressive symptomatology (score ≥ 16; $p = 0.05$). Generally, PRE-M and LP-M women were trending towards higher CES-D scores ($p = 0.06$). Preoperatively, LP-M women expected a lower POP intensity than those in the other three

groups ($p = 0.004$). However, when age was controlled this relationship was no longer statistically significant ($p = 0.33$).

Surgical-Related Factors: A significantly higher proportion of women had cancer rather than prophylactic indication for surgery ($p < 0.001$). Among those with breast cancer, there were no statically significant differences in diagnosis ($p = 0.14$) or procedure ($p = 0.12$), but there was in cancer stage ($p = 0.01$). Specifically, stage 0 was more frequent in PRE-M women than in other menopausal status groups. The groups did not differ on duration of surgery ($p = 0.16$).

(1) Pain Prevalence

POP prevalence was examined both at rest and with movement, at one week and 6 months after surgery. It was found that the prevalence of pain at rest was not significantly different among the groups 1 week ($p = 0.11$) and 6 months ($p = 0.13$) after surgery (Table 2). However, there was a significant difference between the menopausal status groups on prevalence of pain with movement at 1 week ($p = 0.01$; Table 3). LP-M women were more likely to deny pain with movement than all other groups ($p = 0.003$). This difference was no longer evident at the 6-month follow-up ($p = 0.51$). Change in pain prevalence – or persistence – at rest (Table 4, Figure 2) and with movement (Table 4, Figure 3) was also examined. Persistence was found to be significantly different between menopausal status groups for pain at rest ($p = 0.02$). There were a significantly higher proportion of PRE-M women that exhibited "persistent pain" between 1 week and 6 month after surgery ($p = 0.0029$).

Table 2. Prevalence of pain at rest

	1 Week (p=0.11)		6 Months (p=0.13)	
	No	Yes	No	Yes
PRE-M (n = 55)	14 (25.5%)	41 (74.5%)	36 (65.5%)	19 (34.5%)
PERI-M (n =44)	15 (34.1%)	29 (65.9%)	37 (84.1%)	7 (15.9%)
EP-M (n = 41)	13 (31.7%)	28 (68.3%)	32 (78.0%)	9 (22.0%)
LP-M (n = 92)	41 (44.6%)	51 (55.4%)	64 (69.6%)	28 (30.4%)
Total	83 (35.8%)	149 (64.2%)	169 (72.8%)	63 (27.2%)

Values are frequencies (proportion of group total).
PRE-M = premenopause; PERI-M = perimenopause; EP-M = early postmenopause; LP-M = late postmenopause.

Table 3. Prevalence of pain with movement

	1 Week (p=0.01)		6 Months (p=0.51)	
	No	Yes	No	Yes
PRE-M (n = 55)	5 (9.1%)	50 (90.9%)	25 (45.5%)	30 (54.5%)
PERI-M (n =44)	1 (2.3%)	43 (97.7%)	22 (50.0%)	22 (50.0%)
EP-M (n = 41)	5 (12.2%)	36 (87.8%)	20 (48.8%)	21 (51.2%)
LP-M (n = 92)	20 * (21.7%)	72 (78.3%)	51 (55.4%)	41 (44.6%)
Total	31 (13.4%)	201 (86.6%)	118 (50.9%)	114 (49.1%)

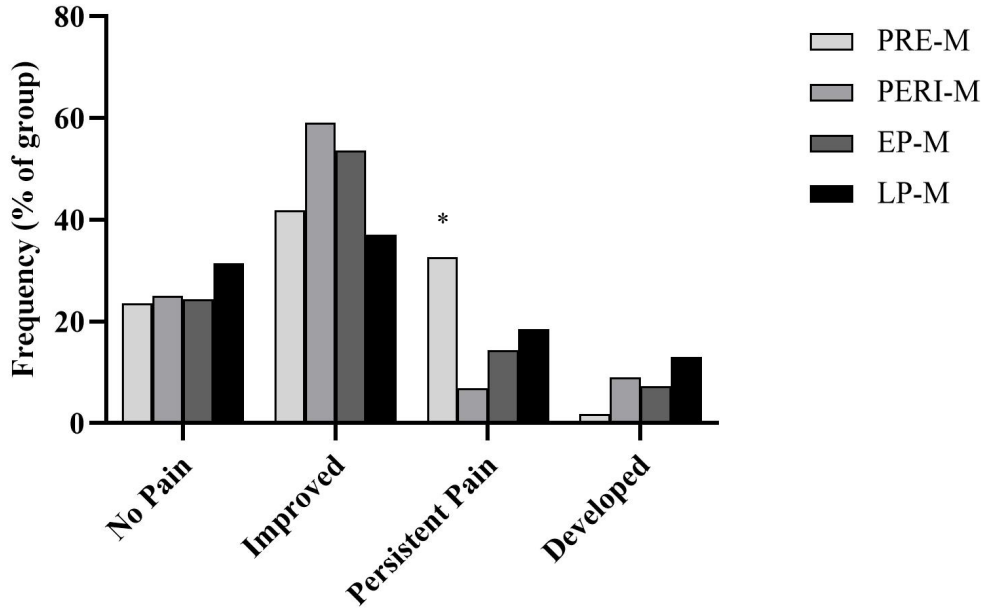
Values are frequencies (proportion of group total).
PRE-M = premenopause; PERI-M = perimenopause; EP-M = early postmenopause; LP-M = late postmenopause.
* = Significant difference from all menopausal status groups

Table 4. Change in pain prevalence (persistence) from 1 week to 6 months

	Total (n=232)	PRE-M (n = 55)	PERI-M (n =44)	EP-M (n = 41)	LP-M (n = 92)	X^2	df	p-value
At Rest								
No pain	63 (27.2%)	13 (23.6%) -0.7	11 (25%) -0.4	10 (24.4%) -0.4	29 (31.5%) 1.9	19.60	9	**0.02**
Improved	105 (45.3%)	23 (41.8%) -0.6	26 (59.1%) 2.0	22 (53.7%) 1.2	34 (37%) -2.1			
Persistent	44 (19%)	18 (32.7%) * 3.0	3 (6.8%) -2.3	6 (14.6%) -0.8	17 (18.5%) -0.2			
Developed	20 (8.6%)	1 (1.8%) -1.9	4 (9.1%) 0.1	3 (7.3%) -0.3	12 (13.0%) 1.2			
With Movement								
No pain	19 (8.2%)	3 (5.5%) -0.8	1 (2.3%) -1.6	2 (4.9%) -0.9	13 (14.1%) 2.7	13.93	9	0.13
Improved	101 (43.5%)	22 (40%) -0.6	20 (45.5%) 0.6	18 (43.9%) 0.1	40 (43.5%) 0.0			
Persistent	100 (43.1%)	28 (50.9%) 1.3	23 (52.3%) 1.0	18 (43.9%) 0.1	32 (34.8%) -2.1			
Developed	12 (5.2%)	2 (3.6%) -0.6	0 (0%) 0.0	3 (7.3%) 0.7	7 (7.6%) 1.4			

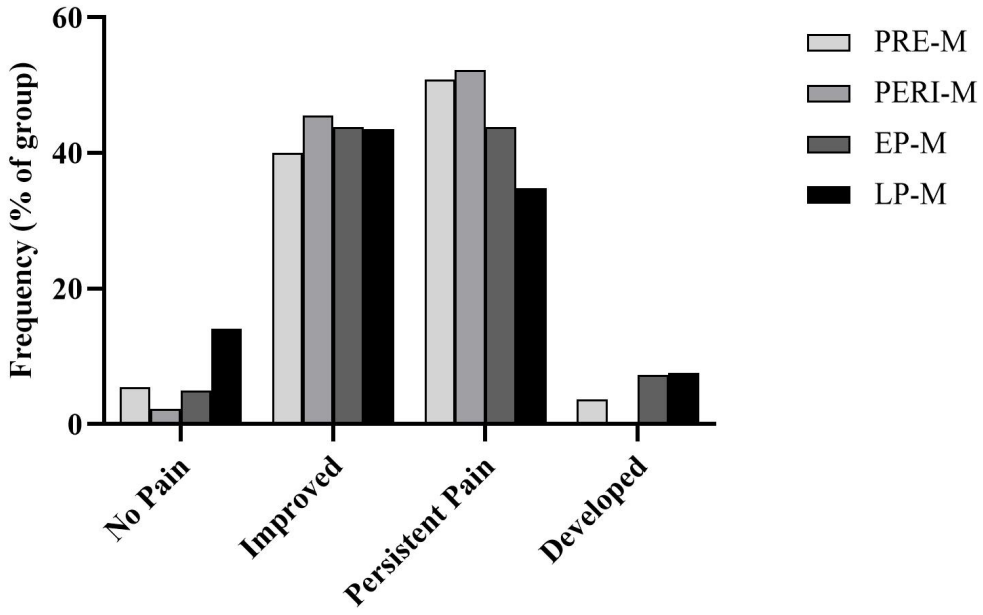
Upper values are frequencies (proportion of group total). Lower values are standardized residuals.
PRE-M = premenopause; PERI-M = perimenopause; EP-M = early postmenopause; LP-M = late postmenopause.
'No pain' means pain was not reported at 1 week or 6 months; 'Improved' means pain was reported at 1 week but not 6 months; 'Persistent' means pain was reported at 1 week and 6 months; 'Developed' means pain was reported at 6 months but not 1 week.
* = Significant difference from all menopausal status groups

Figure 2. Change of pain prevalence at rest, from 1 week to 6 months



PRE-M = premenopause; PERI-M = perimenopause; EP-M = early postmenopause; LP-M = late postmenopause.
* = Significant difference from all menopausal status groups

Figure 3. Change of pain prevalence with movement, from 1 week to 6 months



PRE-M = premenopause; PERI-M = perimenopause; EP-M = early postmenopause; LP-M = late postmenopause

(2) Pain Intensity

Mean NRS-R scores did not differ significantly between menopausal status groups ($p = 0.95$, Table 5). Mean NRS-M scores did not differ among groups either ($p = 0.25$, Table 6). In addition to mean scores, levels of pain at rest and with movement were also examined (Table 7). At 1 week, 83 patients (35.8%) experienced no pain at rest, 113 patients (48.7%) had mild pain, 26 (11.2%) had moderate pain and 10 (4.3%) had severe pain. At 6 months, 169 patients (72.8%) experienced no pain, 52 (22.4%) had mild pain, 8 (3.4%) had moderate pain, and 3 (1.3%) had severe pain. 31 patients (13.4%) had no pain with movement, 114 (49.1%) had mild pain, 64 (27.6%) had moderate pain, and 23 (9.9%) had severe pain 1 week after surgery. At 6 months, 118 patients (50.9%) experienced no pain, 82 (35.3%) had mild pain, 22 (9.5%) had moderate pain, and 10 (4.3%) had severe pain. No statistically significant differences were found among

groups in the levels of pain experienced at rest (p = 0.33) or with movement (p = 0.70). There were also no statistically significant differences in pain intensity between the menopausal status groups when measured on the sensory scale of the SF-MPQ (p = 0.96; Table 8), affective scale (p = 0.66, Table 9), or total scale (p = 0.98, Table 10). Similarly, NWC on the SF-MPQ (Table 11) was not significantly different between the groups (p = 0.13).

Table 5. Pain intensity at rest (NRS-R), adjusted for age and comorbidities

	Mean Score ± SD		**Between-Subject Effects**			**Within-Subject Effects**		
	1 week	6 months	F Statistic	df	p-value	F Statistic	df	p-value
PRE-M	2.09 ± 2.04	0.56 ± 0.87	0.116	3	0.95	0.666	6	0.65
PERI-M	1.84 ± 2.08	0.56 ± 1.37						
EP-M	2.07 ± 2.19	0.59 ± 1.47						
LP-M	1.44 ± 1.94	0.85 ± 1.82						

PRE-M = premenopause; PERI-M = perimenopause; EP-M = early postmenopause; LP-M = late postmenopause;

Table 6. Pain intensity with movement (NRS-M), adjusted for age and comorbidities

	Mean Score ± SD		**Between-Subject Effects**			**Within-Subject Effects**		
	1 week	6 months	F Statistic	df	p-value	F Statistic	df	p-value
PRE-M	3.48 ± 2.45	1.32 ± 1.52	1.374	3	0.25	1.784	6	0.11
PERI-M	4.03 ± 2.56	1.71 ± 2.41						
EP-M	3.32 ± 2.21	1.53 ± 2.03						
LP-M	2.45 ± 2.27	1.45 ± 2.37						

PRE-M = premenopause; PERI-M = perimenopause; EP-M = early postmenopause; LP-M = late postmenopause;

Table 7. Levels of Pain at Rest and Movement

	At Rest		**With Movement**	
Pain Level	**1 Week**	**6 Months**	**1 Week**	**6 Months**
None	83 (35.8%)	169 (72.8%)	31 (13.4%)	118 (50.9%)
Mild	113 (48.7%)	52 (22.4%)	114 (49.1%)	82 (35.3%)
Moderate	26 (11.2%)	8 (3.4%)	64 (27.6%)	22 (9.5%)
Severe	10 (4.3%)	3 (1.3%)	23 (9.9%)	10 (4.3%)

NRS-R: p = 0.33; NRS-M: p = 0.70

Table 8. SF-MPQ Sensory Score, adjusted for age and comorbidities

	Median Score (IQR)		Between-Subject Effects			Within-Subject Effects		
	1 week	6 months	F Statistic	df	p-value	F Statistic	df	p-value
PRE-M	2.50 (4.00)	0.00 (2.00)	0.101	3	0.96	2.310	3	0.08
PERI-M	2.00 (3.75)	0.00 (2.00)						
EP-M	3.50 (4.00)	1.00 (3.00)						
LP-M	2.00 (4.00)	0.50 (2.75)						

PRE-M = premenopause; PERI-M = perimenopause; EP-M = early postmenopause; LP-M = late postmenopause;

Table 9. SF-MPQ Affective Score, adjusted for age and comorbidities

	Median Score (IQR)		Between-Subject Effects			Within-Subject Effects		
	1 week	6 months	F Statistic	df	p-value	F Statistic	df	p-value
PRE-M	0.00 (4.00)	0.00 (0.00)	0.540	3	0.66	1.745	3	0.16
PERI-M	0.00 (3.75)	0.00 (0.00)						
EP-M	0.00 (1.00)	0.00 (1.00)						
LP-M	0.00 (1.00)	0.00 (0.00)						

PRE-M = premenopause; PERI-M = perimenopause; EP-M = early postmenopause; LP-M = late postmenopause;

Table 10. SF-MPQ Total Score, adjusted for age and comorbidities

	Median Score (IQR)		Between-Subject Effects			Within-Subject Effects		
	1 week	6 months	F Statistic	df	p-value	F Statistic	df	p-value
PRE-M	2.00 (4.00)	0.30 (2.00)	0.070	3	0.98	2.320	3	0.08
PERI-M	2.00 (4.00)	0.20 (2.00)						
EP-M	4.00 (4.50)	2.00 (4.00)						
LP-M	2.00 (5.00)	1.00 (3.00)						

PRE-M = premenopause; PERI-M = perimenopause; EP-M = early postmenopause; LP-M = late postmenopause;

Table 11. SF-MPQ Number of Words Chosen, adjusted for age and comorbidities

	Mean Score ± SD		Between-Subject Effects			Within-Subject Effects		
	1 week	6 months	F Statistic	df	p-value	F Statistic	df	p-value
PRE-M	2.61 ± 2.33	1.50 ± 0.80	1.894	3	0.13	1.757	3	0.16
PERI-M	2.50 ± 2.29	1.39 ± 0.70						
EP-M	3.44 ± 3.00	1.94 ± 1.07						
LP-M	2.58 ± 2.48	1.61 ± 0.91						

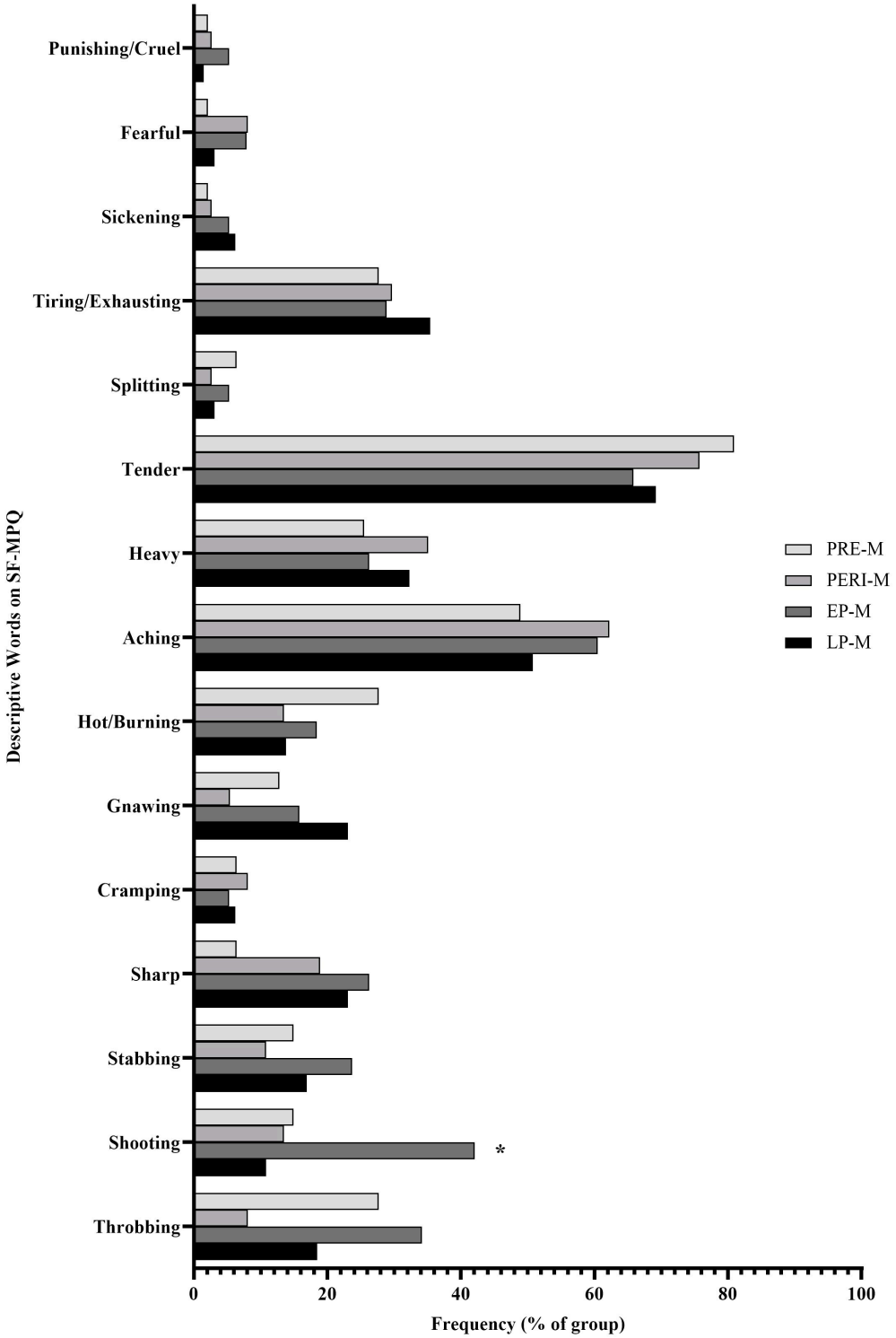
PRE-M = premenopause; PERI-M = perimenopause; EP-M = early postmenopause; LP-M = late postmenopause

(3) Pain Quality

The most commonly chosen words on the SF-MPQ elucidate the quality of women's pain after BCS[31]. Only those who selected at least one word were included in this analysis (1 week: n = 187, 6 months: n = 83). At 1 week (Figure 4), the top two qualities selected by the women were "tender" (PRE-M = 80.9%, PERI-M = 75.5%, EP-M = 65.8%, LP-M = 69.2%) and "aching" (PRE-M = 48.9%, PERI-M = 62.2%, EP-M = 60.5%, LP-M = 50.8%), regardless of their menopausal status group. For EP-M women, "shooting" pain was the next most common descriptor (42.1%) and was chosen more often than by the other menopausal status groups ($p < 0.001$). At 6 months (Figure 5), the most commonly chosen words were "tender" (PRE-M = 64.7%, PERI-M = 66.7%, EP-M = 47.1%, LP-M = 45.9%) and "aching" (PRE-M = 47.1%, PERI-M = 41.7%, EP-M = 35.3%, LP-M = 51.4%) across all groups. There were no statistically significant differences between the proportions of women in each group selecting any of the words at this time point.

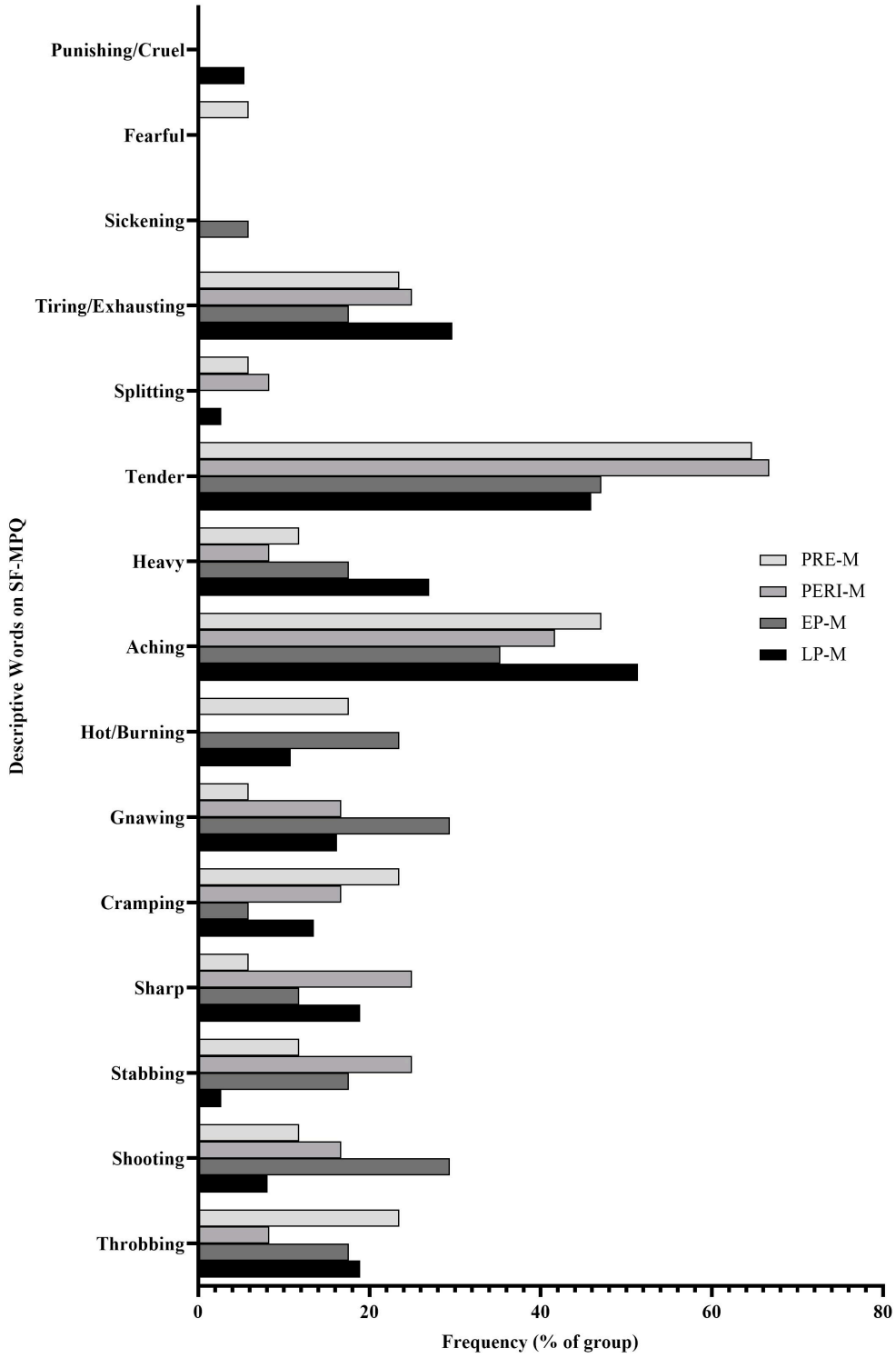
Presence of neuropathic qualities at 1 week and 6 months, and their change were also examined. At 1 week, the Chi-Square Test of Independence showed a difference among groups ($p = 0.03$), however, after applying the Bonferroni correction to the critical p-value, none of the groups were statistically significant (Table 12). At 6 months postoperatively, there were no differences in the proportion of women reaching threshold for neuropathic pain among groups ($p = 0.52$). Change in neuropathic pain was examined using a Chi-Square Test of Independence as well which was found to be significant ($p = 0.02$). Compared to other groups, a significantly higher proportion of LP-M women developed neuropathic pain by 6 months ($p = 0.0028$).

Figure 4. Most commonly chosen words at 1 week on SF-MPQ



PRE-M = premenopause; PERI-M = perimenopause; EP-M = early postmenopause; LP-M = late postmenopause. Only women who selected at least one word on the SF-MPQ to describe their pain were included in this analysis (n=187).
* = Significant difference from all menopausal status groups

Figure 5. Most commonly chosen words at 6 months (SF-MPQ)



PRE-M = premenopause; PERI-M = perimenopause; EP-M = early postmenopause; LP-M = late postmenopause.
Only women who selected at least one word on the SF-MPQ to describe their pain were included in this analysis (n=83).

Table 12. Proportion of Women with Neuropathic Pain

	1 Week (p=0.03)		6 Months (p=0.52)	
	No	Yes	No	Yes
PRE-M (n = 55)	36 (65.5%)	19 (34.5%)	47 (85.5%)	8 (14.5%)
PERI-M (n =44)	36 (81.8%)	8 (18.2%)	39 (88.6%)	5 (11.4%)
EP-M (n = 41)	31 (75.6%)	10 (24.4)	37 (90.2%)	4 (9.8%)
LP-M (n = 92)	78 (84.8%)	14 (15.2%)	75 (81.5%)	17 (18.5%)
Total	179 (77.2%)	53 (22.8%)	198 (85.3%)	34 (14.7%)

PRE-M = premenopause; PERI-M = perimenopause; EP-M = early postmenopause; LP-M = late postmenopause;

Table 13. Change in neuropathic pain from 1 week to 6 months

	Total (n=232)	PRE-M (n = 55)	PERI-M (n =44)	EP-M (n = 41)	LP-M (n = 92)	X^2	df	p-value
No pain	155 (66.8%)	30 (54.5%)	34 (77.3%)	28 (68.3%)	63 (68.5%)			
Improved	43 (18.5%)	17 (30.9%)	5 (11.4%)	9 (22.0%)	12 (13.0%)			
Persistent	10 (4.3%)	2 (2.6%)	3 (6.8%)	3 (7.3%)	2 (2.2%)	19.149	9	0.02
Developed	24 (10.3%)	6 (10.9%)	2 (4.5%)	1 (2.4%)	15 (16.3%) *			

PRE-M = premenopause; PERI-M = perimenopause; EP-M = early postmenopause; LP-M = late postmenopause;
'No pain' means neuropathic pain was not reported at 1 week or 6 months; 'Improved' means neuropathic pain was reported at 1 week but not 6 months; 'Persistent' means neuropathic pain was reported at 1 week and 6 months; 'Developed' means neuropathic pain was reported at 6 months but not 1 week.
* = Significant difference from all menopausal status groups

(4) Impact of Pain on Quality of Life

Table 14. Impact Measures Descriptive Statistics for Women with and without Chronic Pain

	PRE-M		PERI-M		EP-M		LP-M	
Chronic Pain?	**No (n = 23)**	**Yes (n = 32)**	**No (n = 20)**	**Yes (n = 24)**	**No (n = 20)**	**Yes (n = 21)**	**No (n = 51)**	**Yes (n = 41)**
Pain Interference with Daily Life (BPI)								
Pre-Op	0.14 (0.96)	0.64 (1.00)	0.21 (0.96)	0.00 (0.99)	0.96 (3.14)	0.14 (1.93)	0.29 (1.29)	0.42 (0.96)
1 Week	1.50 (5.00)	3.11 (4.45)	1.93 (2.34)	3.36 (4.38)	3.39 (4.08)	2.29 (2.93)	0.57 (2.43)	2.14 (3.89)
6 Months	0.71 (0.90)	0.29 (0.90)	0.88 (0.90)	0.46(0.90)	0.90 (3.86)	0.00 (1.64)	0.07 (0.90)	0.00 (0.90)
Depressive Symptomatology (CES-D)								
Pre-Op	16.07 (18.50)	17.38 (8.98)	9.00 (11.26)	12.31 (9.00)	9.50 (8.00)	12.10 (14.00)	11.00 (16.00)	16.00 (17.31)
1 Week	6.00 (21.00)	11.50 (22.00)	8.50 (12.75)	10.50 (20.25)	10.50 (16.25)	14.00 (22.00)	6.0 (7.00)	7.00 (17.00)
6 Months	2.00 (7.00)	6.50 (6.62)	5.00 (8.00)	6.16 (7.70)	2.00 (5.50)	6.00 (5.74)	2.00 (7.00)	9.37 (18.25)
State Anxiety (STAI-S)								
Pre-Op	45.50 (17.00)	45.28 (21.72)	39.00 (12.96)	43.00 (12.80)	39.00 (17.17)	44.00 (20.00)	40.00 (21.68)	34.00 (17.00)
1 Week	25.00 (14.08)	33.50 (18.25)	28.00 (8.25)	33.00 (16.50)	27.50 (18.50)	28.00 (18.50)	25.00 (6.00)	28.00 (12.00)
6 Months	22.00 (9.40)	26.16 (9.28)	25.00 (13.25)	29.49 (9.79)	24.50 (5.65)	27.00 (4.86)	23.00 (6.00)	28.00 (15.00)
Physical Health-Related Quality of Life (SF-12 PCS)								
Pre-Op	54.33 ± 5.65	53.22 ± 8.20	50.48 ± 7.21	46.00 ± 9.88	52.10 ± 8.13	51.32 ± 6.85	51.78 ± 7.93	50.67 ± 9.29
1 Week	42.20 ± 9.40	35.81 ± 8.61	34.25 ± 8.26	33.94 ± 6.12	34.16 ± 7.66	37.98 ± 9.98	41.03 ±10.03	40.03 ± 12.23
6 Months	49.62 ± 7.11	44.35 ± 9.44	49.41 ± 8.74	41.59 ± 7.32	49.71 ± 6.78	45.29 ± 8.30	49.97 ± 8.94	40.50 ± 17.85
Mental Health-Related Quality of Life (SF-12 MCS)								
Pre-Op	47.19 ± 9.63	44.20 ± 10.59	49.20 ± 7.91	50.15 ± 10.46	50.46 ± 9.16	47.98 ± 10.61	50.43 ± 9.89	50.26 ± 8.11
1 Week	51.31 ± 9.57	47.84 ± 13.73	55.10 ± 6.95	54.97 ± 10.16	54.73 ± 9.52	49.91 ± 10.05	55.58 ± 10.03	53.71 ± 10.04
6 Months	56.07 ± 7.89	52.30 ± 9.61	53.04 ± 8.34	53.28 ± 10.26	55.51 ± 5.99	53.37 ± 8.27	55.47 ± 8.14	45.50 ± 13.02

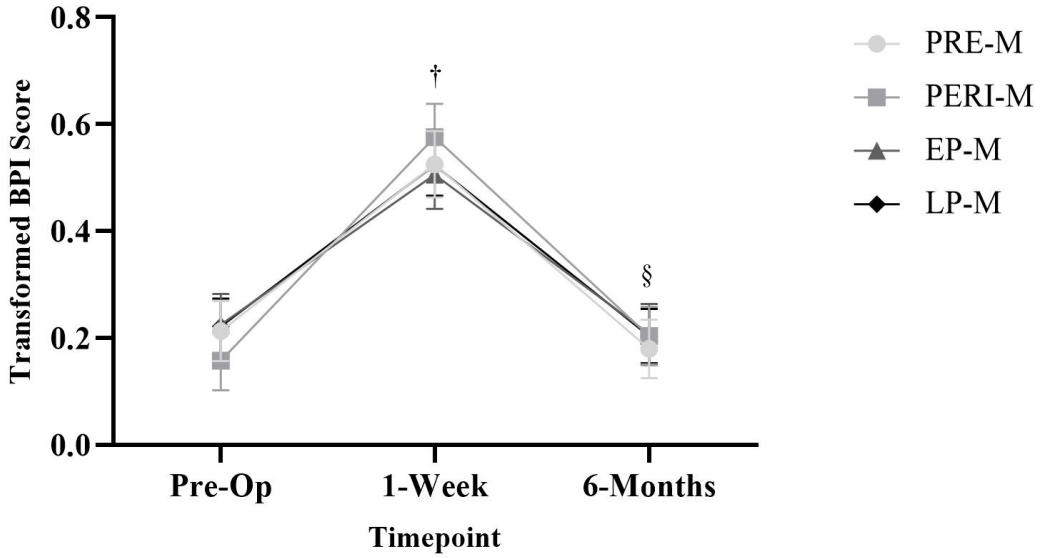
Values are frequency (IQR) and means ± SD.
PRE-M = premenopause; PERI-M = perimenopause; EP-M = early postmenopause; LP-M = late postmenopause;

Pain Interference with Daily Life (BPI-I):

BPI scores were not normally distributed and were transformed using a logarithmic transformation prior to analysis. Medians and interquartile ranges reported in Table 14. No interactions were found between time and chronic pain or menopausal status in relation to BPI-I scores. There was a significant main effect of time on pain interference [$F(2, 224) = 3.132$, $p = 0.05$]; a planned polynomial contrast revealed a quadratic effect ($p = 0.03$). Interference peaked

at 1 week postoperatively, and by 6 months decreased to preoperative values for all menopausal status groups (Figure 6).

Figure 6. Main Effect of Time on Pain Interference with Daily Life (BPI-I)



PRE-M = premenopause; PERI-M = perimenopause; EP-M = early postmenopause; LP-M = late postmenopause;
† = Significant difference from baseline; § = Significant difference from 1 week

Depressive Symptomatology:

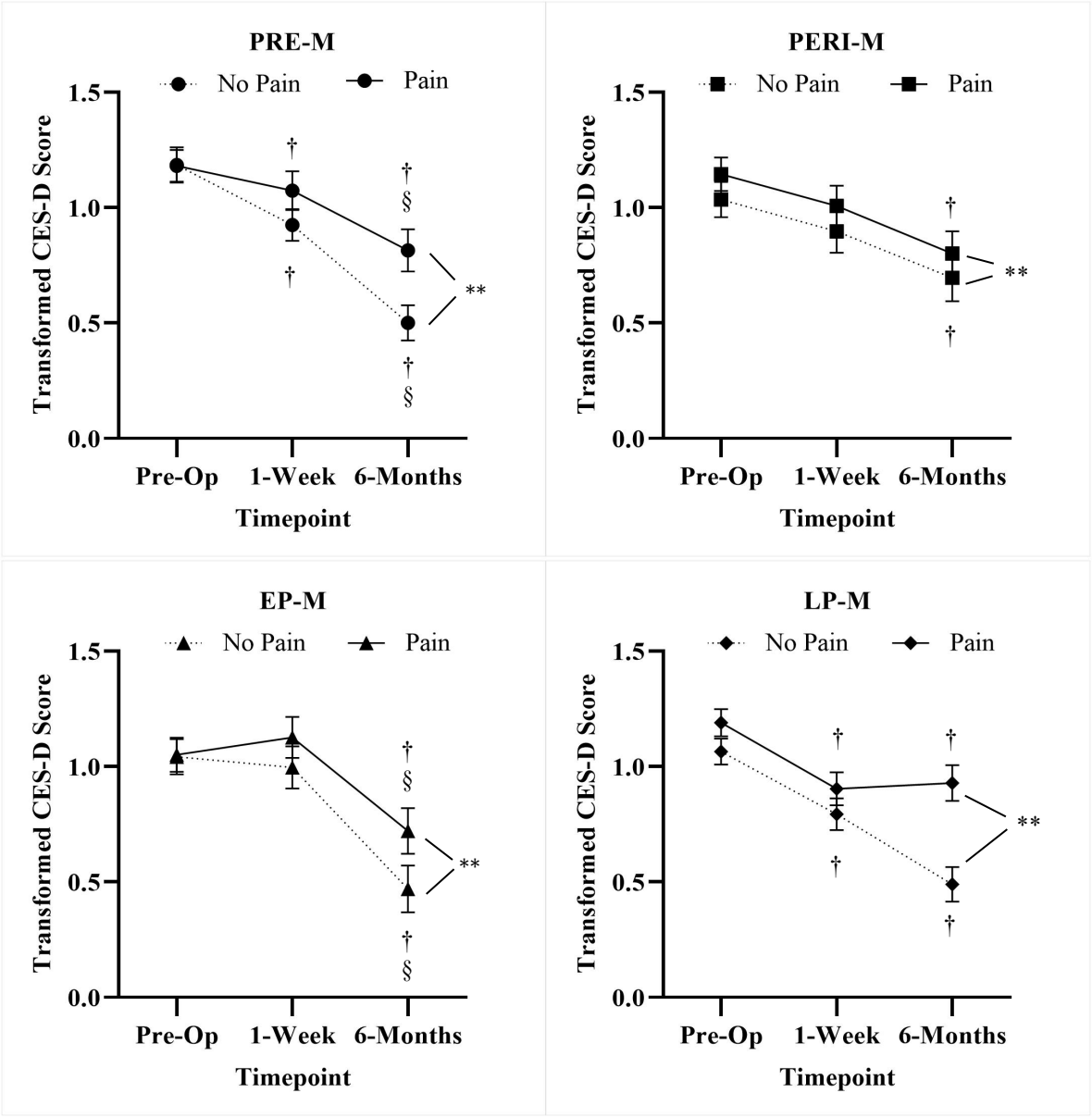
CES-D scores were not normally distributed and were transformed using a logarithmic transformation prior to analysis; medians and interquartile ranges are reported in Table 14. A significant two-way quadratic ($p = 0.001$) interaction was observed between time and menopausal status ($p = 0.003$); that is, the trajectory of scores was different between the menopausal status groups regardless of pain status (Figure 7). Namely, CES-D scores for PRE-M continued to decrease significantly across the three timepoints (all $p < 0.001$); the depressive symptomatology of PERI-M women did not decrease significantly between pre-op and 1 week ($p = 0.07$) but by 6 months, it was lower than pre-op values ($p = 0.03$). Similarly, in EP-M, pre-operative and 1 week postoperative CES-D scores did not differ ($p = 1.00$), but were

significantly decreased by 6 months ($p < 0.001$). Lastly, in LP-M CES-D scores decreased between pre-op and 1 week ($p < 0.001$), but did not change between 1 week and 6 months ($p = 0.07$).

Another two-way interaction was found between time and pain [$F(2,448) = 5.812$, $p = 0.004$)]. A planned polynomial contrast revealed the effect was linear ($p = 0.001$). Furthermore, as indicated by a Bonferroni post-hoc test, CES-D scores were significantly higher at 6 months ($p < 0.001$) but not at 1 week ($p = 0.07$) following surgery in women with chronic pain than women without pain. In other words, prior to the surgery CES-D scores did not differ among the menopausal status groups regardless of their subsequent pain status six months later. At 1 week, there was still no difference in CES-D scores between the 'pain' and 'no pain' groups, but by 6 months post-surgery the scores were significantly different. Although a three-way interaction between time, pain, and menopausal status did not reach statistical significance ($p = 0.38$), it is important to note that the LP-M group with chronic pain had the highest CES-D score 6 months after surgery (median = 9.37), and showed the largest score difference between those with and without chronic pain (2.00 - 9.37; Table 14).

Additionally, with respect to the proportion of women reaching threshold for clinically depressive symptomatology, no significant group differences were found preoperatively or at 1 week. However, by 6 months postoperatively, a significantly higher proportion of LP-M women with chronic pain (36.6%) were above threshold ($p < 0.001$) than women in the other menopausal status groups (Table 15).

Figure 7. Depressive Symptomatology Scores (CES-D) for Women with and without Chronic Pain



PRE-M = premenopause; PERI-M = perimenopause; EP-M = early postmenopause; LP-M = late postmenopause; solid line = women presenting with chronic pain by 6 months (at rest or with movement); dashed line = women who do not develop chronic pain. † = Significant difference from baseline; § = Significant difference from 1 week; ** = Significant difference between 'pain' and 'no pain' group

Table 15. Frequency of Depressive Symptomatology in Women with Chronic Pain

		PRE-M (n = 32)	PERI-M (n = 24)	EP-M (n = 21)	LP-M (n = 41)	X^2	df	p-value
Pre-Op	Below Cutoff	15 (46.9%)	17 (70.8%)	14 (66.7%)	20 (48.8%)	5.06	3	0.17
	Above Cutoff	17 (53.1%)	7 (29.2%)	7 (33.3%)	21 (51.2%)			
1 Week	Below Cutoff	17 (53.1%)	15 (62.5%)	11 (52.4%)	27 (65.9%)	1.75	3	0.63
	Above Cutoff	15 (46.9%)	9 (37.5%)	10 (47.6%)	14 (34.1%)			
6 Months	Below Cutoff	28 (87.5%)	22 (91.7%)	18 (85.7%)	26 (63.4%)	10.50	3	0.02
	Above Cutoff	4 (12.5%)	2 (8.3%)	3 (14.3%)	15 (36.6%) *			

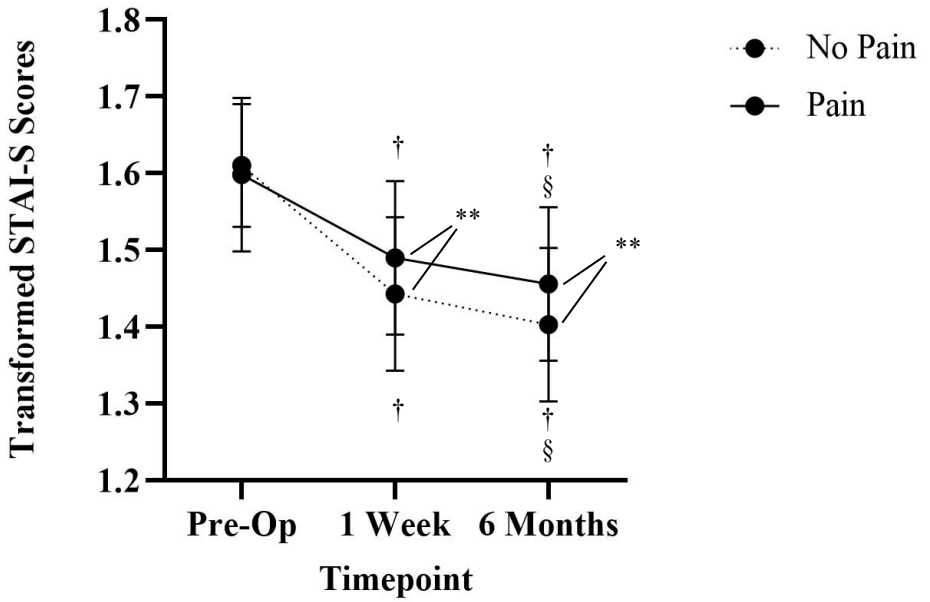
Values are frequencies (% of group). PRE-M = premenopause; PERI-M = perimenopause; EP-M = early postmenopause; LP-M = late postmenopause. Clinical cutoff score for depressive symptomatology is CES-D ≥ 16.
* = Significant difference from all menopausal status groups

State Anxiety:

STAI-S scores were not normally distributed and were transformed using a logarithmic transformation prior to analysis. Medians and interquartile ranges are reported in Table 14. A significant linear interaction was found between time and pain [$F(2,448) = 3.871$, $p = 0.02$]. Anxiety scores decreased significantly between the preoperative assessment, 1-week follow-up, and 6-month follow-up for all menopausal status groups. A Bonferroni post-hoc analysis showed that compared to women who do not develop chronic pain, those that do have significantly higher anxiety scores at 1 week ($p = 0.002$) and 6 months ($p = 0.002$) following surgery but not preoperatively (Figure 8). Furthermore, a trend for a three-way interaction between time, pain, and menopausal status was found ($p = 0.07$), suggesting the trajectory of STAI-S scores for each menopausal status group differs for women who develop chronic pain and those who do not. Although the analysis was not statistically significant, an exploratory, hypothesis-generating post-hoc analysis was conducted out of the author's personal interest. The post-hoc revealed that at 1 week, PRE-M women who do develop chronic pain show a slightly, but not statistically significant, higher anxiety score than their 'no pain' counterpart ($p = 0.06$), but by 6 months after surgery there is no difference ($p = 0.37$). The STAI-S scores for PERI-M and EP-M women with chronic pain were not significantly higher than the 'no pain' group at 1 week ($p = 0.35$ and $p =$

0.54, respectively) or at 6 months (p = 0.42 and p = 0.16, respectively) after surgery. Contrary to other menopausal status groups, LP-M women who went on to develop chronic pain exhibited significantly higher state anxiety scores both at 1 week (p = 0.04) and especially 6 months after surgery (p = 0.006) than those who did not develop chronic pain. As this analysis did not reach statistical significance, a figure is not presented and no definitive conclusions can be drawn.

Figure 8. State Anxiety (STAI-S) in Women with and without Chronic Pain



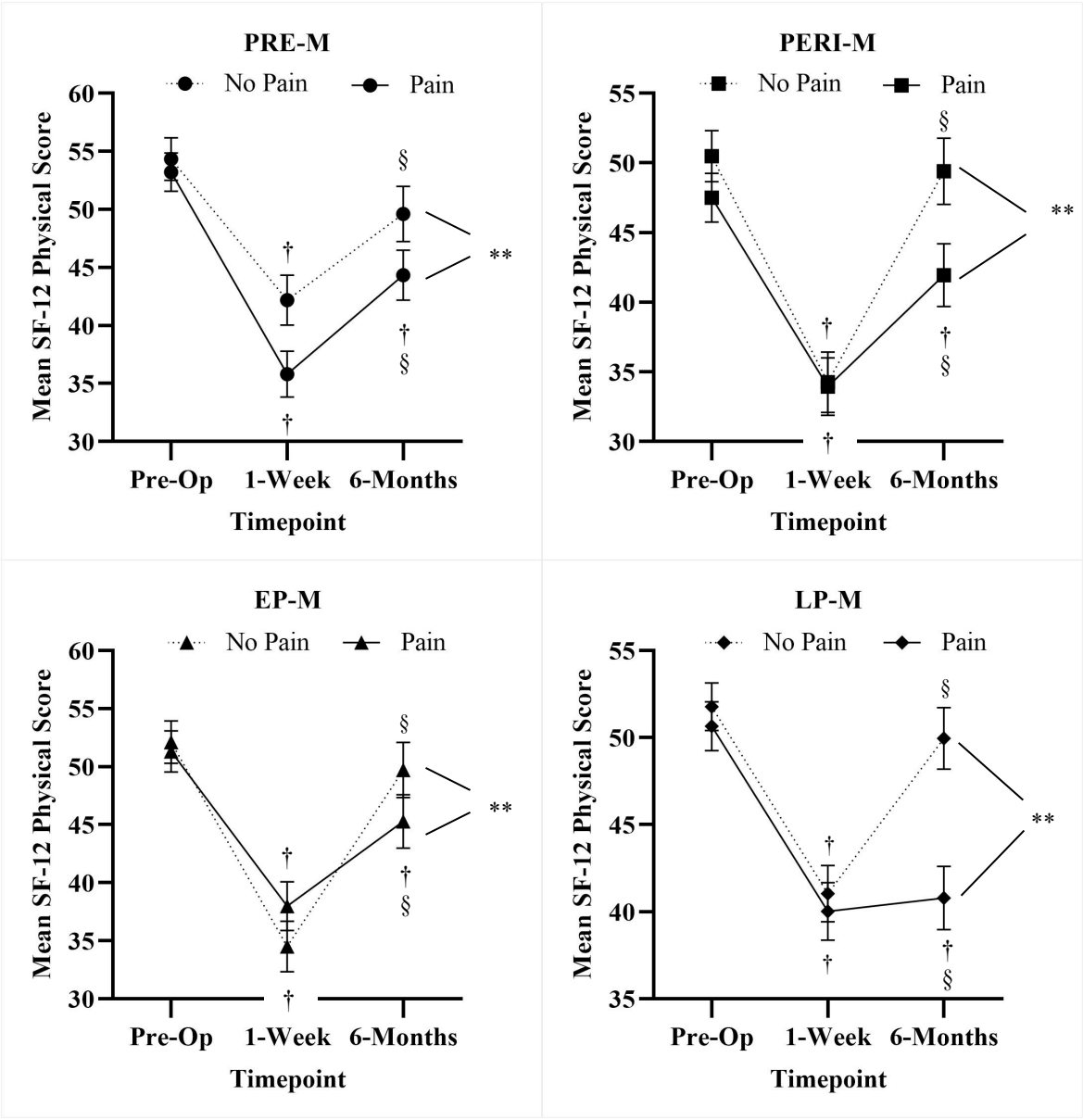
Solid line = women presenting with chronic pain by 6 months (at rest or with movement); dashed line = women who do not develop chronic pain. † = Significant difference from baseline; § = Significant difference from 1 week;
** = Significant difference between 'pain' and 'no pain' group

Physical Health-Related Quality of Life (SF-12 PCS):

A two-way interaction between time and pain was identified [F(2, 444) = 6.566, p = 0.002], and a planned polynomial contrast revealed the relationship is quadratic (p = 0.03). SF-12 scores were highest preoperatively and decreased significantly 1 week after surgery with a subsequent increase to pre-op levels at 6 months. At the 6-month time point the "no pain" groups had higher scores than the "pain" groups (Figure 9). A significant main effect of menopausal

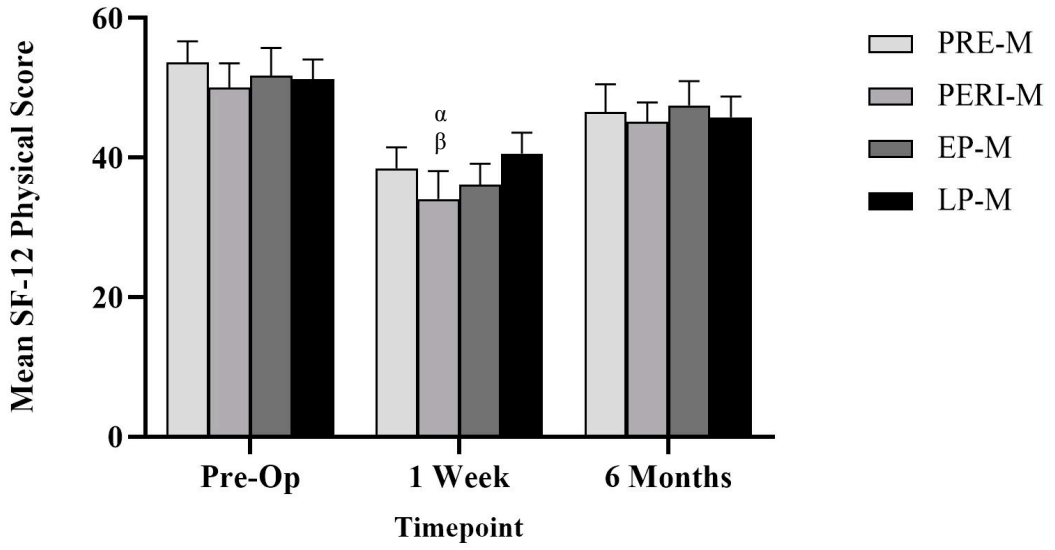
status on SF-12 PCS scores was also found (p = 0.005); Bonferroni`s post-hoc test revealed PERI-M had lower scores than all groups at every time point, but only reached statistical significance compared to PRE-M (p = 0.048) and LP-M (p = 0.007) at 1-week (Figure 10)

Figure 9. Physical Health-Related Quality of Life (SF-12 PCS) in Women with Chronic Pain and Without



PRE-M = premenopause; PERI-M = perimenopause; EP-M = early postmenopause; LP-M = late postmenopause Solid line = women presenting with chronic pain by 6 months (at rest or with movement); dashed line = women who do not develop chronic pain. † = Significant difference from baseline; § = Significant difference from 1 week; ** = Significant difference between 'pain' and 'no pain' group

Figure 10. Main Effect of Menopausal Status on Physical Health-Related Quality of Life



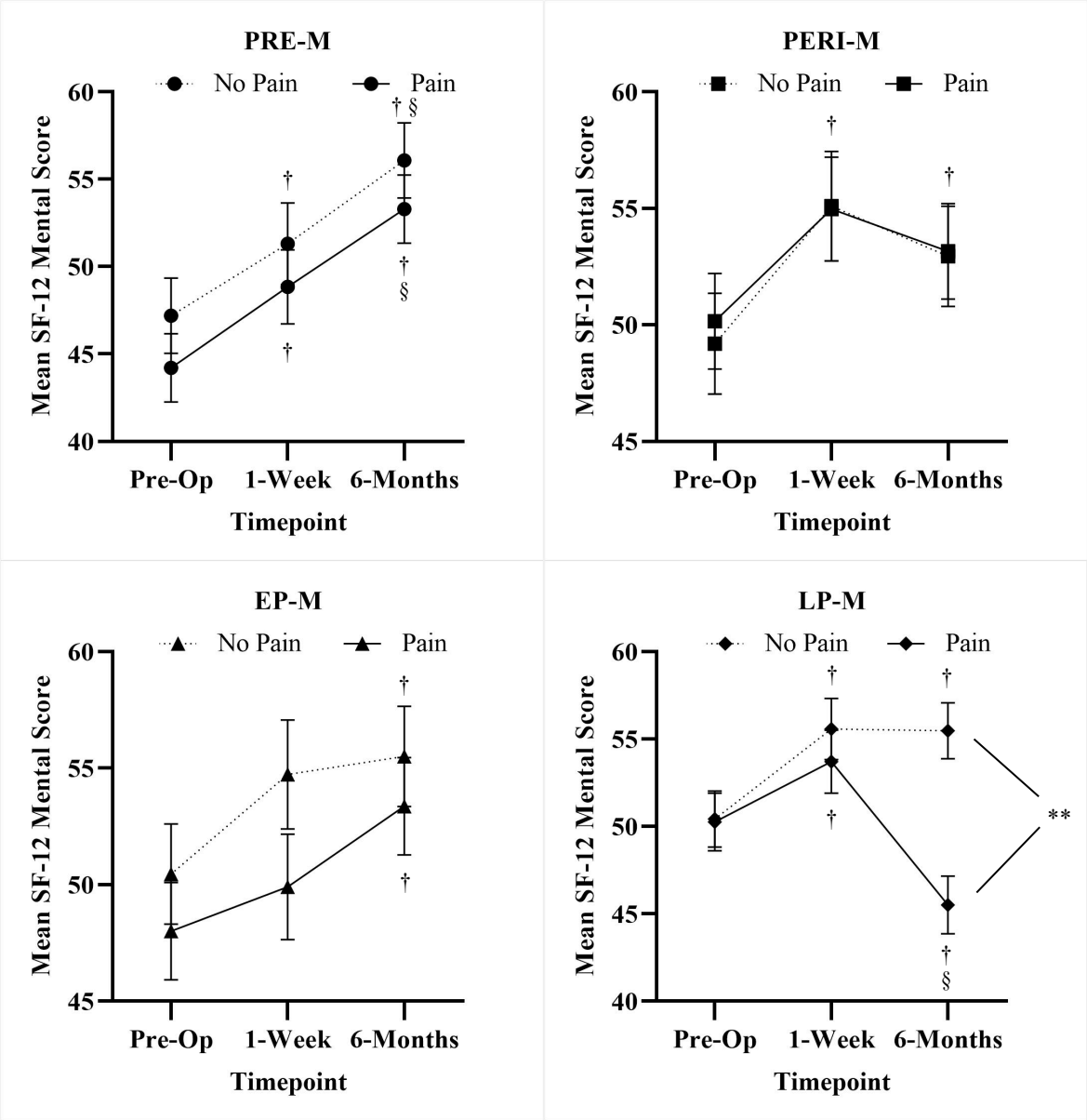
PRE-M = premenopause; PERI-M = perimenopause; EP-M = early postmenopause; LP-M = late postmenopause
α = Significant difference from PRE-M; β = Significant difference from LP-M

Mental Health-Related Quality of Life (SF-12 MCS):

A statistically significant three-way interaction between time, pain and menopausal status [$F(6, 444) = 2.342$, $p = 0.036$] was found in this analysis (Figure 11). That is, the time trajectory of mental HRQoL scores differed between menopausal status groups and depending on the development of chronic pain. PRE-M women had statically equal SF12MCS scores prior to their surgery regardless of whether they went on to develop chronic pain or not ($p = 0.26$). Moreover, they had the lowest pre-op score of all the groups, but only reached a statistically significant difference with LP-M ($p = 0.03$). There was a statically significant increase in a SF12MCS scores by 1 week after surgery (preop vs. 1 week SF12MCS: $p = 0.005$) but again, had the lowest mean score of all the groups reaching a statistically significant difference with PERI-M ($p = 0.04$) and LP-M ($p = 0.03$). However, there was no difference between PRE-M women who did and did not develop chronic pain ($p = 0.22$). Lastly, by 6 months postoperatively, women's scores had increased further (1 week vs. 6 months SF12MCS: $p = 0.005$) but again, did not differ

based on chronic pain status in the PRE-M group ($p = 0.15$). PERI-M women also did not differ between the "pain" and "no pain" groups prior to the surgery ($p = 0.74$), at 1 week ($p = 0.97$) or 6 months ($p = 0.93$). The mental HRQoL scores increased significantly by 1 week after surgery (preop vs. 1 week SF12MCS: $p<0.001$) but remained the same thereafter (1 week vs. 6 months SF12MCS: $p = 0.85$) for PERI-M. Next, the SF12MCS scores for the EP-M group also did not differ between those women who eventually developed chronic pain and those who did not, prior to the surgery ($p = 0.41$), at 1 week ($p = 0.14$) or 6 months post-op ($p = 0.47$). The mental HRQoL scores increased significantly between the preoperative assessment and 6 months ($p = 0.01$) but not between consecutive timepoints (preop vs. 1 week SF12MCS: $p=0.08$, 1 week vs. 6 months SF12MCS: $p = 0.72$). Lastly, the trajectory of the LP-M group varied considerably from the rest of the menopausal status groups. Between the preoperative period and 1 week after surgery, scores increased significantly ($p < 0.001$) and did not differ between the "pain" and "no pain" groups neither at preop ($p = 0.93$), nor at 1 week ($p = 0.39$). However by 6 months, chronic pain affected mental HRQoL significantly in this menopausal status group ($p < 0.001$). While, the scores of the "no pain" did not change (1 week vs. 6 months SF12MCS: $p = 1.00$), for "pain" group, SF12MCS scores decreased significantly (1 week vs. 6 months SF12MCS: $p < 0.001$) to a mean value lower than that at pre-op (50.35 vs. 45.50). At the 6 month time-point, the scores of LP-M women with chronic pain were significantly lower than those of PRE-M ($p = 0.02$), PERI-M ($p = 0.01$), and EP-M ($p = 0.01$) with chronic pain.

Figure 11. Mental Health-Related Quality of Life (SF-12 MCS) in Women with and without Chronic Pain



PRE-M = premenopause; PERI-M = perimenopause; EP-M = early postmenopause; LP-M = late postmenopause; Solid line = women presenting with chronic pain by 6 months (at rest or with movement); dashed line = women who do not develop chronic pain. † = Significant difference from baseline; § = Significant difference from 1 week; ** = Significant difference between 'pain' and 'no pain' group

DISCUSSION

Women undergoing surgery as treatment for breast cancer experience moderate-to-severe APOP, and in some patients, this transitions into chronic pain. With an increasing survival rate, it is important to continue to identify factors that affect patients' postoperative experience, including pain. Given that BCS is often performed when many patients are undergoing menopausal transitions[116], this was an important factor to consider. The present study evaluated women's pain prevalence, intensity, quality, and impact on QoL after BCS based on menopausal status. This is the first study, to our knowledge, to consider the relationship between menopausal status and pain after BCS, while simultaneously examining its long-term psychological impact. The results of the study suggest that despite undergoing the same procedures, each menopausal status group experiences the postoperative period slightly differently. PRE-M women were more likely to exhibit persistent pain up to six months after surgery, but the LP-M group had a higher proportion of women who developed neuropathic pain by six months after surgery. Moreover, LP-M women were impacted by chronic pain to a higher degree than other groups, as observed by their depression, anxiety, and HRQoL scores.

Acute Postoperative Pain Outcomes

The groups did not significantly differ on any preoperative clinical or surgery-related factors with the exception of age and comorbidities. Importantly, we included these factors as covariates in appropriate analyses, thereby removing the effect of age from menopausal status which has not always been done in the past[96]. Assessment of the intensity of APOP at rest is important for making the patient comfortable. But adequate pain relief during movement, deep

breathing, and coughing is important for reducing risks of cardiopulmonary and thromboembolic complications[31].

This study found that 64.2% experienced pain at rest 1 week after surgery, and for almost a quarter of these women, it was rated as moderate-to-severe. A much larger proportion (86.6%) experienced pain with movement, with almost half of these patients reporting moderate-to-severe APOP. Our NRS cutoff of ≥4 to indicate clinically relevant moderate-to-severe pain is comparable with other literature of BCS and other surgical procedures[6,40,43]. Such pain scores have been demonstrated to affect activity, mood, mobility, and are considered an important treatment outcome[43]. The prevalence of moderate-to-severe movement-evoked pain was comparable to existing literature on APOP after BCS[40], however, the proportion of patients with moderate-to-severe resting pain was lower in our study. For example, Bruce et al. (2012)[40] assessed patients on the seventh post-operative day and asked for an average pain rating over the previous week, while in our study patients were asked for a pain report at the time of assessment. This may partially explain the discrepancy as recall and averaging pain ratings introduce memory, recency, and primacy biases into self-report[160–162].

Menopausal status group differences in prevalence of resting pain were not evident at 1 week, but LP-M women were significantly less likely than the other groups to report movement-related pain after surgery. This analysis cannot account for covariates due to limitations of the test, and thus may in fact, confirm previously reported age-related effects[163-165]. Evidence indicates that older adults are more likely to report satisfaction with health services in the context of unmet needs[163], due to misconceptions about pain being a normal part of the aging process[164]. In acute care settings, older patients also seem to have a tendency to minimize their complaints and underreport POP[163]. Proposed explanations for this reluctance include misconceptions about

pain being indicative of severe pathology, potential necessity for additional tests or medications, and fear of loss of independence[165].

Pain was not significantly different between menopausal status groups, at 1 week postoperatively, when measured using the NRS mean score, level of pain (no pain, mild, moderate, severe), or the SF-MPQ sensory, affective and total score. The relationship between acute pain intensity and menopausal status is rarely studied in humans; we rely on animal studies for some insight. For example, Beatty and Fessler (1977) did not find differences between intact and OVX animals when administering an acute electrical shock to adult rat tails[166]. A more recent study by Ceccarelli et al. (2003) also showed that the thermal pain threshold (acute pain model) did not significantly differ between OVX and intact rats[167]. On the other hand, a study by Barrett et al. (2003) found that OVX rats had decreased thermal hyperalgesia after exposure to carrageenan (acute injury model[168]) administration[169]. There are several methodological considerations, however, when making cross-species generalizations. The human reproductive cycle differs from that of rats[110], and may modulate pain sensitivity through an effect on the affective state which is not usually considered in rodents[55]. Also, animal studies analyze nociception either during consistent estrogen exposure or at a single time point after administration, yet hormonal fluctuations appear to be more relevant than absolute levels for some types of pain[89]. Moreover, examining animals that are young and healthy may not be comparable to the human menopausal woman, given older age, surgical history and previous pain experiences[111]. As such, it is important to exercise great caution when making comparisons between the animal and human models[112].

In summary, we found an equally high prevalence of APOP in all menopausal status groups despite administration of analgesics, supporting the need for better understanding of pain

management after BCS. Given that acute pain is one of the most consistently reported predictors of chronic pain[170] and that unrelieved postoperative pain increases the risk of physiological and psychological adverse events[171], better pain management will not only improve the immediate post-surgical experience but could also improve long-term outcomes.

Chronic Postoperative Pain Outcomes

Persistent postsurgical pain develops in 10-50% of patients undergoing various operations, including BCS[9]. Consistent with other studies[9,172,173], we found that over a quarter of women reported BCS-related pain at rest and almost half reported pain with movement six months after surgery. Risk factors for the development of CPOP are multiple, including longer duration of surgery[42,43], type of stitches[44], and intraoperative nerve damage[45,46]. There is also some evidence that more frequent catastrophizing prompts earlier medical treatment and mobilization of support resources[30], and thus better long-term outcomes. However, a more consistent finding in pain literature is that chronic pain patients who do not catastrophize fare better than patients who do catastrophize[47]. Other psychological predictors of CPOP include higher preoperative depression[30] and anxiety[43], and introverted personality[39] have also been identified. This is the first study to consider the relationship between menopausal status and the development of CPOP after BCS.

Pain intensity at 6 months, as measured on the NRS-R, NRS-M, and SF-MPQ, was not found to be statistically significant among menopausal status groups. Out of the full patient sample that experienced pain at rest, 72.8% had no pain, 22.4% had mild pain, 3.4% had moderate pain, and 1.3% had severe pain. Movement-evoked pain was more prevalent in this

sample; 50.9% women had no pain with movement at 6 months, while 35.3% had mild pain, 9.5% had moderate pain, and 4.3% had severe pain.

Among the women with resting pain 6 months after surgery, 19.0% also presented with pain 1 week after surgery ("persistent pain"). Our preliminary results show that the PRE-M group had a significantly higher proportion of women (32.7%) with persistent resting pain than others. This may be an age-related effect as this analysis did not account for covariates, and thus would be consistent with past research which repeatedly shows that younger women are at higher risk for persistent post-surgical pain[30,39,174]. However, evidence also suggests that female gender increases the likelihood of developing CPOP largely due to their endocrinological profile[175]. A larger proportion of women experienced persistence of movement-evoked pain (43.1%) between 1 week and 6 months, but there was no group differences found. More research is required to examine menopausal status as a risk factor for POP persistence.

Postoperative Pain Qualities

Changes in pain quality, or how the pain feels[128], have been reported to affect QoL beyond changes in intensity[176]. Evaluating pain qualities may provide information about the etiology of pain and thus, result in better treatment[177]. Consequently, pain descriptor words on the SF-MPQ were also assessed in this study at 1 week and 6 months after surgery. The most frequently selected words on this questionnaire were "tender" and "aching" at both time points regardless of menopausal status. These words are comparable to qualities commonly selected in studies of other surgical populations[128,130,178]. Specifically for EP-M women, "shooting" pain was the next most common descriptor at 1 week (42.1%), and was chosen significantly more often than by the other menopausal status groups ($p < 0.001$).

ALND is often a necessary part of the surgical procedure, but poses a risk to the intercostobrachial nerve from stretching or transection[11], sometimes resulting in neuropathy. In our study, based on the selection of neuropathic qualities, which included numbness, tingling and pain due to touch, over 20% of women at 1 week and almost 15% at 6 months were classified as having probable neuropathic pain. Bruce et al. (2014)[12] found a slightly higher pain prevalence of predominantly neuropathic origin – 24% at nine months after BCS – while Bredal et al. (2014)[236] reported the occurrence of neuropathy-related symptoms in 33.8% of participants. Furthermore, our results show that at 6 months, half of those with neuropathic pain were women in the LP-M group. The majority of LP-M women with neuropathic pain at 6 months, did not report neuropathic qualities at 1 week suggesting that they are more likely than women with another menopausal status group to develop neuropathic pain over time. This is consistent with data from animal models demonstrating that low estrogen levels are associated with higher incidence of peripheral neuropathy[142]. Similarly, other human studies have also reported on estrogen's protective and reparative effects on neural tissue, both in the central as well as the peripheral nervous system[179,180]. In contrast, Coyle et al. (1995) reported that intact female rats were more likely to develop neuropathic pain than OVX females following partial sciatic nerve ligation[181]. Taken together, these findings suggest that women in LP-M may be at increased risk for neuropathic pain at least in part because of loss of the protective effects of estrogen.

Impact on Quality of Life

With ever increasing evidence in support of the biopsychosocial model of pain, it is suggested that cognitive and emotional processes are crucial contributors to inter-individual differences in the perception and impact of pain[182]. Depression[30] and anxiety[43] are established

risk factors for the development of CPOP, but have also been proposed as an outcome of unresolved pain[183]. Bair et al. (2003)[184] reported a high co-occurrence rate for pain and depression, and McWilliams et al. (2003)[185] found that anxiety disorder was present in over a third of people with chronic pain, versus only 18% in the general population. This is in addition to other negative consequences including diminished sleep quality[186], reduced physical function and activity[187], as well as difficult family[188,189] and workplace interactions[183]. The biopsychosocial model provides a framework for understanding how chronic pain is affected by, and in turn, influences a patient's QoL. In this study, the impact of chronic pain after BCS was assessed by comparing the women who developed it to those who did not on a number of attributes including interference with daily life, depression, anxiety, as well as physical and mental HRQoL.

Pain Interference: It is recommended that functional impairment caused by CPOP is assessed to give the full picture of disability[190–192]. The interference subscale of the BPI is a general measure of the impact of pain on functioning, and includes the following items: general activity, mood, walking ability, normal work, relations with other people, sleep and enjoyment of life. We did not find menopausal status differences in pain interference; therefore, the group was considered as a single sample when describing findings. Prior to the surgery, patients' median interference score was 0.29 with an interquartile range of 0.96 meaning they did not experience substantial interference. A significant main effect of time was found, showing that interference peaked at 1 week with a median of 2.14 and an interquartile range of 3.86. Six months after surgery, the patients' scores returned to near pre-operative values with a median of 0.39 and interquartile range of 0.9.

An observational study of patients enrolled in the European PAIN OUT registry evaluated the incidence of CPOP across 21 hospitals in 11 European countries, where 3120 patients were analyzed immediately after surgery, 1044 six months after surgery and 889 twelve months after surgery[190]. The types of surgeries included in the study were cholecystectomy, surgery for breast cancer, hysterectomy, and knee surgery, among others. It was found that BPI items reflecting functional impairment ('interference subscale' in our study) were significantly correlated with severity of chronic pain. That is, patients with severe CPOP reported that it interfered more with activities and mood at 6 months and 12 months postoperatively, than those with moderate CPOP[190]. In our study, we did not categorize the severity of chronic pain (mild, moderate, severe), but rather, only the presence or absence of it. Our results indicate that development of chronic pain did not have a significant impact on BPI-I values at any of the measurement time points. Although this may seem contrary to the study by Fletcher et al. (2015)[190], it is important to note that BCS was one of the larger surgery groups in the study, yet the incidence of moderate and severe CPOP for this group was relatively low (9% at 12 months). The majority of BCS patients in that study either did not develop chronic pain after the surgery (60.4% at 12 months) or had mild CPOP (30.6% at 12 months), and their BPI-I scores were not significantly different from each other or from the 'moderate pain' group.

Another study by Gjeilo et al. (2010) examined chronic pain at various pain sites and HRQoL after cardiac surgery[193]. Like in the present study, patients were divided into those who did develop chronic pain and those who did not (12 months postoperatively) and asked to complete the BPI, including the severity and interference subscales. It was found that 33% of patients with chronic pain reported moderate to severe levels of interference with "general activity" and "walking", and 23% reported moderate to severe interference with "relations".

Patients reporting chronic pain at the sternum and leg sites showed a trend towards significantly higher BPI scores compared to patients reporting pain at the sternum site only ($p=0.051$)[193]. However, similarly to our findings, there was no significant difference in interference scores when comparing patients with and without chronic pain[193].

Although the BPI has been validated for use in the breast cancer population[134] and in patients with CPOP[135], our results indicate that chronic pain did not have a significant effect on activity and daily functioning. However, several studies[194-196] suggest that a three-factor model including pain severity, and specifically distinguishing between activity/physical interference, affective/emotional interference is more appropriate for some types of pain. As such, it can be argued that our failure to find BPI-I differences between women who developed chronic pain and those who did not by 6 months after BCS, may be due our choice not to separate physical and emotional interference.

A 2008 study by Holen et al. aimed to explore the differences in responses to the interference items of the BPI questionnaire, by comparing patients with cancer-related chronic pain (arising from the diagnosis or treatment) and patients with non-cancer-related chronic pain[194]. Pain interference was indexed into interference with physical functions, interference with psychological functions, and total interference. It was found that patients with cancer-related pain reported higher values of physical interference, while those with non-cancer-related pain had higher values of psychological interference. The results also suggest that patients had difficulty isolating pain ratings from level of interference[194]. Furthermore, a study by Atkinson et al. (2011)[195] examined the construct validity of BPI by comparing a two-factor model (pain intensity and pain interference) to a three-factor model (pain intensity, activity/physical interference, affective/emotional interference). Based on a confirmatory factor analysis conduced

on a range of demographic variables (disease, age, ethnicity) in patients with HIV/AIDS or cancer, it was suggested that the three-factor model be used in clinical research instead of the existing two-factor model[195]. Building on these findings and addressing previous methodological concerns, the authors evaluated their three-factor model on data collected from 184 prostate cancer patients, and found that the three-factor model was superior to the two-factor model and thus selected as the best fit for the data[196]. Using data from patients in ambulatory settings with arthritis, injury/trauma related pain, back/neck pain, and postoperative pain, another study also analyzed the three-factor model against the two-factor. Contrary to the previous studies, Lapane et al. (2014)[197] found that a two-factor structure performed better than the three-factor, meaning it may be more appropriate for non-cancer pain. Taken together, the findings suggest that each of the three factors (pain intensity, activity interference, affective interference) varied in importance depending on the origin of pain. In the case of the present study, analyzing a combined interference score may have obscured the effect of chronic pain on physical and psychological interference individually. Evidently, the diversity of the patient cohorts with respect to the underlying cause of pain, must be considered[197]. Moreover, assessment of the differential contribution of the factors may be an important avenue for future research, and as suggested by the authors, with a focus on differences between acute and chronic pain[197].

Depression: Depression is a well established risk factor for the development of CPOP[30], but pain itself has also been shown to lead to depressive symptomatology[183,198]. Moreover, the comorbidity of these two conditions may have an additive adverse impact on QoL, disability, and response to treatment[199–204]. In our study, we examined the relationship between chronic pain after BCS and CES-D scores. Similar to a number of other postoperative studies[182,205–207], our patients' median CES-D scores were highest preoperatively and continued to decrease between

the preoperative period and 6 months after surgery. In other words, perhaps due to all of the potential health, lifestyle, and economic consequences, women exhibited more depressive symptoms before undergoing their surgery, but improved throughout their recovery time[208]. Consistent with a large body of literature[184,187,209,210], our results show that women who developed chronic pain exhibited significantly higher CES-D scores. Since there was no difference between the 'pain' and 'no pain' groups before surgery, it is presumable that preoperative CES-D scores did not predict chronic pain. One week postoperatively, the scores for the chronic pain group were slightly higher and trending towards significance, and by 6 months, the difference was even greater. Although the present study did not examine the by-directional relationship in-depth, whereby depression and chronic pain influence one another[204], our results suggest it is also evident in the BCS patient population. Further research is warranted to continue exploring the intimate linkage, and more specifically the cause-effect relationship between chronic pain and depression[204].

There was a significant interaction also observed between CES-D scores and menopausal status. That is, controlling for age and comorbidities, the trajectory of depressive symptomatology differed between the menopausal status groups. While PRE-M women continued to show improvement between the three time-points, PERI-M and EP-M women did not have a significant reduction in scores between pre-op and 1 week, but by 6 months were on par with the PRE-M group. In the LP-M group however, although the scores decreased by 1 week after surgery as compared to their preoperative values, unfortunately they remained unchanged between 1 week and 6 months. Although a three-way interaction did not reach statistical significance, six months after surgery the LP-M group *with* chronic pain had the highest median CES-D score and trended towards the largest score difference between those with

and without chronic pain. In addition, compared to other menopausal status groups, there was a significantly higher proportion of LP-M women with chronic pain reaching the threshold for clinically relevant depression scores. Depressive symptomatology in the menopausal transition has been examined in the past, but literature focusing on mental health after menopause (rather than during the transition) is limited despite encompassing up to a third of a woman's life[119]. Importantly, comparison between studies should be made with caution as the definition of the postmenopause varies considerably, with some authors describing a period lasting 2-3 years, while others a period of over 15+ years[119,211]. Moreover, those who subcategorize EP-M and LP-M have used between 2 and 8 years since final menstrual period as the marker. In 2008, Woods et al. summarized the findings of a 15-year study exploring depressed mood across the menopausal transition and into EP-M (up to 5 years since last menstruation). They found that age was modestly negatively associated with CES-D scores, while menopausal status showed no relationship at all[211]. A 2014 Penn Ovarian Aging Study[212] analyzed CES-D scores for 203 women, with (n=90) and without (n=113) a history of depression . Overall, the number of women reaching clinically significant CES-D scores (≥16) decreased by approximately 15% each year after menopause. The Women's Healthy Aging Project is an ongoing epidemiological study examining factors that contribute to healthy aging in Australia. A 2017 study by Campbell et al.[213] used twenty years of data from the project to assess the prevalence of negative mood and depressive symptoms (CES-D short form) in regards to chronological aging and reproductive aging. The results demonstrated that both negative mood and depressive symptoms were significantly higher in EP-M than in LP-M, but age had a stronger association than menopausal status with mood[213]. In summary, past research seems contrary to our findings in that EP-M women score higher on the CES-D; this may be a result of a number of methodological

differences. Firstly, and most importantly, to our knowledge there are no studies that examine depressive symptomatology in postmenopausal women specifically after surgery, which may be a key differentiating factor. Moreover, distinguishing between the effects of biological and reproductive ageing on depressive symptoms is most accurately captured in longitudinal studies with repeated measures and time since last menstrual period[119]. We divided the groups before surgery, but it is plausible that some women may have transitioned within the 6 months follow-up period. As a result, an objective for future analyses is to consider menopausal transitions through the full two years of the larger UHN study; this will be guided by the findings of the current analysis. Finally, surgically induced postmenopausal women have been shown to generally exhibit higher scores on measures of depressive symptomatology[214–216]. A limitation of the present study was not considering women who entered into menopause as a result of oophorectomy or hysterectomy as a separate group. Our objective however, was to examine variation specifically based on preoperative menopausal status (including PRE-M and PERI-M), and as such, the participants were allocated accordingly. The differing effect of natural and surgical menopause on pain may be explored in future studies.

Anxiety: Admission to hospital and the prospect of surgery is naturally accepted as anxiety provoking, which results in behavioural and cognitive effects that alter the course of recovery. Numerous studies have demonstrated positive relationships between anxiety and pain, where the less anxious patients generally experience less pain[217]. There is however a focus in research on predicting and preventing POP, therefore, many studies approach anxiety as a preoperative risk factor[12,30,40,218,219].

A significant interaction was found between time and pain. In contrast to some other studies[5,218,220], preoperative anxiety levels did not predict CPOP, but those who developed

chronic pain had higher levels of anxiety 1 week after surgery than their 'no pain' counterparts; this difference was even more pronounced after 6 months. Taillefer et al. studied patients 1-3 years after cardiac surgery including those who underwent coronary artery bypass and/or valve replacement[221]. Similar to our results, they found that when patients with and without CPOP were compared, the former group had significantly higher levels of anxiety, and they perceived their HRQoL as more compromised (discussed further under *Health-Related Quality of Life*)[221]. Importantly, it is difficult to ascertain whether continued anxiety after surgery prolonged the recovery period and induced CPOP, or whether the persistence of pain led to development of anxiety in these patients[217,222]. This is an important consideration for future research, as it will enable clinicians to correctly target the source of reduced QoL.

Arguably more noteworthy is an interaction between time, pain, and menopausal status that was trending towards a significant relationship. Although this trend was not statistically significant, limiting conclusions, it was explored further in the interest of hypothesis generation and the author's personal interest. This exploration showed that the trend is consistent with a pattern distinguishing the LP-M group. One week after surgery, PRE-M women who went on to develop chronic pain show slightly, albeit not significantly, higher anxiety scores than those who did develop chronic pain. However, by 6 months after surgery, they are no longer statically differently. Likewise, the STAI-S scores for PERI-M and EP-M women with chronic pain were not significantly higher than the 'no pain' group at 1 week or at 6 months after surgery. LP-M women who went on to develop chronic pain exhibited significantly higher state anxiety scores both at 1 week and especially 6 months after surgery than those who did not develop chronic pain. That is, chronic pain seems to have impacted the anxiety scores of LP-M women to a greater degree than other menopausal status groups. Alternatively, LP-M exhibited worse anxiety

throughout their recovery, which increased their likelihood of developing CPOP. As mentioned previously, examining the cause and effect relationship of these pain and anxiety is beyond the scope of this study. Building on our other results, which indicate that the LP-M group *with* chronic pain had a significantly higher likelihood of reaching threshold for clinically relevant depression scores, there seems to be a pattern emerging. When comparing anxiety scores instead of depressive symptomatology, LP-M women with chronic pain also seem to fair worse than other menopausal study groups.

The prevalence of anxiety symptoms in women is considerable, with close to half of women 40-55 years old reporting nervousness, tension, or irritability in the past two weeks or at the moment[223,224] and a quarter reporting frequent irritability or nervousness[225]. Studies report conflicting results with regards to the prevalence of anxiety symptoms during different stages of the menopausal transition and beyond[226]. Some studies indicate no statistically significant differences by menopausal status groups[227,228] and others find that PERI-M women have significantly higher rates of anxiety symptoms than PRE-M women[225,229]. Research examining anxiety in postmenopause is less robust, and studies distinguishing between EP-M and LP-M are scarce. Elsabach et al. (2007) analyzed cognitive function and mood in healthy early and LP-M women, defining these groups identically to our methods, and found that neither anxiety nor depression, as measured by the hospital anxiety and depression scale (HAD), differed significantly between the two groups[121]. This is in contrast to our findings and may be attributed to the patient population. As previously stated, PERI-M women have generally been shown to be at significantly greater risk for anxiety symptoms than PRE-M or postmenopausal women[225,229] in the general population. To our knowledge, specific differences in anxiety between healthy EP-M and LP-M women have not been examined. Surgical populations and those with oncological

diagnoses are likely to exhibit different characteristics simply due to the psychological effects of real or perceived decline in health. One older study by Levy et al. (1992) focused the emotional distress of women undergoing lumpectomies and mastectomies[230]. Emotional distress was measured at baseline, 3 months, and 15 months after surgery using the Profile of Mood States (POMS), which includes six domains – anxiety, anger, depression, confusion, vigor, and fatigue. The women were categorized into PRE-M and PERI-M vs. EP-M and LP-M (combined into 'postmenopausal') and compared using repeated measures ANCOVA. Similar to our study, it was found that irrespective of menopausal status, there was a significant reduction in emotional distress and a significant increase in functional status (discussed further under *Health-Related Quality of Life*) over time[230]. However, when the effect of menopausal status was examined, PRE-M women trended towards higher anxiety scores than the postmenopausal group at every time point[230]. This is similar to our results in which the PRE-M group had slightly, although not significantly, higher anxiety scores. However, this trend was seen only at the 1-week follow-up, and not at 6 months. Pain was not a factor in the study by Levy et al. (1992)[230] In summary, comparison of menopausal status groups in relation to surgical recovery (including POP) is understudied and further research is warranted. This is especially true of the breast cancer population, as the disease is most prevalent at a time when patients are also undergoing major reproductive status transitions, and there may be an additive psychological effect to the one already being experienced as a surgical or oncological population[116].

Health-Related Quality of Life (physical and mental): Chronic pain may cause significant emotional, physical, economic, and social impacts, change family roles and relationships, affect careers, and cause individuals to withdraw from society[237-238]. Like the BPI-I, the SF-12 measures limitations on functioning in daily life. The BPI-I specifically examines the effect of

pain on interference, but without distinguishing between activity and emotional interference[195,196]. In contrast, the SF-12 examines HRQoL, captures bodily pain if present, and has the capacity to derive separate scores for physical and mental health[231]. The physical composite score (PCS) encompasses four domains: physical functioning, physical role fulfillment, bodily pain, and general health[139]. The mental composite score (MCS) also has four domains: vitality, social functioning, emotional role fulfilment, and mental health[139].

Our results indicate that PCS scores were significantly affected by an interaction between time and pain, regardless of menopausal status. That is, women's QoL as it relates to physical functioning changed over time and in relation to whether the patient developed chronic pain or not. This is in line with previously conducted research on chronic pain and its effect on HRQoL[237,239-243]. A large-scale 2008 study by Turk et al.[237] aimed to understand the subjective experience of patients being treated for chronic pain conditions, specifically outcomes related to QoL. The most prevalent conditions included were lower back pain (55%), neck/shoulder pain (46%), and neuropathic pain (39%). Aspects of daily life that were negatively impacted were identified through smaller focus groups, and later confirmed via large web-based questionnaires including the BPI and SF-12. As expected by the authors, people with chronic pain participating in this study were more impaired in their health status compared with the general population. Participants reported that most if not all aspects of their lives are significantly affected by chronic pain, particularly enjoyment of life in general, fatigue, weakness, sleep-related problems, and emotional well-being. Furthermore, physical HRQoL has also been specifically examined in relation to POP. A small pilot project by Strassels et al. (2004)[239] analyzed a surgical population including those undergoing prostatectomy, hip replacement and knee replacement. It is important to note that this study included a predominantly male sample (79.3%). Participants completed

questionnaires, including the SF-36 (the long version of the SF-12) one month after their respective procedure. Across all three surgical groups, patients scored lower than North American norms on physical functioning, physical roles, vitality, as well as social functioning and mental health. Although this study examined the short-term postoperative period, similar ones have been conducted with a more longitudinal perspective. A study of patients who underwent an inguinal hernia repair by Poobalan et al. (2001)[240] demonstrated that 30% of patients developed CPOP. Analysis of HRQoL, measured on the SF-36, revealed that there were significant differences between patients with and without chronic pain but only on social functioning and mental health rather the PCS domains. Importantly, these patients were followed up with an average of 43 (3.5 years) months after their procedure, at which point the impact of POP may be different than in the first year. In 2003, Bruce et al.[241] examined QoL in patients who develop chronic pain after cardiac surgery. Two years following the procedure, the SF-36 was administered to 1080 participants, 436 (40.4%) of whom experienced chronic pain at the chest or leg (post saphenous vein graft) site. It was found that HRQoL scores were significantly lower in participants with chronic pain at both surgical sites than those with pain at one site only. Then, a general trend was observed whereby participants with pain at one site have lower scores that the pain-free group. In another historic cohort study, Bruce and Krukowski (2005)[242] utilized a different questionnaire, but also analyzed QoL in people with chronic pain after gastrointestinal surgery. Similar to the SF-12 and SF-36, the EORTC QLQ-C30 questionnaire is composed of functional scales that evaluate physical, role, emotional, cognitive, social function, and one global health status scale. At the 4-year follow-up, 40/200 (20%) patients reported pain lasting more than three months postoperatively (considered chronic[11]), and 20/200 (10.5%) patients reported that they continued to experience chronic pain resulting from that surgery. At follow-up,

QoL scores in all domains were significantly lower in patients reporting chronic pain than those who were pain-free, independent of age, gender, and cancer status. Lastly, Macdonald et al. (2005)[243] reported that although QoL scores (measured on the SF-36) of post-mastectomy patients improved over time, as in our study, they were still significantly lower in women with post-mastectomy pain syndrome than in women whose pain had resolved. This was consistent across all domains except emotional role fulfillment. Consistent with this, our study further documents the negative impact of chronic pain on HRQoL in the BCS population.

As described earlier, mental HRQoL may also differ between patients who develop chronic pain and those who do not. This was demonstrated in our results with an added layer of complexity. A significant three-way interaction was identified between time, chronic pain, and menopausal status in the women's MCS scores. The trajectory of women's recovery with respect to mental HRQoL differed among the menopausal status groups, and was further influenced by presence of chronic pain. PRE-M women exhibited a significant increase in their mental health status between the preoperative assessment and the 1 week follow-up, but continued to score lower than the other groups. By the last follow-up, HRQoL scores had not increased further and did not differ between women who developed chronic pain and those who did not; this pattern is similar to women in the PERI-M and EP-M groups. Based on our results, chronic pain may have a greater impact on physical functioning than mental well-being for PRE-M, PERI-M and EP-M women 6 months after BCS. The trajectory of the LP-M group varied considerably from the rest. MCS scores increased significantly from the preoperative period to 1 week post-op, and did not differ between the 'pain' and 'no pain' groups. However, by 6 months, our results demonstrate a significant decline in mental HRQoL in the LP-M group with chronic pain. This pattern is similar to that in the CES-D and STAI-S scores, whereby LP-M women were impacted by

chronic pain to a significantly higher degree than the rest. Given that there were no differences between menopausal status groups in pain intensity or quality at 1 week or 6 months post-operatively, significant variability in the impact measures highlights the multifaceted and individual nature of pain. To our knowledge, this is the first study to examine menopausal status differences in pain after BCS through a biopsychosocial perspective, and is exploratory in nature. As such, future research is necessary to replicate and extend the present findings.

CONCLUSION

The aim of the present study was to examine the relationship between menopausal status and clinical pain after BCS from a biopsychosocial perspective. Many assessments of POP focus on pain intensity, pain relief, and satisfaction with medical care[31]. While these measures are crucial in the immediate postoperative period to provide adequate relief, severity is only one dimension of the pain experience[32]. Once the surgical wound has healed, many women report persistent pain that negatively impacts their QoL[6,34]. Gonadal hormones have long been proposed to affect pain sensitivity in experimental trials[55], and clinical pain has been shown to differ in characteristics with changes in reproductive function[96]. Given that BCS is performed when many patients are undergoing menopausal transitions[116], this may be a contributing factor to the variability of their pain experiences.

Strengths: This is the first study to examine pain differences by menopausal status in the BCS population. Moreover, among research on other surgical populations, it is the first to adopt a biopsychosocial framework of pain. This approach revealed that despite comparable pain intensity after BCS, women in each menopausal status group varied with respect to their mental health outcomes. Furthermore, our key analyses controlled for age and comorbidities, thereby removing the possibility of confounding by either of those factors.

Limitations: Despite the novelty of the study, there were several limitations that must be acknowledged. Firstly, this study was conducted at a single institution, with a relatively homogenous racial sample (Caucasian). As such, findings should be confirmed with multi-institutional research with more diverse patient populations. Next, categorization of women into menopausal status group was done in accordance with World Health Organization recommendations[103] as well as guidelines set out by the Stages of Reproductive Aging Workshop[104]. Nonetheless, comparison of findings with existing literature should be made with caution as other definitions of menopausal status (for example, based solely on an arbitrary age threshold of 50 or 55) continue to be employed by researchers today[97]. Lastly, group comparisons on categorical variables did not account for covariates due to limitations of the chi-square test, and as such, may confound age and menopausal status effects. When considering alternatives, the Cochran-Mantel-Haenszel Method[244], which allows for inclusion of covariates, was examined but later rejected as a result of two unmet assumptions. Firstly, for correct utilization of this method, the risk factor (independent variable) and outcome variables must be dichotomous; menopausal status has four rather than two groups. Also, the strata variable (covariate) must be categorical, whereas in the present study age and comorbidities were both measured on a continuous scale. Importantly, the key analyses and findings of this study (as described under *Impact of Pain on Quality of Life* of the results section) in fact control for age and comorbidities. This is the first study to adopt such controls.

Clinical Implications: Despite continuous efforts to identify risk factors for chronic pain and subsequent QoL issues, there seems to be a gap in our ever-expanding knowledge and current clinical practices. Although Canadian guidelines recommend offering psychosocial support including discussion of fatigue, weight management, as well as physical and sexual

functioning, this is not universally implemented[233]. Moreover, the availability of treatment options and rehabilitative resources varies widely across Canadian provinces and territories[234]. Although the standardization of rehabilitation efforts will likely entail additional costs on the health care system, failure to improve the quality of postoperative care may lead to increased morbidity, reduced ability to perform on the job, as well premature retirement from the workforce, and as such substantial costs for society[235].

Throughout their recovery, BCS patients are normally followed by an oncologist whose area of expertise and primary focus is on immediate pain relief and even more so, the detection of cancer recurrence[232]. Our results demonstrate that women's experience after surgery varies according to their menopausal status, and this factor should be considered when approaching postoperative care strategies. While acute and CPOP pain intensity may not vary greatly between women, their long-term recovery trajectories do, especially with respect to mental health. The LP-M group exhibited a unique pattern whereby they were impacted by chronic pain to a greater degree than women in other menopausal status groups. Firstly, they did not decrease in depressive symptomatology scores by 6 months after surgery. Also, compared to other groups, LP-M women with chronic pain comprised the highest proportion of those scoring above threshold for clinically relevant depression. In addition, these women had the largest anxiety score difference between those with and without chronic pain and showed a significant decline in mental HRQoL in the presence of chronic pain. Our findings suggest that this group is most vulnerable to mental health issues after BCS and requires tailored postoperative care management. It is thus our recommendation that mental health counselling (individual, group, or family) be offered to all BCS patients, but be specifically prescribed as part of standard care for LP-M women.

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APPENDIX A: QUESTIONNAIRES

Short Orientation-Memory-Concentration Test (SOMC)

Ask each question. Score 0 for incorrect answer, and indicated score for each correct answer or part of answer correct. Self-correction is allowed. Indicate date of test at top.

Question	Scoring if correct		Score
What year is it now?	4		
Answer			
What month is it now?	3		
Answer			
Repeat this address			
Address chosen (A, B, C, D)			
About what time is it now? (Correct if within one hour)	3		
Answer			
Count backwards from 20 to 1 *Two points off for each error*	4 or 2		
Say the months in reverse order *Two points off for each error*	4 or 2		
Repeat the address given *Two points off for each error*	10, 8, 6, 4, or 2		
TOTAL SCORE			

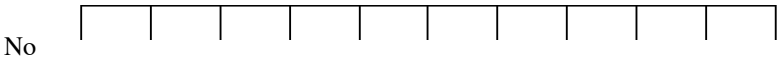
Address A	**Address B**	**Address C**	**Address D**
Mr. John / Brown, 42 / West Street, Gateshead	Mr. Joe / Smith, 34 / Church Road Banbury	Mr. Tom / White, 26 / Station Road, Aylesbury	Mr. Philip / Jones, 18 / North Way, Oxford

/ = marks separate items within address

Researcher's Initials: _____

Numeric Rating Scale – Rest (NRS-R)

Please circle the number below which best represents your ***present*** pain, the pain you are feeling right at this moment.

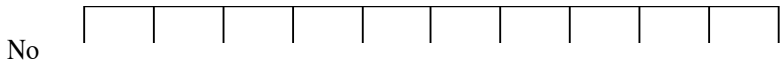


No pain 0 1 2 3 4 5 6 7 8 9 10 Pain as bad as it could be

Numeric Rating Scale – Movement (NRS-M)

Instructions: Patient is to roll from a supine to side-lying position and perform two maximal inspirations before rating their pain.

Please circle the number below which best represents your ***present*** pain, the pain you are feeling right at this moment.



No pain 0 1 2 3 4 5 6 7 8 9 10 Pain as bad as it could be

Short-Form McGill Pain Questionnaire (SF-MPQ)

Please indicate which words best describe your pain at present. I will read you each word and if the word describes your pain, I will ask you to rate the intensity of that characteristic as mild, moderate or severe.

	NONE	MILD	MODERATE	SEVERE
THROBBING	0)_____	1)____	2)____	3)____
SHOOTING	0)_____	1)____	2)____	3)____
STABBING	0)_____	1)____	2)____	3)____
SHARP	0)_____	1)____	2)____	3)____
CRAMPING	0)_____	1)____	2)____	3)____
GNAWING	0)_____	1)____	2)____	3)____
HOT-BURNING	0)_____	1)____	2)____	3)____
ACHING	0)_____	1)____	2)____	3)____
HEAVY	0)_____	1)____	2)____	3)____
TENDER	0)_____	1)____	2)____	3)____
SPLITTING	0)_____	1)____	2)____	3)____
TIRING-EXHAUSTING	0)_____	1)____	2)____	3)____
SICKENING	0)_____	1)____	2)____	3)____
FEARFUL	0)_____	1)____	2)____	3)____
PUNISHING-CRUEL	0)_____	1)____	2)____	3)____

PPI

Please choose the word which best describes your pain at the present moment.

0 NO PAIN ____
1 MILD ____
2 DISCOMFORTING ____
3 DISTRESSING ____
4 HORRIBLE ____
5 EXCRUCIATING ____

NEUROPATHIC PAIN QUESTIONNAIRE – Short Form

Please use the items below to rate your pain as it usually feels. Indicate a number which represents your pain on each scale. For example, if you have no tingling pain, you would rate the first item "0". If you have the worst tingling pain imaginable, you would rate it "100". IF neither of those fits your pain because it is in between, choose a number which fits your pain.

1. Tingling Pain

0 ← ═══════════ → 100

Please rate your usual pain: _____

No Tingling Pain

Worst Tingling Pain Imaginable

2. Numbness

0 ← ═══════════ → 100

Please rate your usual pain: _____

No Numbness Sensation

Worst Numbness Imaginable

3. Increased pain due to touch

0 ← ═══════════ → 100

Please rate your usual pain: _____

No Increase At All

Greatest Increase Imaginable

Note: BPI Interference Scale starts on Question #9

9) Please circle the one number that describes how, during the past 24 hours, pain has interfered with your:

A. General activity

0	1	2	3	4	5	6	7	8	9	10
Does Not Interfere										Completely Interferes

B. Mood

0	1	2	3	4	5	6	7	8	9	10
Does Not Interfere										Completely Interferes

C. Walking ability

0	1	2	3	4	5	6	7	8	9	10
Does Not Interfere										Completely Interferes

D. Normal work (includes both work outside the home and housework).

0	1	2	3	4	5	6	7	8	9	10
Does Not Interfere										Completely Interferes

E. Relations with other people.

0	1	2	3	4	5	6	7	8	9	10
Does Not Interfere										Completely Interferes

F. Sleep

0	1	2	3	4	5	6	7	8	9	10
Does Not Interfere										Completely Interferes

G. Enjoyment of life

0	1	2	3	4	5	6	7	8	9	10
Does Not Interfere										Completely Interferes

Charlson Comorbidity Index (CCI)
(Charlson et al., 1987)

Patient Age: _____ years

Does the Patient Have: (check appropriate response)

AIDS?	__ YES	__ NO
Cerebrovascular Disease?	__ YES	__ NO
Chronic Pulmonary Disease?	__ YES	__ NO
Congestive Heart Failure?	__ YES	__ NO
Connective Tissue Disease?	__ YES	__ NO
Dementia?	__ YES	__ NO
Hemiplegia?	__ YES	__ NO
Leukemia?	__ YES	__ NO
Malignant Lymphoma?	__ YES	__ NO
Myocardial Infarction?	__ YES	__ NO
Peripheral Vascular Disease?	__ YES	__ NO
Ulcer Disease?	__ YES	__ NO

Select the appropriate column for each condition; give only 1 answer per row

Diabetes Mellitus	__ NONE	__ Without End Organ Damage	__ With End Organ Damage	
Liver Disease	__ NONE	__ MILD	__ MODERATE	__ SEVERE
Renal Disease	__ NONE	__ MILD	__ MODERATE	__ SEVERE
Malignant Solid Tumour	__ NONE	__ MILD	__ MODERATE	__ SEVERE

SF-12® Patient Questionnaire

Patient Initials _____ _____ _____ **Date of Birth:** ___/___/___ **Patkey:** _____

Surgeon Name: _____ **Date:** _____

Examination Period:
____ Preop (1)
____ Immediate Postop (2)
____ 1 Year (3)
____ 3 Year (4)
____ 5 Year (5)
____ Other (specify) (6): _____

SF-12®:
This information will help your doctors keep track of how you feel and how well you are able to do your usual activities. Answer every question by placing a check mark on the line in front of the appropriate answer. It is not specific for arthritis. If you are unsure about how to answer a question, please give the best answer you can and make a written comment beside your answer.

1. In general, would you say your health is:
   _____ Excellent (1)
   _____ Very Good (2)
   _____ Good (3)
   _____ Fair (4)
   _____ Poor (5)

The following two questions are about activities you might do during a typical day. Does YOUR HEALTH NOW LIMIT YOU in these activities? If so, how much?

2. MODERATE ACTIVITIES, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf:
   _____ Yes, Limited A Lot (1)
   _____ Yes, Limited A Little (2)
   _____ No, Not Limited At All (3)

3. Climbing SEVERAL flights of stairs:
   _____ Yes, Limited A Lot (1)
   _____ Yes, Limited A Little (2)
   _____ No, Not Limited At All (3)

During the PAST 4 WEEKS have you had any of the following problems with your work or other regular activities AS A RESULT OF YOUR PHYSICAL HEALTH?

4. ACCOMPLISHED LESS than you would like:
   _____ Yes (1)
   _____ No (2)

5. Were limited in the KIND of work or other activities:
   _____ Yes (1)
   _____ No (2)

Patient Initials _____ _____ _____ **Date of Birth:** ___/___/___ **Patkey:** _____

Surgeon Name: _____ **Date:** _____

Examination Period:
____ Preop (1)
____ Immediate Postop (2)
____ 1 Year (3)
____ 3 Year (4)
____ 5 Year (5)
____ Other (specify) (6): _____

SF-12® Cont'd:

During the PAST 4 WEEKS, were you limited in the kind of work you do or other regular activities AS A RESULT OF ANY EMOTIONAL PROBLEMS (such as feeling depressed or anxious)?

6. ACCOMPLISHED LESS than you would like:
   _____ Yes (1)
   _____ No (2)

7. Didn't do work or other activities as CAREFULLY as usual:
   _____ Yes (1)
   _____ No (2)

8. During the PAST 4 WEEKS, how much did PAIN interfere with your normal work (including both work outside the home and housework)?
   _____ Not At All (1)
   _____ A Little Bit (2)
   _____ Moderately (3)
   _____ Quite A Bit (4)
   _____ Extremely (5)

The next three questions are about how you feel and how things have been DURING THE PAST 4 WEEKS. For each question, please give the one answer that comes closest to the way you have been feeling. How much of the time during the PAST 4 WEEKS –

9. Have you felt calm and peaceful?
   _____ All of the Time (1)
   _____ Most of the Time (2)
   _____ A Good Bit of the Time (3)
   _____ Some of the Time (4)
   _____ A Little of the Time (5)
   _____ None of the Time (6)

Surgeon Initials _____ **Date:** _____

Patient Initials _____ _____ _____ **Date of Birth:** ___/___/___ **Patkey:** _____

Surgeon Name: _____ **Date:** _____

Examination Period:
____ Preop (1)
____ Immediate Postop (2)
____ 1 Year (3)
____ 3 Year (4)
____ 5 Year (5)
____ Other (specify) (6): _____

SF-12® Cont'd:

10. Did you have a lot of energy?
    _____ All of the Time (1)
    _____ Most of the Time (2)
    _____ A Good Bit of the Time (3)
    _____ Some of the Time (4)
    _____ A Little of the Time (5)
    _____ None of the Time (6)

11. Have you felt downhearted and blue?
    _____ All of the Time (1)
    _____ Most of the Time (2)
    _____ A Good Bit of the Time (3)
    _____ Some of the Time (4)
    _____ A Little of the Time (5)
    _____ None of the Time (6)

12. During the PAST 4 WEEKS, how much of the time has your PHYSICAL HEALTH OR EMOTIONAL PROBLEMS interfered with your social activities (like visiting with friends, relatives, etc.)?
    _____ All of the Time (1)
    _____ Most of the Time (2)
    _____ A Good Bit of the Time (3)
    _____ Some of the Time (4)
    _____ A Little of the Time (5)
    _____ None of the Time (6)

Surgeon Signature_____ **Date**_____

CES-D

Below is a list of the ways you might have felt or behaved. Please tell me how often you have felt this way during the past week.

Rarely or none of the time (less than 1 day)
Some or a little of the time (1-2 days)
Occasionally or a moderate amount of the time (3-4 days)
Most or all of the time (5-7 days)

During the Past Week	Rarely	A little	Moderate	Most
1. I was bothered by things that usually don't bother me…….	0	1	2	3
2. I did not feel like eating; my appetite was poor…….	0	1	2	3
3. I felt that I could not shake off the blues Even with help from my family or friends….	0	1	2	3
4. I felt that I was just as good as other people...	0	1	2	3
5. I had trouble keeping my mind on what I was doing……...	0	1	2	3
6. I felt depressed……	0	1	2	3
7. I felt that everything I did was an effort…….	0	1	2	3
8. I felt hopeful about the future…….	0	1	2	3
9. I thought my life had been a failure……	0	1	2	3
10. I felt fearful…….	0	1	2	3
11. My sleep was restless…….	0	1	2	3
12. I was happy…….	0	1	2	3

Pain Catastrophizing Scale (PCS)

Everyone experiences painful situations at some point in their lives. Such experiences may include headaches, tooth pain, joint or muscle pain. People are often exposed to situations that may cause pain such as illness, injury, dental procedures or surgery.

We are interested in the types of thoughts and feelings that you have when you are in pain. Listed below are thirteen statements describing different thoughts and feelings that may be associated with pain. Using the following scale, please indicate the degree to which you have these thoughts and feelings when you are experiencing pain.

0	1	2	3	4
Not at all	*To a slight degree*	*To a moderate degree*	*To a great degree*	*All the time*

When I am in pain…

1. I worry all the time about whether the pain will end.	**1**	**2**	**3**	**4**	**5**
2. I feel I can't go on.	**1**	**2**	**3**	**4**	**5**
3. It's terrible and I think it's never going to get any better.	**1**	**2**	**3**	**4**	**5**
4. It's awful and I feel that it overwhelms me.	**1**	**2**	**3**	**4**	**5**

0	1	2	3	4
Not at all	*To a slight degree*	*To a moderate degree*	*To a great degree*	*All the time*

5. I feel I can't stand it anymore.	**1**	**2**	**3**	**4**	**5**
6. I become afraid that the pain will get worse.	**1**	**2**	**3**	**4**	**5**
7. I keep thinking of other painful events.	**1**	**2**	**3**	**4**	**5**
8. I anxiously want the pain to go away.	**1**	**2**	**3**	**4**	**5**
9. I can't seem to keep it out of my mind.	**1**	**2**	**3**	**4**	**5**
10. I keep thinking about how much it hurts.	**1**	**2**	**3**	**4**	**5**
11. I keep thinking about how badly I want the pain to stop.	**1**	**2**	**3**	**4**	**5**
12. There's nothing I can do to reduce the intensity of the pain.	**1**	**2**	**3**	**4**	**5**
13. I wonder whether something serious may happen.	**1**	**2**	**3**	**4**	**5**

STAI - T

Instructions: Read each statement and then select the appropriate response to indicate how you generally feel. Do not spend too much time on any one statement, but give the answer which seems to describe your present feelings best.

	Not At All	A Little	Somewhat	Very Much So
1. I feel calm				
2. I feel secure				
3. I feel tense				
4. I feel strained				
5. I feel at ease				
6. I feel upset				
7. I am presently worrying over possible misfortunes				
8. I feel satisfied				
9. I feel frightened				
10. I feel uncomfortable				
11. I feel self confident				
12. I feel nervous				
13. I feel jittery				
14. I feel indecisive				
15. I am relaxed				
16. I feel content				
17. I am worried				
18. I feel confused				
19. I feel steady				
20. I feel pleasant				

State-Trait Anxiety Inventory (STAI-S)

DIRECTIONS: A number of statements which people have used to describe themselves are given below. Read each statement and then blacken the appropriate circle to the right of the statement to indicate how you *feel* right now, that is, *at this moment*. There are no right or wrong answers. Do not spend too much time on any one statement but give the answers which seem to describe your present feelings best.

	not at all	somewhat	moderately so	very much so
1. I feel calm ..	○	○	○	○
2. I feel secure	○	○	○	○
3. I am tense	○	○	○	○
4. I am regretful	○	○	○	○
5. I feel at ease	○	○	○	○
6. I feel upset	○	○	○	○
7. I am presently worrying over possible misfortunes	○	○	○	○
8. I feel rested	○	○	○	○
9. I feel anxious	○	○	○	○
10. I feel comfortable	○	○	○	○
11. I feel self-confident	○	○	○	○
12. I feel nervous	○	○	○	○
13. I am jittery	○	○	○	○
14. I feel “high strung”	○	○	○	○
15. I am relaxed	○	○	○	○
16. I feel content	○	○	○	○
17. I am worried	○	○	○	○
18. I feel over-excited and “rattled”	○	○	○	○
19. I feel joyful	○	○	○	○
20. I feel pleasant	○	○	○	○

Researcher’s Initials: _____