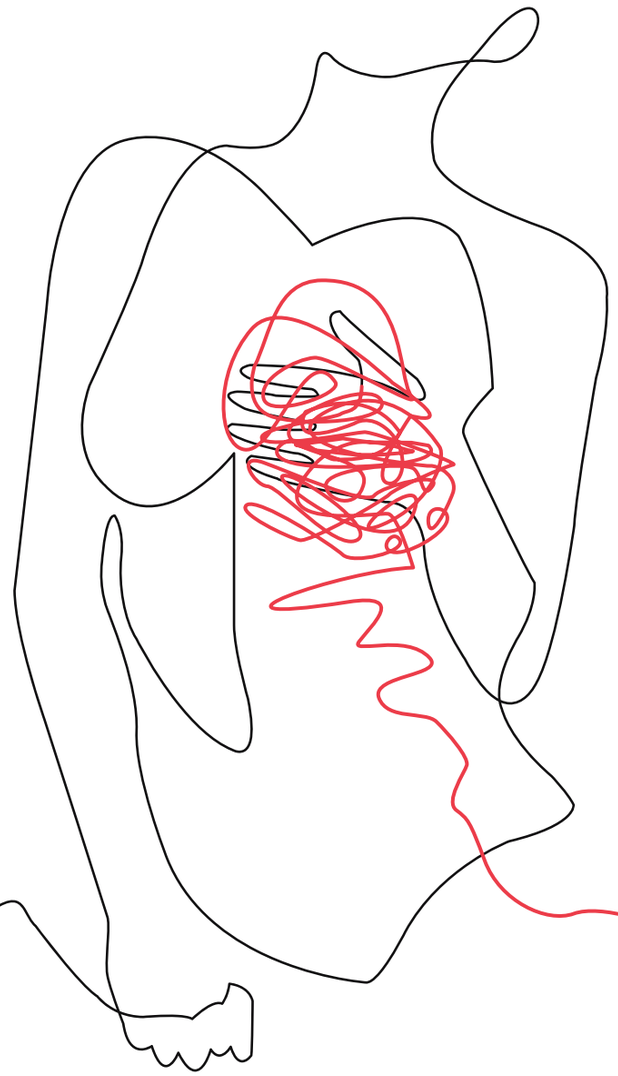
Persistent pain in cancer survivors: how to assess in clinical practice



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Dissertation presented in partial fulfillment of the requirements for the joint degree of
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PERSISTENT PAIN IN CANCER SURVIVORS: HOW TO ASSESS IN CLINICAL PRACTICE

AANHOUDENDE PIJN BIJ KANKEROVERLEVENDEN: HOE TE BEOORDELEN IN DE KLINISCHE PRAKTIJK

Dissertation presented in partial fulfillment of the requirements for the joint degree of Doctor of Medical Sciences (University of Antwerp) and Doctor of Biomedical Sciences (KU Leuven) to be defended by Vincent HAENEN

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Abbreviations

95% CI	95% Confidence interval
ACP	Abdominal coital pain
ACR	American College of Rheumatology
ADG	An De Groef
ADT	Androgen deprivation therapy
AI	Aromatase inhibitor
ALND	Axillary lymph node dissection
ANOVA	Analysis of variance
AUC	Area under the curve
BCPT	Breast cancer prevention trial symptom checklist
BCS	Breast cancer survivor
BMI	Body mass index
BPC	Blood pressure cuff
BPI	Brief Pain Inventory
CIPN	Chemotherapy-induced peripheral neuropathy
CPTe	Cold pressor test
CPTh	Cold pain threshold
CPM	Conditioned pain modulation
CRT	Chemoradiotherapy
CSI	Central sensitization inventory
CT	Chemotherapy
CVI	Content validity index
CVR	Content validity ratio
DASH	Disability of the arm, shoulder and hand questionnaire
DASS-21	Depression, anxiety, stress scale
DCIS	Ductal carcinoma in situ
DFNS	German Research Network on Neuropathic Pain
DL	Dorien Lups
DN4	Douleur Neuropathique en 4 questions
DP	Deep dyspareunia

EBRT	External beam radiation therapy
ED	Entry dyspareunia
EFIC	European Pain Federation
EHS	Erection hardness scale
EORTC-QLQ-C30	European Organization for Research and Treatment for Cancer Quality of Life Questionnaire
ER+/PR+	Estrogen receptor positive / Progesterone receptor positive
FM	Fibromyalgia
HER2	Human epidermal growth factor receptor 2
HPT	Heat pain threshold
HR+	Hormone receptor positive
HT	Hormone therapy
IASP	International Association for the Study of Pain
ICC	Interclass correlation coefficient
ICD-11	International Classification of Diseases, 11th revision
I-CVI	Item level content validity index
IDC	Invasive ductal carcinoma
ILC	Invasive lobular carcinoma
IMMPACT	Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials
IQR	Interquartile range
LCIS	Lobular carcinoma in situ
JBI	Joanna Briggs Institute
KAPS	Kwan's arm problem scale
LE	Lumpectomy
M	Median
m	Minutes
ME	Mastectomy
MEv	Margaux Evenepoel
MCTF	Musculoskeletal clinical translation framework
MDT	Mechanical detection threshold

MME	Modified mastectomy
mN	Millinewton
MPT	Mechanical pain threshold
MRI	Magnetic resonance imaging
NPSI	Neuropathic pain symptom inventory
NRS	Numeric rating scale
NPQ	Neurophysiology of pain questionnaire
NPSI	Neuropathic pain symptom inventory
NSAID	Non-steroidal anti-inflammatory drugs
PDI	Pain disability index
PT	Physical therapist
PCS	Pain catastrophizing scale
PMPS	Persistent mastectomy pain syndrome
PPBCS	Persistent pain after breast cancer surgery
PPT	Pressure pain threshold
PRISMA	Preferred reporting items for systematic reviews and meta-analyses
PRO	Patient reported outcome
PROSPERO	International prospective register of systematic reviews
QoL	Quality of life
QST	Quantitative sensory testing
RASQ	Rheumatoid arthritis symptom questionnaire
RCT	Randomized controlled trial
RT	Radiation therapy
s	Seconds
S-CVI	Scale level content validity index
SD	Standard deviation
SEm	Standard error of measurement
SF-36	36-Item short form health survey
SLNB	Sentinel lymph node biopsy
SNRI	Serotonin and norepinephrine reuptake inhibitors

SPADI	Shoulder pain and disability index
SSFS	Shot sexual functional scale
SSS	Symptom severity scale
STROBE	Strengthening the reporting of observational studies in epidemiology
SU	Simone Ubaghs
TdB	Tom De Baerdemaecker
TNM	Tumor-node-metastases staging
TRIPOD	Transparent Reporting of a multivariable prediction model for Individual Prognosis or Diagnosis
TS	Temporal summation
TSA-2	Advanced Thermosensory Stimulator
VAS	Visual analogue scale
VATS	Video-assisted thoracoscopic surgery
VH	Vincent Haenen
WDT	Warmth detection threshold
WPI	Widespread pain index

English summary

Breast cancer is the most prevalent form of cancer in women worldwide. In Belgium, approximately one in nine women is diagnosed with breast cancer during their lifetime. Although advancements in the detection and treatment of breast cancer have led to improved survival rates, many breast cancer survivors still experience various side effects. Pain is a prevalent and long-lasting side effect of breast cancer treatments. Pain arises from the complex interplay of biological, psychological, and social factors and can substantially impact an individual's physical and psychosocial well-being. To improve physical and psychosocial well-being, it is crucial to assess and manage pain adequately. A mechanism-based approach to pain, which involves identifying the mechanistic pain descriptor that contribute to its experience, can be considered a component of such adequate pain assessment. Three commonly recognized mechanistic pain descriptors are nociceptive, neuropathic, and nociplastic pain. Nociceptive pain arises from the activation of specialized nerve fibers that detect danger, called nociceptors, in response to threatened tissue damage or inflammation. Neuropathic pain arises from damage or disease affecting the nervous system, and nociplastic pain refers to pain that arises from the altered processing of noxious stimuli without ongoing tissue damage or inflammation. By incorporating a mechanism-based approach, healthcare providers can tailor treatment strategies and improve pain management, ultimately enhancing the quality of life of breast cancer survivors who experience chronic pain.

The ultimate aim of this clinically-orientated doctoral thesis was to develop a set of feasible clinical prediction models for the presence of nociceptive, neuropathic, and nociplastic pain in breast cancer survivors experiencing chronic pain. Concurrently, this doctoral thesis aimed to improve insights into the prevalence of these mechanistic pain descriptors in solid cancer survivors and to investigate the neurophysiological processes underlying persistent pain after breast cancer treatment.

To improve knowledge on the presence of persistent pain, mechanistic pain descriptors, and other pain characteristics in solid cancer survivors, a systematic

review of the existing literature was performed (**Chapter 1**). This review demonstrated that approximately half of solid cancer survivors experience persistent pain. However, the results of this review should be interpreted with caution because of the substantial unexplained heterogeneity. Additionally, we were unable to provide prevalence data on the presence of the different mechanistic pain descriptors or other pain characteristics in solid cancer survivors, owing to a lack of data in the existing literature.

Fortunately, not all cancer survivors experience persistent pain; however, it remains unclear why some breast cancer survivors experience persistent pain while others do not. Several studies have suggested that breast cancer survivors with persistent pain may have impairments in the processing of nociceptive signals within the peripheral and central somatosensory nervous system, which are instrumental in the perception of pain. In **Chapter 2**, the somatosensory profiles of breast cancer survivors with and without persistent pain were compared with those of healthy controls (negative control group) and patients with fibromyalgia (positive control group), who are known to exhibit impairments in the central processing of nociceptive signals. The results of this cross-sectional study indicate that breast cancer survivors with persistent pain exhibit decreased sensitivity (hypoesthesia) to thermal and mechanical stimuli and hyperesthesia (or increased sensitivity, hyperalgesia) to pressure in the trunk region. Furthermore, breast cancer survivors with pain showed heightened facilitation of nociceptive signals (increased temporal summation of pain), but maintained normal inhibition of nociceptive signals (normal conditioned pain modulation), similar to healthy controls and breast cancer survivors without pain. Finally, they showed a heightened psychosocial burden similar to patients with fibromyalgia.

In clinical practice, the evaluation of somatosensory function using dynamic quantitative sensory testing remains challenging. Conditioned pain modulation and temporal summation are dynamic quantitative sensory testing paradigms used to evaluate the processing of nociceptive signals within the central somatosensory

nervous system. Previous studies have suggested that these dynamic paradigms can provide important information for the stratification and decision-making in clinical practice, aligning with a mechanism-based approach to pain. However, dynamic quantitative sensory testing is time-consuming, expensive, and requires special training, making its use unfeasible in clinical settings. In **Chapter 3**, we investigated the concurrent validity of clinically applicable alternatives to dynamic quantitative sensory testing. The findings of this study suggest that alternatives for conditioned pain modulation using either a blood pressure cuff or a cold water bath are well correlated with each other. Alternatives to temporal summation using either a weighted monofilament or an algometer were also found to be well correlated at a remote non-painful location. These findings indicate that the clinically applicable alternatives are interchangeable; however, they were not correlated with their respective reference standards.

The development of clinically applicable alternatives for the evaluation of central nociceptive processing are well-intentioned; however, they are not routinely implemented in clinical practice. Using an online survey, physical therapists were asked to judge the feasibility, utility, face, and content validity of several clinically applicable quantitative sensory testing protocols including conditioned pain modulation and temporal summation (**Chapter 4**). Most physical therapists agreed on the feasibility and face validity; however, the utility and content validity received ambiguous ratings. This study also demonstrated that physical therapists showed limited interest in incorporating quantitative sensory testing into their clinical practice owing to time constraints and the lack of required materials.

Quantitative sensory testing paradigms have recently been recommended for their use in clinical guidelines for both nociplastic and neuropathic pain. Although these clinical guidelines aim to improve the clinical evaluation of pain and consequently, pain management, they remain unvalidated and fail to determine the diagnostic probability for the presence of such a mechanistic pain descriptor. Providing clinicians with the probability of the presence of a mechanistic pain descriptor would

improve the mechanistic approach to pain. Using a cross-sectional design with 92 breast cancer survivors, we developed three clinical prediction models for the ascription of nociceptive, neuropathic, and nociplastic pain in breast cancer survivors (**Chapter 5**). In total, a set of 15 predictors was selected, encompassing various factors, including patient and treatment characteristics, and variables specific to a mechanistic pain descriptor. The predictors body mass index, age, type of breast surgery, type of axillary surgery, and use of radiation therapy were included in all three models. Difference in pain intensity during rest and activity, general limited shoulder range of motion, and local pain were considered predictors of the nociceptive pain model. The neuropathic pain model included the presence of a burning sensation, hypoesthesia to touch, and neuroanatomical distribution of pain or sensory dysfunction. The score on the central sensitization inventory questionnaire, pressure pain thresholds at a remote location, presence of widespread pain, and presence of preoperative pain were selected for the nociplastic pain model. Quantitative sensory testing paradigms were judged to be unfeasible for use in clinical practice; thus, they were not selected as predictors. Although the developed models demonstrated moderate discriminative ability and the capability to provide accurate probabilistic predictions, the lack of external validation using independent datasets and real-world settings limits their immediate implementation in clinical practice.

This doctoral thesis provides insights into the clinical application of quantitative sensory testing from a mechanism-based perspective to pain in breast cancer survivors. Future research should prioritize the validation of methods to evaluate mechanistic pain descriptors in cancer survivors and consequently provide important updates on the prevalence of these mechanistic pain descriptors within this population. In addition, improvements in the clinical assessment of pain are warranted. Future research should involve healthcare providers to improve the implementation of tools aimed at improving pain assessment and subsequently, pain management. By addressing these issues, we can enhance our understanding of pain

in breast cancer survivors and in future provide better care to breast cancer survivors with persistent pain.

Dutch summary

Borstkanker is de meest voorkomende vorm van kanker bij vrouwen wereldwijd. In België wordt ongeveer één op de negen vrouwen tijdens hun leven gediagnosticeerd met borstkanker. Hoewel vooruitgang in de detectie en behandeling van borstkanker heeft geleid tot verbeterde overlevingskansen, ervaren veel overlevenden van borstkanker nog steeds verschillende bijwerkingen. Pijn is een veelvoorkomende en langdurige bijwerking van de behandeling van borstkanker. Pijn ontstaat door de complexe wisselwerking van biologische, psychologische en sociale factoren en kan aanzienlijke gevolgen hebben voor de lichamelijke en psychosociale welzijn van een individu. Om het lichamelijke en psychosociale welzijn te verbeteren, is het essentieel om pijn adequaat te beoordelen en te behandelen. Een mechanisme-gebaseerde benadering van pijn, waarbij de pijnmechanismen die bijdragen aan de ervaring van pijn worden geïdentificeerd, kan worden beschouwd als een component van een dergelijke adequate pijnbeoordeling. Drie veelvoorkomende erkende pijnmechanismen zijn nociceptieve, neuropathische en nociplastische pijn. Nociceptieve pijn ontstaat door de activatie van gespecialiseerde zenuwvezels, nociceptoren genaamd, die gevaar detecteren als reactie op dreigende weefselschade of ontsteking. Neuropathische pijn ontstaat door schade of ziekte die het zenuwstelsel aantast, en nociplastische pijn verwijst naar pijn die ontstaat door de veranderde verwerking van nociceptieve prikkels zonder duidelijke weefselschade of ontsteking. Door een mechanisme-gebaseerde benadering toe te passen, kunnen zorgverleners behandelstrategieën op maat maken en pijnmanagement verbeteren, waardoor de kwaliteit van leven van borstkankeroverlevenden die chronische pijn ervaren, uiteindelijk wordt verbeterd.

Het ultieme doel van dit klinisch georiënteerde proefschrift was om haalbare klinische voorspellingsmodellen te ontwikkelen voor de aanwezigheid van nociceptieve, neuropathische en nociplastische pijn bij borstkankeroverlevenden die chronische pijn ervaren. Tegelijkertijd had dit proefschrift tot doel inzicht te bieden in de prevalentie van deze pijnmechanismen bij overlevenden van solide kanker en

de neurofysiologische processen te onderzoeken die ten grondslag liggen aan chronische pijn na de behandeling van borstkanker.

Om de kennis over de aanwezigheid van aanhoudende pijn, pijnmechanismen en andere pijnkenmerken bij overlevenden van solide kanker te verbeteren, werd een systematische literatuurreview uitgevoerd (Hoofdstuk 1). Deze review toonde aan dat ongeveer de helft van de overlevenden van solide kanker chronische pijn ervaart. De resultaten van deze review moeten echter voorzichtig worden geïnterpreteerd vanwege de aanzienlijke onverklaarde heterogeniteit. Bovendien konden we geen prevalentiegegevens verstrekken over de aanwezigheid van de verschillende erkende pijnmechanismen of andere pijnkenmerken bij overlevenden van solide kanker, vanwege een gebrek aan gegevens in de bestaande literatuur.

Gelukkig ervaren niet alle kankeroverlevenden aanhoudende pijn; het blijft echter onduidelijk waarom sommige borstkankeroverlevenden aanhoudende pijn ervaren terwijl anderen dat niet doen. Verschillende onderzoeken hebben gesuggereerd dat borstkankeroverlevenden met aanhoudende pijn beperkingen kunnen hebben in de verwerking van nociceptieve signalen in het perifere en centrale somatosensorische zenuwstelsel. Het somatosensorische zenuwstelsel in zijn geheel speelt een belangrijke rol bij de waarneming en ervaring van pijn. In Hoofdstuk 2 werden de somatosensorische profielen van borstkankeroverlevenden met en zonder aanhoudende pijn vergeleken met die van gezonde controles (negatieve controlegroep) en patiënten met fibromyalgie (positieve controlegroep), die bekend staan om veranderingen in de centrale verwerking van nociceptieve signalen. De resultaten van deze cross-sectionele studie geven aan dat borstkankeroverlevenden met chronische pijn verminderde gevoeligheid (hypoesthesie) vertonen voor thermische en mechanische stimuli en hyperesthesie (of verhoogde gevoeligheid) voor druk in het gebied van de borst en flank. Bovendien vertoonden borstkankeroverlevenden met pijn verhoogde facilitering van nociceptieve signalen (toegenomen temporale sommatie van pijn), maar behielden ze een normale remming van nociceptieve signalen (normale geconditioneerde pijnmodulatie),

vergelijkbaar met gezonde controles en borstkankeroverlevenden zonder pijn. Tot slot vertoonden ze een verhoogde psychosociale last, vergelijkbaar met patiënten met fibromyalgie.

In de klinische praktijk blijft de evaluatie van somatosensorische functie met behulp van dynamische kwantitatieve sensorische testmethoden een uitdaging. Geconditioneerde pijnmodulatie en temporale sommatie zijn dynamische kwantitatieve sensorische testmethoden die de verwerking van nociceptieve signalen binnen het centrale somatosensorische zenuwstelsel evalueren. Eerdere studies hebben gesuggereerd dat deze dynamische methoden belangrijke informatie kunnen bieden voor stratificatie en besluitvorming in de klinische praktijk, in overeenstemming met een mechanisme-gebaseerde benadering van pijn. Dynamische kwantitatieve sensorische tests zijn echter tijdrovend, kostelijk en vereisen speciale training, waardoor ze niet haalbaar zijn in klinische setting. In Hoofdstuk 3 hebben we de concurrente validiteit van klinisch toepasbare alternatieven voor dynamische kwantitatieve sensorische testmethoden onderzocht. De bevindingen van dit onderzoek suggereren dat klinische alternatieven voor geconditioneerde pijnmodulatie met behulp van een bloeddrukmanchet of een koudwaterbad goed met elkaar gecorreleerd zijn. Alternatieven voor temporale sommatie met behulp van een monofilament of een algometer bleken ook goed gecorreleerd te zijn op een afgelegen niet-pijnlijke locatie. Deze bevindingen geven aan dat de klinisch toepasbare alternatieven uitwisselbaar zijn; ze waren echter niet gecorreleerd met hun respectieve referentiestandaarden.

De ontwikkeling van klinisch toepasbare alternatieven voor de evaluatie van centrale nociceptieve verwerking is goedbedoeld; ze worden echter niet routinematig toegepast in de klinische praktijk. Met behulp van een online enquête werden Nederlandstaligen kinesitherapeuten gevraagd naar de haalbaarheid, bruikbaarheid, gezichts- en inhoudsvaliditeit van verschillende klinisch toepasbare kwantitatieve sensorische testmethoden, waaronder geconditioneerde pijnmodulatie en

temporale sommatie (Hoofdstuk 4). De meeste kinesitherapeuten waren het eens over de haalbaarheid en de gezichtsvaliditeit; echter, de bruikbaarheid en inhoudsvaliditeit kregen ambigue beoordelingen. Dit onderzoek toonde ook aan dat kinesitherapeuten beperkte interesse toonden in het opnemen van kwantitatieve sensorische testmethoden in hun klinische praktijk vanwege tijdsbeperkingen en het ontbreken van benodigde materialen.

Kwantitatieve sensorische testmethoden zijn recentelijk aanbevolen voor gebruik door klinische richtlijnen voor zowel nociplastische als neuropathische pijn. Hoewel deze klinische richtlijnen tot doel hebben de klinische evaluatie van pijn en daardoor pijnmanagement te verbeteren, zijn ze niet gevalideerd en bepalen ze niet de diagnostische waarschijnlijkheid voor de aanwezigheid van een dergelijk pijnmechanisme. Het verstrekken van de waarschijnlijkheid van de aanwezigheid van een pijnmechanisme zou de mechanisme-gebaseerde benadering van pijn verbeteren. Met behulp van een cross-sectioneel onderzoek met 92 overlevenden van borstkanker hebben we drie klinische voorspellingsmodellen ontwikkeld voor het toekennen van nociceptieve, neuropathische en nociplastische pijn bij borstkankeroverlevenden (Hoofdstuk 5). In totaal werd een set van 15 voorspellers geselecteerd, die verschillende factoren omvatten, waaronder patiënt- en behandeleigenschappen, en specifieke variabelen met betrekking tot pijnmechanismen. De voorspellers body mass index, leeftijd, type borstoperatie, type okseloperatie en gebruik van radiotherapie werden in alle drie de modellen opgenomen. Verschil in pijnintensiteit tijdens rust en activiteit, algemene beperkte schouderbewegelijkheid en lokale pijn werden beschouwd als voorspellers van nociceptieve pijn. Het neuropathische pijnmodel omvatte de aanwezigheid van een branderig gevoel, hypoesthesie bij aanraking en neuroanatomische verdeling van pijn of sensorische disfunctie. De score op de vragenlijst voor centrale sensitisatie, drukpijndrempels op een afgelegen locatie, aanwezigheid van wijdverspreide pijn en aanwezigheid van preoperatieve pijn werden geselecteerd voor het nociplastische pijnmodel. Kwantitatieve sensorische testmethoden werden als onhaalbaar

beoordeeld voor gebruik in de klinische praktijk en werden dus niet geselecteerd als voorspellers. Hoewel de ontwikkelde modellen een matige onderscheidende capaciteit en het vermogen toonden om nauwkeurige probabilistische voorspellingen te leveren, beperkt het gebrek aan externe validatie met behulp van onafhankelijke datasets en real-world omgevingen hun onmiddellijke implementatie in de klinische praktijk.

Dit doctoraatsproefschrift biedt inzichten in de klinische toepassing van kwantitatieve sensorische testen vanuit een mechanisme-gebaseerd perspectief op pijn bij overlevenden van borstkanker. Toekomstig onderzoek moet prioriteit geven aan de validatie van methoden om pijnmechanismen bij kankeroverlevenden te evalueren en daardoor belangrijke updates te verstrekken over de prevalentie van deze pijnmechanismen binnen deze populatie. Bovendien zijn verbeteringen in de klinische beoordeling van pijn gerechtvaardigd. Toekomstig onderzoek moet zorgverleners betrekken om de implementatie van instrumenten ter verbetering van de pijnbeoordeling en vervolgens het pijnmanagement te verbeteren. Door deze kwesties aan te pakken, kunnen we ons begrip van pijn bij borstkankeroverlevenden verbeteren en in de toekomst een betere zorg bieden.

General introduction

The general introduction of this doctoral thesis is structured into three main parts. The first part will provide an overview of breast cancer, its diagnosis and treatment. Part two will discuss pain after breast cancer treatment, exploring its classifications, underlying mechanisms, evaluation, and relationship with breast cancer treatment. Lastly, the research outline of this doctoral thesis is presented with its specific objectives.

1. Breast cancer

1.1 Definition

Breast cancer is a malignant tumor that arises from the cells of milk-producing lobules or ducts and spreads throughout breast tissue. It is possible that cancerous cells migrate into the blood vessels or lymphatic system, allowing them to move away from the breast tissue and further into the body, where they can manifest as metastases.

1.2 Epidemiology

Breast cancer is the most common malignancy and the leading cause of cancer-related deaths among women worldwide, with an estimated 2.3 million new cases diagnosed in 2020.[1] In Europe, one in eleven women will receive a breast cancer diagnosis during the course of their life.[2] In 2021, age-standardized incidence rates ranged from 23.1 cases per 100,000 women aged 15-39 and peaked at 437 new cases in 100,000 women aged 70 years or older.[3] In the same year, 11,319 women residing in Belgium were diagnosed with breast cancer.[3] Nevertheless, the relative 5-year survival rate has increased to 92% despite breast cancer's high incidence.[3] In men, breast cancer occurs in less than 1% of all breast cancer cases.[1]

1.3 Diagnosis and classification

Diagnosis and screening are important aspects of breast cancer management, as early detection and treatment can significantly improve treatment and survival outcomes.[4] The diagnosis of breast cancer involves a combination of physical examination, imaging, and pathological assessment. Physical examination includes

visual inspection and palpation of the breast and locoregional lymph nodes. During visual inspection, the breasts are screened for redness, retraction of the nipple(s), bleeding, or ulceration(s). Palpation of the breast involves screening for the presence of skin thickening and a (non-)painful lump in the breast or axilla.[5] Imaging typically involves a bilateral mammography using X-ray imaging and, in some cases, ultrasound and/or magnetic resonance imaging (MRI).[4] A final pathological diagnosis of breast cancer is made based on the histopathological findings of the core needle biopsy confirming the presence of malignant tumor cells in the suspected breast tissue.[4] This diagnosis provides important prognostic and therapeutic information, such as breast cancer type, stage, location, and the hormone sensitivity of cancer cells.[6]

Based on this information, breast cancers can be classified into several subtypes. Regarding **location**, breast cancer is divided into two broad categories: invasive and non-invasive (in situ). In the latter type, the cells that line the breast duct and/or lobe have transformed into cancer cells, but have not spread through the duct or lobe walls into the surrounding breast tissue. Based on the location of the cancer cells, non-invasive (or in situ) breast cancer is categorized as *ductal carcinoma in situ* (DCIS) and *lobular carcinoma in situ* (LCIS). When cancer cells spread from the ducts and/or lobes to the surrounding breast tissue, it is defined as an invasive breast cancer.[7,8] A distinction between a ductal and a lobular type is made: *invasive ductal carcinoma* (IDC) or *invasive lobular carcinoma* (ILC).[7,8] Invasive breast cancer is more likely to spread to other tissues outside the breast through blood vessels or the lymphatic system.[7,8] Clinical and radiographic examinations of the lungs, skeleton, and liver, as well as blood tests, are usually performed to rule out metastases in distant tissues.[4]

Further distinction in breast cancer types is based on the **hormonal characteristics** of the cancer cells. Cancer cells can express receptors to which hormones or proteins such as estrogen, progesterone, or the human epidermal growth factor receptor 2 (HER2) protein can bind.[7,8] The presence of such receptors is defined as hormone-

positive (ER+/PR+) or HER2-positive breast cancer, and upon binding, can stimulate tumor growth. It is possible that these receptors are absent, resulting in triple-negative breast cancer.[9]

Besides several categories and subtypes, breast cancer is described in stages using the **tumor-node-metastasis (TNM) staging** developed by the American Joint Committee on Cancer (**Table 1**).[10] T (Tx-4) refers to the size of the tumor, N (Nx-N3) refers to the number of regional lymph nodes affected by the cancer, and M describes the presence of distant metastases (M0-M1). These TNM categories are combined to generate a breast cancer stage that ranges from stage 0 (non-invasive breast cancer) to Stage IV (metastatic breast cancer).[11]

Table 1. Tumor-node-metastasis (TNM) staging of breast cancer.

TNM	Primary tumor (T)	Regional lymph node (N)	Distant metastasis (M)
x	Primary tumor cannot be assessed	Regional lymph nodes cannot be assessed	Presence of distant metastases cannot be assessed
0	No evidence of primary tumor	Tumor not spread to regional lymph nodes	No distant metastases
is	Ductal carcinoma in situ		
1	Tumor ≤ 20 mm	Tumor spread to 1-3 ipsilateral axillary lymph node(s) and/or ipsilateral mammary nodes detected by sentinel lymph node biopsy	
2	Tumor > 20 mm but ≤ 50 mm	Tumor spread to 4-9 ipsilateral axillary lymph nodes, or to ipsilateral mammary nodes	Distant metastases
3	Tumor > 50 mm	Tumor spread to 10 or more ipsilateral axillary lymph nodes, or to ipsilateral infraclavicular lymph nodes; Tumor spread to at least one axillary lymph node and to internal mammary nodes; Tumor spread to ipsilateral supraclavicular lymph nodes	
4	Tumor of any size with direct extension to the chest wall and/or skin		

1.4 Treatment

The choice of breast cancer treatment depends on several factors, including the stage and subtype of the cancer, the location of the tumor, and the patient's overall health and preferences.[4] The treatment typically involves several modalities selected by a multidisciplinary team of healthcare providers.[4] Primary treatment modalities include surgery, radiation therapy, chemotherapy, hormonal therapy, and targeted therapy. Chemotherapy, hormonal therapy, and targeted therapy are considered systemic therapies as they are administered through the bloodstream.[4,12]

Surgery is the most frequent treatment for breast cancer and involves the removal of the tumor and surrounding tissues. Depending on the tumor size and location, breast-conserving surgery (such as lumpectomy or wide local excision) or mastectomy (also known as amputation of the entire breast) can be performed. During breast cancer surgery a sentinel lymph node biopsy (SLNB) can be performed to determine the spread of cancer to the axillary lymph nodes.[13] The sentinel lymph node is the first axillary lymph node to receive lymphatic drainage from the tumor. The sentinel lymph node is removed and sent to a pathologist for evaluation. If the SLNB is positive for cancer cells, it is likely that they have spread to other lymph nodes, prompting an axillary lymph node dissection (ALND). The presence of cancer cells or micrometastases in the sentinel lymph node determines not only whether an ALND is required, but also whether adjuvant therapy (such as chemotherapy or radiation therapy) is required.[13] An ALND is a surgical procedure that removes affected lymph nodes from the axilla.

Following breast cancer surgery, *radiation therapy* is commonly prescribed to destroy any remaining cancer cells within the tissues using high-energy ionizing radiation.[4,6,12] High-energy particles such as X-rays or protons damage the genetic material (DNA) of cancer cells (and healthy cells), preventing them from dividing and eventually killing them. The location and dose of radiation therapy are determined by the type of breast cancer surgery (lumpectomy, wide local excision, or mastectomy) and the cancer stage. Typically, the breast (in case of breast conserving

surgery), chest wall, or axilla is radiated using the lowest dose necessary to eliminate cancer cells while causing the least permanent damage to healthy tissues. Depending on the extent of cancer spread, radiation to other regional lymph nodes (parasternal, supraclavicular, or internal mammary lymph nodes) may be required. By delivering the radiation in small, precise doses over a period of several weeks, damage to the healthy tissue is minimized and has the opportunity to recover between sessions.[4,6,12]

Chemotherapy uses cytotoxic drugs to kill rapidly dividing cancer cells by damaging their DNA within these cancer cells. Cytotoxic drugs can also cause damage or death to rapid-dividing healthy cells, such as those found in hair follicles, digestive tract, bone marrow, and peripheral nerve endings. As such, chemotherapy can cause hair loss, nausea, vomiting, increased risk of infection, and nerve damage in the fingertips and/or toes.[4,6,12]

Endocrine therapy is used to treat estrogen- or progesterone-positive (ER +/PR +) breast cancers. Hormonal therapy works by either inhibiting the production of these hormones or by blocking the hormone receptors on the tumor cells, which prevents the growth and division of breast cancer cells.[4,6,12] Inhibition of estrogen production is accomplished by blocking the protein aromatase, resulting in decreased estrogen levels in the body, which consequently impedes the growth of estrogen-sensitive cancer cells. This class of drugs is known as aromatase inhibitors and includes letrozole, anastrozole, and exemestane. Another approach to hormonal therapy involves blocking the hormone receptors on cancer cells. Tamoxifen is a selective estrogen receptor modulator that competes with estrogen for binding to hormone receptors, thereby preventing estrogen binding. As a result, cancer cells are prevented from receiving the hormonal signals needed for growth and division, and the growth of cancer cells is slowed or halted.[24,254,6,12]

Targeted therapy is another type of systemic cancer treatment that specifically targets and inhibits the activity of receptors or pathways located in cancer cells and

is required for cancer cell growth and survival. The most common indication for breast cancer-targeted therapy is HER2-positive breast cancer. HER2 is a protein that is overexpressed in approximately 20% of breast cancers and induces tumor cell growth and division. Targeted drugs, such as trastuzumab, pertuzumab, and ado-trastuzumab emtansine (T-DM1), bind to the HER2 protein and block its activity, thereby inhibiting the growth of HER2-positive breast cancer cells. These drugs are designed to be more selective and less toxic than traditional cytotoxic drugs used in chemotherapy, which can damage healthy cells and cancer cells.[4,6,12]

2. Pain after breast cancer treatment

2.1 Epidemiology and definitions

Pain is a common side effect of breast cancer treatment, with prevalence rates ranging from 2% to 78%.[14] Pain is usually felt in the breast, chest wall, axilla, and/or medial upper arm[15] however it's possible that pain is present in other areas in a widespread manner.[16]

Pain is defined by the International Association for the Study of Pain (IASP) as "An unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or protentional tissue damage." The IASP also adds that "Pain is always a personal experience that is influenced to varying degrees by biological, psychological, and social factors".[17] This addition provides understanding that an individual's pain experience is influenced by a dynamic relationship between biological, psychological, behavioral, and social factors.

Pain can be present acutely after surgery or injury, but can also be prolonged, resulting in chronic pain. Chronic pain is known to have a substantial impact on a person's quality of life, including physical function, sleep, emotional well-being, and fear of cancer recurrence.[18–20] Chronic or persistent pain are considered to be equal terms and are often used interchangeably. In this doctoral thesis, both terms will be used to describe prolonged pain. Besides classifying pain as acute or chronic, the IASP introduced three biologically based mechanistic pain descriptors: nociceptive

pain, neuropathic pain, and nociplastic pain. The definitions of these mechanistic pain descriptors are listed in **Table 2.**

Table 2. Definition of pain and three biologically based mechanistic pain descriptors by the IASP

Pain		
An unpleasant sensory and emotional experience associated with or resembling that associated with, actual or potential tissue damage.		
Nociceptive pain	**Neuropathic pain**	**Nociplastic pain**
Pain that arises from actual or threatened damage to non-neural tissue and is due to the activation of nociceptors.	Pain caused by a lesion or disease of the somatosensory nervous system.	Pain that arises from altered nociception despite no clear evidence of threatened tissue damage causing activation of peripheral nociception or evidence for disease or lesion of the somatosensory system causing pain.

In addition to the classification based on the biological mechanism of pain, the IASP together with the representatives of the World Health Organization (WHO) established a classification system for the International Classification of Diseases (ICD-11) to accurately classify chronic cancer-related pain (**Figure 1**).[21] Chronic cancer-related pain refers to chronic pain that arises either from the primary cancer or its metastases (chronic cancer pain) or from the cancer treatment (chronic post-cancer treatment pain) and will be the focus of this doctoral project.[21] Local and systemic cancer therapies can cause chronic pain. Due to the multimodal nature of cancer therapy, it is not always possible to differentiate the exact cause of chronic post-cancer treatment pain. For these cases, the standard diagnosis of chronic post-cancer treatment pain will suffice. More specific subdiagnoses, such as chronic post-radiotherapy pain, could be utilized if the cause of the pain is easily identified, or if just one treatment was administered.[21]

All the mentioned classification systems (IASP, ICD-11) have the intention to improve management strategies for patients experiencing chronic pain, to improve uniformity in used terminology, and to stimulate future research.[21] Although the biopsychosocial model of pain applies to all pain classifications, it relies on the somatosensory nervous system to perceive the pain. Without the somatosensory

nervous system, one does not experience a sense of touch, pressure, temperature, vibration, or pain.

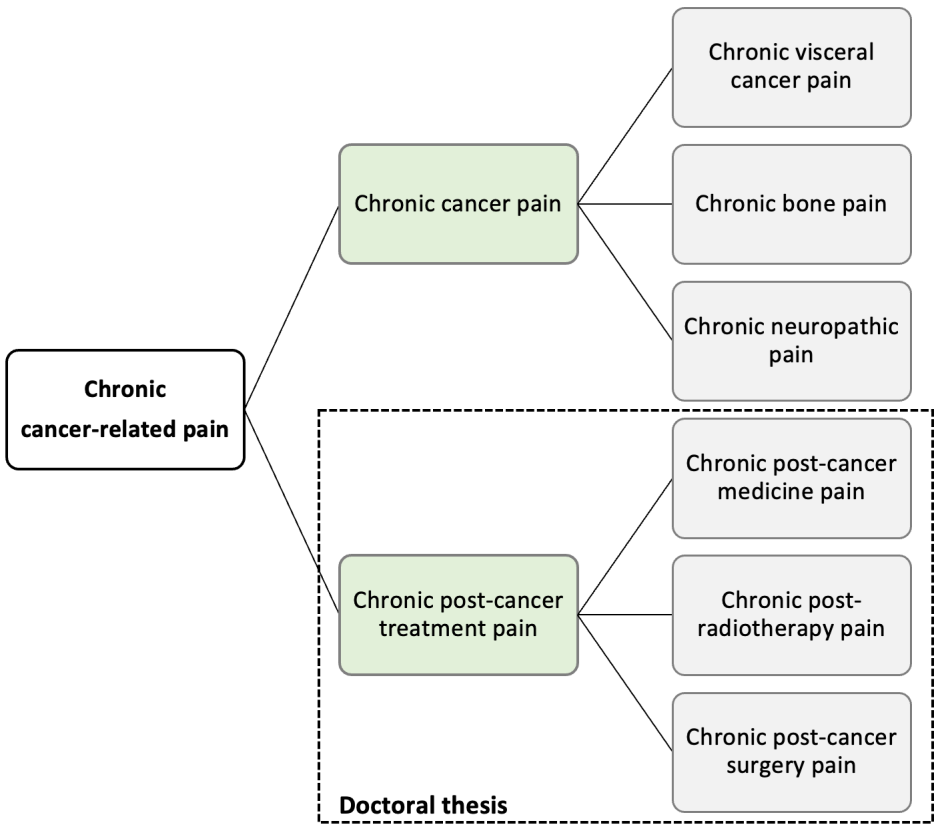


Figure 1. Chronic cancer-related pain as presented in the International Classification of Diseases (ICD-11).

2.2 Somatosensory functioning and pain

The somatosensory nervous system is part of the complex sensory nervous system and informs us of our surroundings and provides signals to react to certain situations. The somatosensory processing of noxious or other sensory signals is usually divided into four stages: transduction, transmission, modulation, and perception. *Transduction* is the conversion of a physical signal (such as heat, pressure, touch, or vibration) to an electrical signal. Different types of receptors and free nerve endings can be used to detect different stimuli. Physical stimuli such as light touch can be detected by mechanoreceptors in the skin. Noxious stimuli or stimuli that are damaging or threaten to damage normal tissues are detected by afferents called nociceptors: mechano-heat nociceptors, cold nociceptors, polymodal nociceptors sensitive to heat, pinch, and cold, and wide-dynamic range afferents.[22] Whenever a stimulus is strong enough, voltage-gated ion channels in the cell membrane will become activated, causing depolarization. When depolarization is sufficient, it can induce an electrical signal (action potential).[23] *Transmission* occurs when the axon of the primary afferent (nociceptor) transmits a (nociceptive) signal from the periphery to the spinal cord (or medulla) (**Figure 2**). Nociceptive primary afferents can be divided into two groups based on their axon conduction velocity: Aδ and C fibers.[23] Aδ fiber afferents are myelinated fast-conducting neurons that are predominantly sensitive to cold or mechanical stimuli. C fiber afferents are unmyelinated slow-conducting polymodal neurons that are sensitive to mechanical, chemical, and thermal stimuli. Sudden, short-lasting, and localized sharp pain is an example of pain mediated by Aδ fibers, whereas long-lasting and poorly localized pain is an example of pain mediated by C fibers.[23] A third group of fibers are Aβ fibers, rapidly conducting and thickly myelinated fibers that convey mechanical sensation of non-noxious stimuli, vibration, and proprioception.[23] In the dorsal horn, the primary afferent nociceptors terminate near secondary afferent neuron cells where synaptic transmission takes place.[24,25] Once the nociceptive signal reaches the terminal of the primary afferent nociceptor, it releases chemical transmitter substances into the

synapse between the terminus of the primary afferent nociceptor and adjacent secondary afferent neuron.[24] Synaptic transmission is mediated in large part by glutamate and peptides (e.g., substance P).[24] Secondary afferent neuron decussate and ascend in the anterolateral quadrant of the white matter in the spinal cord to reach the brainstem and thalamus (**Figure 2**). The thalamus is responsible for the strict segregation of place- and modality-specific responses and acts as a relay station. Information that has been processed by the thalamus is transmitted to the sensory cortex (postcentral gyrus) and associated brain regions such as the anterior cingulate cortex, prefrontal cortex, insula, amygdala, hippocampus, cerebellum and the mesolimbic reward circuit.[22,23,26] These regions are not exclusively activated by nociception or solely restricted to pain perception, but also serve other neurological functions including cognition, emotion, motivation and sensation which are functionally connected in the context of nociception and ultimately influence the experience of pain.[27,28]

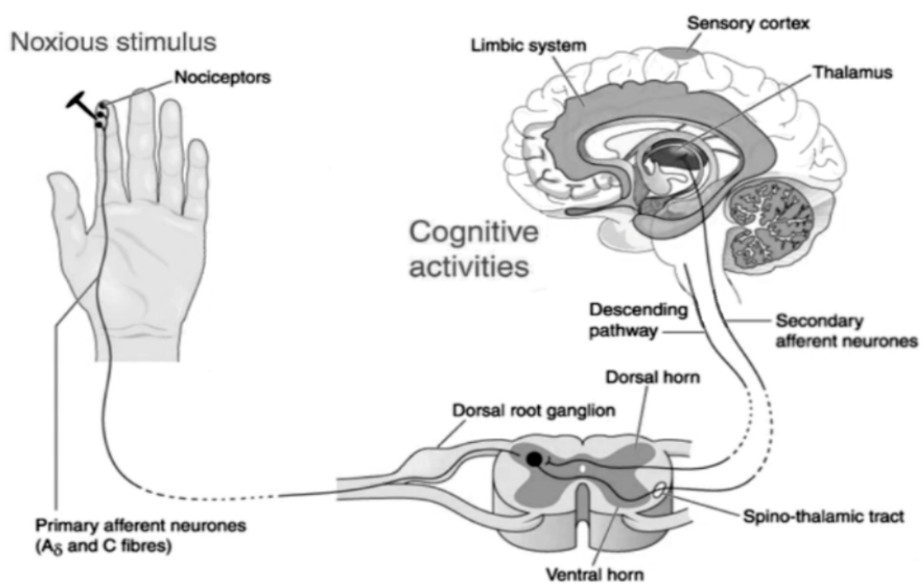


Figure 2. Schematic overview of somatosensory processing of noxious stimuli. Illustration from Haenen et al.[29]

Modulation of these incoming sensory or noxious signals can happen in both the peripheral and central somatosensory nervous system through top-down (descending) and bottom-up (ascending) mechanisms.[23] At the level of the dorsal horn, sensory signals can be facilitated or inhibited, respectively increasing or decreasing the intensity of the incoming signal via presynaptic and postsynaptic modulation.[23] In addition, plasticity in synaptic strength, which is the ability to increase synaptic connections is important considering somatosensory modulation.[23] At this level, the gate control theory, first discovered by Melzack & Wall, which is based on presynaptic inhibition, could be seen as a form of ascending inhibition. Non-noxious stimulation can suppress the noxious stimulus by 'closing the gate' at the level of the spinal cord via an inhibitory interneuron, hindering the noxious signal to reach the thalamus.[30] In case of descending inhibition, primary afferent terminals are inhibited largely due to release of norepinephrine in the dorsal horn.[31] Descending facilitation may occur via serotonergic mechanisms intensifying incoming signals and/or lowering the threshold for transmitting signals from the dorsal horn to the thalamus.[28,32] Modulation can also occur at the level of the brain. Different brain regions receive sensory input and contribute to the processing of an incoming (noxious) signal. The evaluation of signals by the brain determines the degree of modulation in the brain and consequently, the spinal cord through descending inhibition or facilitation of (noxious) signals. Psychosocial factors such as stress and fear are associated with the aforementioned brain regions and can therefore influence the processing and modulation of these signals.[30,33] All these processes help us perceive sensory and noxious inputs. Perception involves the synthesis of multiple incoming signals into something coherent. Perception is a multi-step process including numerous factors such as attention, expectation, and interpretation.[34] Additionally, in therapeutic settings, context-related factors such as beliefs and therapy expectations, and the use of placebo (e.g., effects due to a positive healthcare context) and nocebo (e.g., effects due to a negative healthcare context) are known to influence the perception of pain.[35]

2.3 Altered somatosensory functioning and pain

When tissues and neurons are injured (e.g., due to different cancer treatment modalities), **peripheral and central sensitization** can occur via products of tissue inflammation and neuronal processes, respectively.[36] The definitions of peripheral and central sensitization are presented in **Table 3**.

Table 3. Definition and clinical signs of peripheral and central sensitization according to the IASP.

Sensitization	Definition by IASP	Clinical manifestation
Peripheral sensitization	Increased responsiveness and reduced threshold of nociceptive neurons in the *periphery* to the stimulation of their receptive fields.	Primary or localized hyperalgesia
Central sensitization	Increased responsiveness of nociceptive neurons in the *central nervous system* to their normal or subthreshold afferent input. Increased responsiveness is due to dysfunction of endogenous pain control systems within the central nervous system.	Secondary or widespread hyperalgesia

Peripheral sensitization emerges from the activity of inflammatory chemicals generated at the damaged tissue site by both sensory nerve fibers and inflammatory cells.[37] A clinical manifestation of peripheral sensitization is primary hyperalgesia which consists of a painful response to stimuli that are not normally painful within the area of injury and/or inflammation.[37] Hyperalgesia can extend beyond the area of injury or treatment through the involvement of the central somatosensory nervous system, termed central sensitization. In case of central sensitization, pain is perceived as a result of alterations in the central somatosensory nervous system (dorsal horn or supraspinal), rather than reflecting the presence of peripheral noxious stimuli.[38] Central sensitization is characterized by a variety of mechanisms, such as increased facilitation (ascending and descending) and decreased descending inhibition of nociceptive signals.[37] A common clinical manifestation of central sensitization, is secondary or widespread hyperalgesia in remote, unaffected tissue.[39]

Both peripheral (local) and central (widespread) sensitization are neurophysiological states characterized by aberrant sensory excitability or gain of somatosensory function, such as hyperalgesia and allodynia (**Table 4**). Conversely, hypoalgesia represents an aberrant loss of somatosensory function due to damage to the tissues and neurons (**Table 4**). Both loss and gain of somatosensory function can be quantified using static and dynamic quantitative sensory testing (QST).

Table 4. Definitions of altered somatosensory functioning

Sensory alterations		Definition by IASP
Loss of somatosensory function	Hypoesthesia	Decreased sensitivity to stimulation
	Hypoalgesia	Diminished pain in response to a normally painful stimulus
Gain of somatosensory function (central or peripheral sensitization)	Hyperesthesia	Increased sensitivity to stimulation*
	Dysesthesia	An unpleasant abnormal sensation, whether spontaneous or evoked
	Hyperalgesia	Increased pain from a stimulus that normally provokes pain
	Allodynia	Pain due to a stimulus that does not normally provoke pain

*The term hyperesthesia (or sensitization) covers both hyperalgesia and allodynia. However, more specific terms should be used whenever their definitions are satisfied. IASP= International Association for the Study of Pain.

2.4 Evaluation of somatosensory functioning and pain

Quantitative sensory testing has been shown to be useful for the evaluation of somatosensory functioning in terms of loss or gain of sensory function within different populations, and has helped to gain insight into the pathophysiological mechanisms of somatosensory dysfunction such as hypo- and hyperesthesia.[40] QST consists of multiple psychophysical tests assessing the different properties of the somatosensory nervous system by evaluating the function of Aβ, Aδ, and C fibers, as well as central pathways.[41–43] QST protocols can be divided into a static and dynamic part. Static QST typically includes the assessment of detection and pain thresholds, such as warm and cold detection, heat and cold pain, mechanical detection and pain, pressure pain, and vibration detection.[41–43] A gain in somatosensory functioning (hyperesthesia) or a loss in somatosensory functioning (hypoesthesia) can be evaluated using detection thresholds. When altered central somatosensory

processing is suspected, increased sensitivity can also be observed in remote areas (secondary or widespread hyperalgesia).[44] Dynamic QST protocols assess the spinal and supraspinal processes by evaluating the response to several stimuli instead of one static sensory threshold. Dynamic QST protocols such as temporal summation (TS) and conditioned pain modulation (CPM) are used to assess spinal and supraspinal processes, respectively.[45] TS refers to the bottom-up wind-up phenomenon (or as mentioned above, ascending facilitation) in which repetitive activation of C and Aδ fibers produces a progressive increase in evoked responses of dorsal horn neurons.[46] In case of aberrated somatosensory processing, neuronal activity due to wind-up is exaggerated in amplitude and duration resulting in TS of pain.[45,47] CPM is the human counterpart of diffuse noxious inhibitory control in animals and explores the top-down inhibitory effect of the somatosensory nervous system using the 'pain inhibits pain' principle in which a noxious stimulus exerts inhibitory effects on subsequent noxious stimuli.[48] In case of aberrant central somatosensory processing of nociceptive signals, a decrease of pain can be absent due to the impaired inhibitory effects.[45,47,49] Commonly used QST procedures, their test methodology and associated peripheral or central sensory pathway are shown in **Table 5**.

QST protocols can be used to evaluate somatosensory processing associated with the presence of one or more mechanistic pain descriptors (nociceptive, neuropathic, nociplastic).[17] QST using thermal, touch, vibration detection thresholds, and pinprick sensation can be used to confirm the suspicion of *neuropathic pain* in its neuroanatomical area of innervation, as is suggested in recent guidelines.[42,50,51] For *nociplastic pain*, guidelines propose QST for the evaluation of (hyper)sensitivity to one of the following stimuli in the region of pain: mechanical allodynia and heat or cold allodynia.[52] Furthermore, CPM and TS at local and distant body regions are proposed to evaluate aberrations of central nociceptive processing by the somatosensory nervous system.[52] For *nociceptive pain*, no guidelines exist and therefore no recommendation for the use of QST can be made. QST might be less

useful for the evaluation of nociceptive pain because only limited changes in somatosensory functioning are suspected.

Table 5. Summary of quantitative sensory testing modalities, test methods and associated peripheral or central pathways.

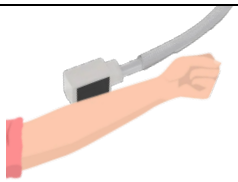
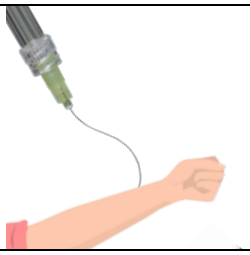
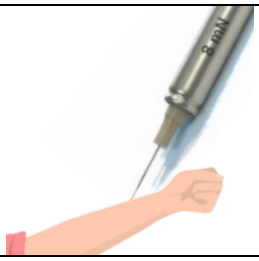
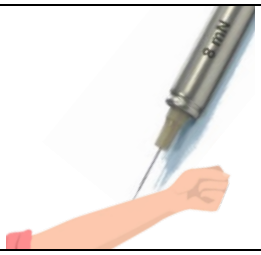
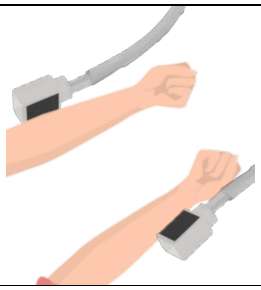
Instrument	Laboratory test procedure	Peripheral nerve fiber or central pathway
Thermal detection & pain thresholds		
Computerized thermal test 	Temperature when a change from a thermoneutral state to a distinct/painful warm (WDT, HPT) or cold (CDT, CPT) sensation is experienced.	Peripheral nerve fiber: • Detection: - Warmth: C - Cold: Aδ • Pain: Aδ, C Central pathway: • Spinothalamic
Mechanical detection thresholds		
Weighted monofilaments (von Frey) 	Series of ascending and descending stimulus intensities are given and the stimulus intensity that is first / last identified is recorded (MDT).	Peripheral nerve fiber: • Detection: Aβ Central pathway: • Lemniscal
Mechanical pain thresholds		
Pinprick stimulator 	Series of ascending and descending stimulus intensities are given and the stimulus intensity that is identified as painful (MPT) is recorded.	Peripheral nerve fiber: • Pain: Aδ, (C) Central pathway: • Spinothalamic
Pressure pain thresholds		
Pressure algometer 	Amount of pressure by which the perception of pressure turns into a painful (not unbearable) sensation.	Peripheral nerve fiber: • Pain: C, (Aδ) Central pathway: • Spinothalamic

Table 5. Continued

Temporal summation			
Pinprick stimulator or weighted monofilament (256 mN)		Pain rating after a single stimulation, after train of pinprick stimuli (wind-up) and seconds after a final stimulus (aftersensations).	Peripheral nerve fiber: • Pain: C Central pathway: • Spinothalamic
Conditioned pain modulation			
Computerized thermal test (two-thermodes)		Pain rating during single and simultaneous application of two noxious stimuli.	Peripheral nerve fiber: • Pain: C, (Aδ) Central pathway: • Spino-bulbo-spinal loop[53]

Adapted from Hall et al., 2015[40]. CDT= Cold detection threshold, CPT= Cold pain threshold, WDT= Warmth detection threshold, HPT= Heat pain threshold, MDT= Mechanical detection threshold, MPT= Mechanical pain threshold.

QST encompasses various paradigms, and its reliability can greatly vary depending on the specific paradigm being investigated and the population in which it is applied. In studies involving healthy individuals, static QST consistently exhibits good-to-excellent reliability, whereas dynamic QST tends to show a wider range of reliability, from poor to good. Moreover, when assessing stability over a 4-month period, static QST appears to be relatively stable, while dynamic QST displays considerable variability over time.[54] In the case of breast cancer survivors, the reliability of QST methods also varies depending on the particular paradigm utilized. For static mechanical tests, reliability scores fall within the range of moderate to excellent, indicating a strong level of consistency when assessing mechanical sensory thresholds. Conversely, static thermal tests exhibit reliability that ranges from moderate to good, reflecting a reasonable degree of consistency in evaluating thermal sensory thresholds. Regarding dynamic QST paradigms, TS demonstrates reliability scores ranging from moderate to good, whereas CPM displays weaker to

moderate reliability in this specific population.[55] Regarding the validity of QST, there is a significant lack of research, both in general and particularly within the context of cancer survivors.

2.5 Altered somatosensory functioning and pain after breast cancer treatment

Breast cancer treatment often leads to changes in sensory function.[56,57] In one study, approximately half of all breast cancer survivors who underwent surgery and 70% of those with chronic post-surgical pain experienced sensory disturbances in the surgical area or the area surrounding it, up to seven years after the surgery.[57] A more recent cohort study revealed that larger areas of hypoesthesia in the surgical region are associated with more severe pain in this region.[58] However, the precise relationship between the severity of altered sensation and pain in the treated area in breast cancer survivors is not fully understood. In addition to local changes in sensory function, central aberrations in somatosensory processing may also occur. Breast cancer survivors can experience both neuropathic and non-neuropathic pain mechanisms.[16] Various QST methods have been used to investigate the somatosensory system in breast cancer survivors with chronic pain. These studies have compared both the affected and unaffected sides, survivors with and without pain, and healthy controls, while examining both surgical and remote areas.[56,59–61] These findings suggest that breast cancer survivors with chronic pain tend to have reduced sensitivity for mechanical and thermal detection, as well as pain thresholds in the surgical area.[56,59–61] Furthermore, when evaluated in remote areas using dynamic QST methods, breast cancer survivors also tend to show aberrations in central somatosensory processing.[59–61] Nonetheless, due to the variation in methods and small sample sizes in previous studies, there is still a lack of clarity regarding mechanistic pain descriptors in breast cancer survivors. Moreover, most research on pain in breast cancer survivors utilizes a symptom-orientated classification[62,63] (e.g., post-mastectomy pain syndrome, aromatase inhibitor-associated musculoskeletal symptoms) or pain classification based on intensity[14,64] (e.g., moderate vs. severe pain). With research evolving from the musculoskeletal field and with increasing

knowledge of the presence of aberrations in central somatosensory processing in breast cancer survivors, it might be helpful for research and clinic to utilize a mechanism-based classification system, as mentioned above (nociceptive pain, neuropathic pain, and nociplastic pain) in this cancer population as well. Given this, we recently published a narrative review providing a comprehensive overview of side effects related to breast cancer treatment in relation to the somatosensory system using a mechanism-based perspective in breast cancer survivors with chronic pain.[29] This narrative review can be found here. For the purpose of this doctoral thesis, I will provide a limited overview of breast cancer treatment modalities in relation to nociceptive, neuropathic and nociplastic pain (see 2.4.1 - 2.4.4). In addition, it is important to consider that breast cancer treatment is often multimodal; therefore, it is possible that modalities interact with each other, inducing a multifactorial cause for a certain pain mechanism, or a multitude of pain mechanisms. Furthermore, other biopsychosocial factors influence the somatosensory nervous system and contribute to the development and/or maintenance of chronic pain in survivors of breast cancer. **Table 5** presents an overview of these factors found in the current literature.

Table 6. Biopsychosocial risk factors associated with persistent pain in survivors of breast cancer

Risk factor	**Reference**
Younger age	Andersen et al., 2015[65]; De Oliveira et al., 2014[66]; Gärtner et al., 2009[67]; Mejdahl et al., 2013[57]; Schou Bredal et al., 2014[65]; Ghadimi et al., 2023[68]; Hamood et al., 2017[69]17-10-2023 22:39:00
High Body Mass Index	Meretoja et al., 2017[70]
Preoperative pain	Andersen et al., 2015[71]; Meretoja et al., 2017[70]; Meretoja et al., 2014[71]; Villa et al., 2021[72]; Raza et al., 2021[73]
Acute post-operative pain	Andersen et al., 2015[65]; Bruce et al., 2014[74]; Meretoja et al., 2017[70]; Ghadimi et al., 2023[68]; Villa et al., 2021[72]; Raza et al., 2021[73]
Loneliness	Ghadimi et al., 2023[68]
Pain catastrophizing	Bruce et al., 2014[74]
Anxiety	Bruce et al., 2014[74]; Meretoja et al., 2014[71]; Miaskowski et al., 2012[75]
Depressive symptoms	Miaskowski et al., 2012[75]
Sleep disturbance	Miaskowski et al., 2012[75]

2.5.1 Surgical treatment

Surgical treatment of breast cancer consists of performing either breast-conserving surgery or mastectomy in combination with an axillary procedure, such as SLNB or ALND. Several studies have investigated the relationship between the type of breast surgery and the persistence of pain after breast cancer treatment; however, their findings remain inconclusive.[76–78] Numerous studies have identified ALND as a significant risk factor for chronic post-surgical (neuropathic) pain in breast cancer survivors. Performing an ALND increases the risk of lesions to the intercostobrachial nerve (ICBN) which is a sensory nerve innervating the axilla, lateral chest, and medial upper arm.[79] ICBN resection during ALND can lead to sensory abnormalities in the area it innervates and is associated with intercostobrachial neuralgia (a type of chronic neuropathic pain).[80] The exact relationship of ICBN lesions and chronic post-surgical pain remains unclear at this point. Studies reported that both resection and preservation of the ICBN is associated with chronic post-surgical pain.[77,79] Despite being commonly avoided during surgery, nerves located in vulnerable anatomical areas, such as the pectoral nerves, long thoracic nerve, and thoracodorsal nerve, are still at risk of being damaged during the perioperative period.[81] Lesions to these nerves increase the risk of developing sensory abnormalities or even neuropathic pain.[81,82] Consequently, breast cancer survivors often present with aberrant sensitivity for mechanical and thermal detection and pain thresholds in the surgical area.[58–60,80] Besides injury to neuronal tissues, surgery can impact non-neuronal tissues leading to scar tissue formation and soft tissue adhesions consequently decreasing range of motion of the upper limb.[83,84] In general, surgical treatment contributes to sensory alterations locally by injuring neuronal and non-neuronal tissues. Surgery can be associated with mechanistic pain descriptors, such as nociceptive pain, neuropathic pain, and/or potentially nociplastic pain.

2.5.2 Radiation therapy

Owing to advancements in treatment, radiation therapy is now administered using the lowest dose necessary to eliminate cancer cells while causing the least

permanent damage to healthy tissues. Even though low radiation doses are used, it is possible that both neuronal and non-neuronal tissues are harmed during this process. The mechanisms of radiation induced side effects are not fully understood but may involve fibrosis, ischemia, and inflammatory factors.[85] Radiation therapy is associated with an increased risk of localized chronic pain[86], and possibly impedes the recovery of mechanical detection and mechanical pain thresholds in patients with intercostobrachial neuropathy over a one-year follow-up. [80] Taken together, radiation therapy influences the sensitivity of local tissues and is possibly associated with nociceptive, neuropathic, and possibly nociplastic pain mechanisms.

2.5.3 Chemotherapy

Cytotoxic drugs such as taxanes (e.g., paclitaxel and docetaxel) or platinum-based agents (e.g., cisplatin, oxaliplatin or carboplatin) are commonly used in the treatment for breast cancer, but are known to cause chemotherapy-induced peripheral neuropathy (CIPN). The prevalence of CIPN after the administration of taxanes is high, up to 70%, and can persist for several years.[87,88] A small study showed that CIPN was painful in 39% and that pain was mostly mild but associated with lower quality of life.[89] Multiple mechanisms have been examined, with the most widely accepted mechanism being a “dying back” process with axonal degeneration of sensory neurons, leading to loss of intra-epidermal nerve endings.[90] Other mechanisms such as irreversible cell injury, changes in the excitability of peripheral nerves, and neuroinflammation are mentioned.[90] The involvement of the somatosensory nervous system in CIPN indicates that chemotherapy induces neuropathy, and in some cases neuropathic pain. Potentially, in the long term, it could contribute to the development of nociplastic pain; however, current evidence is lacking.

2.5.4 Endocrine therapy

Tamoxifen and aromatase inhibitors are commonly used endocrine treatments for breast cancer, and are known to cause osteoporosis, widespread arthralgia, and

musculoskeletal pain. Arthralgia and musculoskeletal pain affect approximately half of the aromatase inhibitor users.[91,92] Although the specific pathophysiology of aromatase inhibitor-induced arthralgia and musculoskeletal pain remains unclear, current theories point to estrogen deprivation as a crucial element contributing to bone and cartilage degeneration and the development of musculoskeletal symptoms.[91,93] Furthermore, estrogen seems to influence somatosensory processing due to its anti-nociceptive properties and anti-inflammatory function, decreasing the synthesis of inflammatory cytokines.[93,94] Based on the proposed mechanisms, endocrine therapy might be associated with nociceptive and nociplastic pain mechanisms; however, evidence remains nonexistent.

2.6 Treatment of pain

A detailed description of the treatment of pain after breast cancer is not within the scope of this doctoral thesis. However, the current evidence-based practice for the management of chronic pain (after breast cancer) involves a multimodal and multidisciplinary approach using the biopsychosocial framework of pain.[95] This approach usually combines pharmacological and non-pharmacological modalities, such as physical therapy and psychotherapy. It is important that within this multimodal approach, the patient's individual needs and preferences are also considered.[95] While multimodal approaches are generally considered the most effective way to manage chronic pain, studies demonstrate limited effects for reducing pain in non-cancer populations.[96,97] In a cancer population, unfortunately there remains a scarcity of high quality research investigating the effect of multimodal approaches to pain related to cancer or its treatment. the non-cancer population might be due to the used symptom-based approach to pain, rather than a mechanism-based approach to pain. Several studies in non-cancer populations have suggested that such a mechanism-based approach to pain might provide better treatment outcomes.[97–100] A mechanism-based approach to pain involves identifying the underlying biological mechanisms of pain (or mechanistic pain descriptor) and tailoring the treatment accordingly. By targeting the underlying mechanisms

improved pain management, reduced medication use, and improved quality of life for patients experiencing pain can be facilitated.[98–100] To target the underlying mechanisms of pain, it is imperative that a thorough assessment of the individual's pain is undertaken and that a certain mechanistic pain descriptor is identified.[100,101] Within such a thorough assessment, clinical prediction models can play a valuable role. Diagnostic clinical prediction models use multiple variables or so called "predictors" to determine the risk or probability of a particular health outcome. These clinical prediction models generally use clinically feasible predictors and aim to inform clinicians further guiding clinical decision-making. In general, there are two different kinds of prediction models: (1) diagnostic prediction models, which establish the existence of a specific (but unidentified) sickness or injury, and (2) prognostic prediction models, which predict whether a specific event or injury will take place in the future. Clinical prediction models are not meant to replace clinical expertise and expert knowledge, but aid physicians to choose the best course of action (or inaction, such as wait and see) for their patients.[102] In medicine, clinical prediction models are frequently used to estimate a patient's risk (between 0% and 100%) or probability (between 0 and 1) of experiencing an event such as heart failure[103], stroke[104], and major osteoporotic or hip fracture[105]. In pain research, diagnostic clinical prediction models that can determine the probability for the presence of a certain mechanistic pain descriptor are lacking. This gap in knowledge is particularly significant, given the potential role such models could play in effectively managing persistent pain following breast cancer treatment.

3. Research objectives and doctoral thesis outline

The main aim of this project was to develop three feasible clinical diagnostic prediction models for the presence of nociceptive, neuropathic, and nociplastic pain in breast cancer survivors experiencing chronic pain (**Chapter 5**). To develop such models, we first systematically reviewed the existing literature on the prevalence of pain in solid cancer survivors, including breast cancer survivors. In addition to examining the prevalence of pain, our study also sought to conduct a comprehensive review of pain characteristics and mechanisms within this specific population, addressing a gap in the existing literature as no study has performed such review.(**Chapter 1**) As the precise relationship between the amount of sensitivity (e.g., hyper- or hypoesthesia) and pain in the treated and remote areas in breast cancer survivors is not fully understood, we investigated whether breast cancer survivors with and without chronic pain differ in somatosensory profiling in terms of loss and gain of function compared with healthy controls and patients with fibromyalgia (**Chapter 2**). Although QST is useful for revealing abnormal somatosensory function, it has limitations that make it impractical for clinical use. These limitations include the high cost of equipment, the time-consuming nature of testing, and the need for standardized procedures. As we aim to develop a valid and clinically usable model, we investigated whether clinically applicable alternatives to dynamic QST (e.g., bedside QST) have sufficient concurrent validity in comparison to a respective reference protocol (**Chapter 3**). For this purpose, two bedside alternatives for TS and CPM are compared to a reference protocol in a group of breast cancer survivors experiencing chronic pain. In addition to its validity, the feasibility of a collection of bedside QST alternatives for the assessment of somatosensory function in breast cancer survivors was investigated in physical therapists (**Chapter 4**). This study provides information on the facilitators of and barriers to the implementation of bedside QST alternatives in clinical practice. Altogether, these studies collectively aim to provide insights for the development of

three clinical diagnostic prediction models for the presence of nociceptive, neuropathic and nociplastic pain in breast cancer survivors.

3.1 Research objectives

The following research questions were addressed in this doctoral thesis:

1. What is the prevalence of pain and what are the characteristics of pain experienced by survivors of solid cancers?
2. What are the differences in somatosensory function in terms of loss and gain in function between breast cancer survivors with and without persistent pain using reference data from healthy controls and patients with fibromyalgia?
3. What is the concurrent validity of the clinically applicable protocols for dynamic quantitative sensory testing in breast cancer survivors with persistent pain when compared to a reference test?
4. How do physical therapists perceive the feasibility, utility, and validity, including face and content validity, of utilizing bedside quantitative sensory testing to assess somatosensory function in cancer survivors with persistent pain?
5. How can mechanistic pain descriptor such as nociceptive, neuropathic, and nociplastic pain be evaluated in clinical practice in breast cancer survivors with persistent pain using clinical prediction models, and what is the internal validity of these models for the evaluation of mechanistic pain descriptors in such patients?

3.2 Research outlines

In **Chapter 1**, the existing literature regarding the prevalence and characteristics of pain in survivors of solid cancers is systematically reviewed.

Chapter 2 describes the somatosensory profiles in terms of loss and gain in function of breast cancer survivors with and without persistent pain and of patients with fibromyalgia using reference data from healthy controls.

Chapter 3 investigates the concurrent validity of two clinically applicable testing protocols for conditioned pain modulation and temporal summation in breast cancer survivors with persistent pain by comparing clinical protocols with a reference protocol.

Chapter 4 examines whether bedside quantitative sensory testing is feasible, useful, and has sufficient face and content validity for the assessment of somatosensory function among cancer survivors with persistent pain among Dutch-speaking physical therapists.

In **Chapter 5,** three different preliminary diagnostic clinical prediction models are developed and internally validated for the presence of predominant nociceptive, neuropathic, and nociplastic pain in breast cancer survivors with persistent pain.

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Chapter 1

Pain prevalence and characteristics in survivors of solid cancers: a systematic review and meta-analysis.

Pain prevalence and characteristics in survivors of solid cancers: a systematic review and meta-analysis

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Abstract

Purpose: The latest systematic review on the prevalence of pain in cancer survivors was published five years ago. This review aimed to provide an extended overview on the prevalence of pain, pain mechanisms, pain characteristics, and assessment methods in cancer survivors.

Methods: A systematic search was conducted on 17th of April 2020 using Medline, Embase, Scopus, Web of Science, and Cochrane looking at studies from 2014 to 2020. Studies had to report pain prevalence rates in cancer survivors with a solid tumor who had finished curative treatment at least three months ago. Methodological quality was assessed by two independent reviewers using the Joanna Briggs Institute quality appraisal tool. The characteristics of the included studies, participants, and the reported pain prevalence rates were extracted. The reported prevalence rates of the individual studies were pooled in a meta-analysis. Meta-regressions were performed to identify the possible determinants of the pooled pain prevalence.

Results: After deduplication, 7,300 articles were screened, of which 38 were included in the meta-analysis. Risk of bias was rated as low in 26 articles and moderate in 12 articles. The pooled pain prevalence was 47% (95%CI 39 - 55), with a heterogeneity of 98.99%.

Conclusion: This meta-analysis suggests that nearly half of cancer survivors report pain after completing curative treatment at least three months ago. However, substantial unexplained heterogeneity warrants cautious interpretation of these results. Meta-regression using cancer type, treatment location, pain measurement, and follow-up time as covariates could not explain the factors influencing the high heterogeneity.

Keywords: Cancer-related pain, cancer survivor, pain prevalence, systematic review, meta-analysis, meta-regression

Introduction

Cancer remains a major cause of morbidity and mortality worldwide. With 19.3 million new cases of cancer and 10.0 million cancer-related deaths recorded worldwide in 2020, it is one of the leading causes of death.[1] Although the incidence of cancer has increased, mortality rates have generally declined since the 1990s, resulting in more cancer survivors.

Several definitions of cancer survivorship exist.[2–4] This review utilized the European Organization of Research and Treatment of Cancer (EORTC) Survivorship Task Force which defines cancer survivorship as "patients who have completed their primary treatment, and have no evidence of active disease".[5]

These cancer survivors experience a wide range of side effects, often associated with poorer quality of life (QoL).[6,7] Cancer-related pain is frequently reported by cancer survivors. A systematic review published in 2016 investigated the prevalence of pain in cancer patients and cancer survivors, in studies published from 2005 to 2014.[8] Van den Beuken-van Everdingen et al. concluded that 39.3% of all cancer survivors experience pain after completing curative cancer treatment. In addition, pain was rated as moderate to severe by 27.6% of cancer survivors suffering from pain. Moderate pain was defined as pain ranging from five to six on the numeric rating scale (NRS) from 0-10, whereas severe pain was defined as pain equal or above seven on the NRS.[8,9] Although the results of this systematic review offer valuable information, clinically relevant insights related to pain during and after cancer treatment could perhaps be improved. Additionally, research on pain and cancer has improved substantially since 2014; therefore, an update might be necessary.

Identifying the dominant pain mechanism has become increasingly important in musculoskeletal pain research. It is postulated that mechanism-based pain management could provide more effective analgesia.[10–12] Four pain mechanisms, defined by the International Association for the Study of Pain (IAS), are widely used in pain research. *Nociceptive pain* is defined as 'pain due to activation of the

peripheral receptive terminals in response to noxious and potentially noxious chemical, mechanical or thermal stimuli' or as 'pain arising from actual or threat of damage to non-neural tissue due to the activation of nociceptor'.[13] *Neuropathic pain* is known as pain arising as a direct consequence of a lesion or disease affecting the somatosensory system.[14,15] *Nociplastic pain* is defined by the IASP as pain that arises from altered nociception, despite that there is no clear evidence of actual or threatened tissue damage causing the activation of nociceptors or evidence for disease or lesion of the somatosensory system causing the pain.[16] Lastly, the term *mixed pain* can be utilized when multiple pain mechanisms are present simultaneously.[17] Limited amount of studies are available reporting on the prevalence of different pain mechanisms in cancer survivors and currently no systematic overview is available.[18,19] It is not fully known to which extent nociplastic or mixed pain is present in this population. In addition, even though guidelines have been proposed to assess pain after cancer it seems they are not well adopted.[17] It appears that different criteria (i.e., pain is defined as at least 4 on the NRS versus pain is defined as at least 1 on the NRS) and assessment methods (i.e., numerical scales, psychophysiological tests, or questionnaires) are used to assess and define pain. To our knowledge, these criteria for assessing pain have not been considered in previous studies or systematic reviews.

The introduction of a mechanism-based approach to pain, combined with the increased amount of published research on the prevalence of pain during and after cancer treatment, warrants a new overview on this topic. Therefore, the goal of this systematic review was to summarize the pain prevalence rates in survivors of different solid cancer types who finished curative treatment. In addition, whenever available, the prevalence rates of the different pain mechanisms were presented together with the different pain characteristics and assessment methods for pain.

Methods

This systematic review adhered to the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement (PRISMA), and was registered with the International Prospective Register of Systematic Reviews on 11 November 2020 (PROSPERO reference CRD42016038870).[20]

Search strategy

A systematic search of the literature was conducted on April 17, 2020, for studies published from 2014 onwards using the Medline, PubMed, Embase, Scopus, Web of Science, and Cochrane databases. The keywords that were used are listed in Table 1. The search strategies were adapted to the database. Gray literature and ongoing studies were not included in this systematic search. Appendix 1 provides a detailed description of the search strategies used.

Table 1. Keywords included in the search strategy for all four databases.

Key words	Medline – MeSH Headings
Pain	Pain
AND	
Epidemiology **OR** prevalence	Epidemiology Prevalence
AND	
Cancer **OR** neoplasm **OR** neoplastic **OR** tumor **OR** tumour **OR** tumoral **OR** tumoural **OR** tumourous **OR** tumorous **OR** metastatic **OR** metastasis **OR** oncology **OR** oncological **OR** oncologic	Neoplasms Neoplasm metastasis

Study selection

Inclusion criteria were defined as follows: original prospective studies (cohort, cross-sectional, and randomized controlled trials (RCTs)), studies published between 2014 and 2020, studies that included cancer survivors who finished curative treatment with a minimum of three months after the last (adjuvant) treatment modality (endocrine therapy excluded), from which prevalence data on cancer-related pain could be extracted or calculated, and adult study populations. Articles that were

published in January 2014 were screened and excluded if they were already included in the previous systematic review of van den Beuken-van Everdingen et al.[8] Included articles had to be published in English, Dutch, French, or German. Articles were excluded if they did not differentiate between patients with and without cancer (mixed population) or if they reported pain during or from childhood cancer (age < 18 years at the time of diagnosis). Studies performed in pain clinics were excluded to prevent a selection bias. Studies investigating advanced cancer stage (stage IV), metastases, or palliative status were excluded because these stages are associated with a wide range of comorbidities. In addition, studies on patients treated with non-curative intent were excluded, as treatment can be presumed to be ongoing. Studies that included the following were also excluded: patients suffering from hematological malignancies such as leukemia, lymphoma, or myeloma; patients residing in nursing homes; and cancer patients reporting cancer-(related)pain before cancer diagnosis or treatment. Studies investigating chemotherapy-induced peripheral neuropathy (CIPN) were excluded as CIPN was considered to be a condition with predominantly sensory symptoms with pain not always being a significant presenting symptom.[21] If prevalence data were pooled (e.g., no pain and mild pain were grouped together) or could not be calculated, the studies were excluded. RCTs that included cancer survivors but did not provide baseline prevalence data were excluded. Retrospective studies, conference proceedings, editorials, letters, reviews, case studies, congress reports, and secondary analyses were excluded. If the disease stage, prevalence data, or other data were not present or were unclear, the respective authors were contacted. Studies were excluded if this information remained unclear after contacting the authors.

One reviewer (VH) performed the searches. Duplicates were identified using Endnote and Rayyan and were excluded by the same reviewer. Three reviewers independently screened the titles (VH, TdB, and MEv) and, subsequently, the abstracts. Two reviewers (VH & MEv) independently examined the full texts of the selected articles. Disagreements were resolved through consensus. A fourth

reviewer (ADG) was involved when disagreements were not resolved through consensus.

Data Extraction

The first reviewer (VH) extracted all the data using a digital data extraction platform (Covidence). The extracted data were checked by a second reviewer (MEv). The extracted data included author, year of publication, study design, population, continent, sample size, method of data collection (questionnaire, medical record, interview), and prevalence data. The following data regarding patient characteristics were extracted: age, sex, type of cancer, cancer stage, type of treatment, method of pain measurement, follow-up time after the last treatment, type of pain, pain severity, pain prevalence, and if reported the type of pain mechanism. The primary outcome was the prevalence of pain in cancer survivors at least three months after completing curative treatment.

Quality appraisal

Included studies were evaluated for their methodological quality using the critical appraisal tool for prevalence studies developed by the Joanna Briggs Institute (JBI).[22] Before quality appraisal, both reviewers (VH and MEv) calibrated the individual criteria for the appraisal tool. The reviewers independently appraised the methodological quality of each study. A third reviewer (ADG) was involved when disagreements were not resolved through consensus. Each item was given a score of 0 (yes/unclear) or 1 (no), and scores were summarized across all items to produce an overall score of quality. The overall score ranges from 0 or low risk of bias to 9 or high risk of bias. Whereas the JBI tool does not provide categories on risk of bias, the similar critical appraisal tool by Hoy et al. does provide categories on the overall score: 7–9: 'high risk of bias', 4–6: 'moderate risk of bias' and 0–3: 'low risk of bias'.[23]

Data synthesis

Before performing the meta-analysis, statistical heterogeneity was evaluated using between-study variance, τ^2, I^2, and Q statistics. In addition, heterogeneity was

assessed through visual inspection of forest plots.[24] When the studies presented with low statistical heterogeneity, then data were pooled using a fixed-effects model. A random-effects model was adopted when studies had moderate or high statistical heterogeneity.[24] The Freeman-Tukey double arcsine transformation was used in an effort to normalize the distribution of the proportions and to stabilize the variance.[25] To compute the pooled estimate of the transformed values, the DerSimonian and Laird method was used.[26] Small-study effects were explored by visual assessment of asymmetry of the funnel plots and calculation of the Egger's test.[24] If a study reported multiple pain prevalence rates on one or several follow-up occasions, the highest reported prevalence rate was used.[27]

Four univariate meta-regression analyses were performed to examine potential causes of heterogeneity: cancer type (breast, lung, gynecological, rectal, and prostate), cancer treatment location (localized vs. localized and systemic), pain measurement method (pain-specific, non-pain-specific, NRS/Visual Analogue Scale (VAS), study specific, not specified, and a combination of questionnaires), and follow-up time after the last treatment modality (in months:3, 6, 12, 24, 36, 48, 60+). Analysis was performed with R statistical software version 3.6.2., using the metafor package.[28,29]

A narrative description of the results was performed if the included studies differed significantly in design, settings, and outcome measures, or if insufficient data were presented. In addition, the available information on pain characteristics (severity and different pain mechanisms) and assessment methods for pain were discussed narratively.

Results

Search results

A total of 7,300 articles were retrieved, with 1.740 eligible for full-text review. The search results and screening process are shown in Figure 1. *Thirty-eight* articles were included in the analysis.

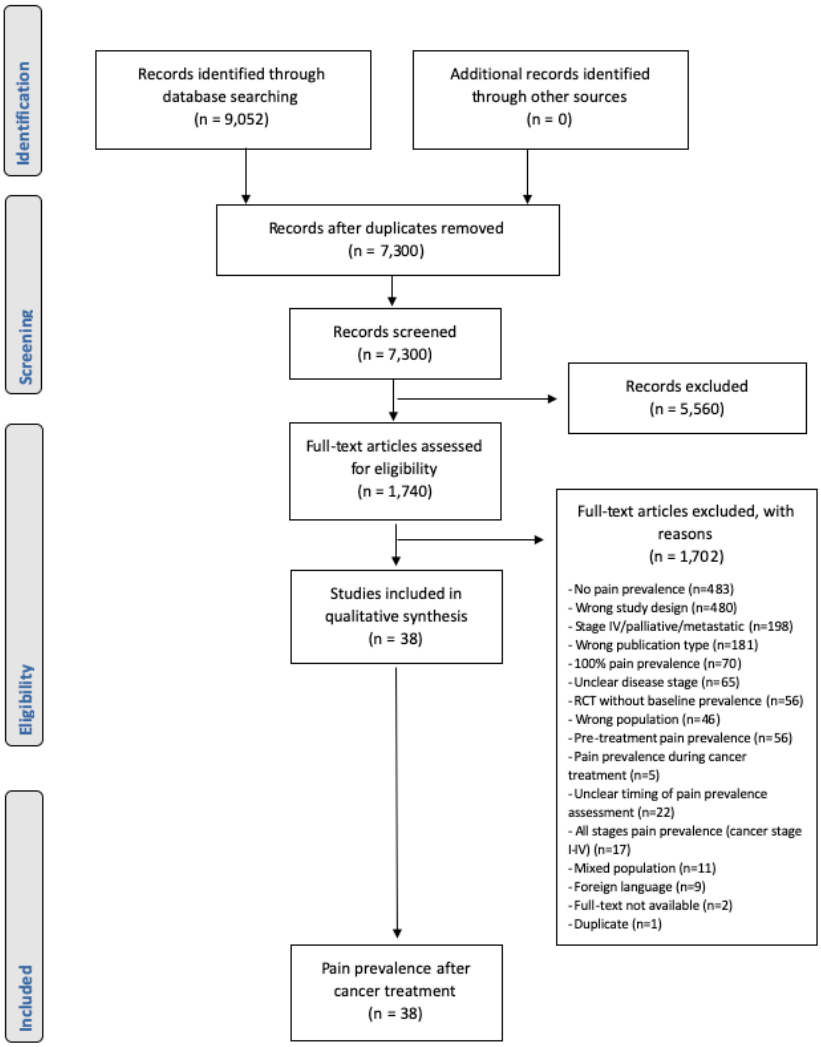

Figure 1. Flow chart

Study characteristics

A total of 14,394 participants were included for this systematic review. The prevalence of pain in the included studies ranged from 2% to 88.2%, with a median pain prevalence of 50.3%. The median sample size was 186.5 (range 31 - 2,923), the median age was 59.4 (range 46.3 - 71). Follow-up periods ranged from three months to more than ten years after last cancer treatment modality. The majority of studies (94.8%) were performed in high income countries using a cross-sectional [30–47] or cohort study design [48–66] (Appendix 3).[67] Studies examining pain prevalence in breast cancer survivors were most prevalent (n=30, 80.9%, 11,996 participants).[30–34,36,37,39,40,42,43,45–47,49,50,53–64,66,68] As a result, 84.2% of studies included solely female participant. Other populations consisted of lung cancer (n=3)[41,52,65], gynecological cancer (n=3)[38,48,51], rectal cancer (n=1)[44] and prostate cancer (n=1)[35] (Appendix 3). Five studies [37,41,43,48,65] included solely one type of cancer stage (stage 0: n=1; stage I: n=3, stage III: n =1). Six studies included only survivors of stages I-II cancer [38,49,53,59,60,63]. All other studies (n=27) included multiple cancer stages, ranging from 0 to III. All studies used a questionnaire to assess pain, with the Brief Pain Inventory (BPI) being the most utilized (23.7%).[31,33,41,42,47,52,60,64,65] Different pain definitions and criteria for assessing pain were utilized in all included studies (see Appendix 3 for further information). Six studies [41,44,47,52,62,66] did not specify which type of pain was researched (e.g., arthralgia, arm pain, and shoulder pain). Twenty-two studies [31–33,37,39,40,43,44,46,47,49–52,54–56,59,63,64,66,68] reported pain severity (Appendix 3). Seven cohort studies [48,52,53,55,57,62,65] have reported pain prevalence rates on multiple follow-up occasions. A detailed overview of all included studies is provided in Appendix 3.

Risk of bias

Among the 38 included studies, 12 studies [31,36,37,41,44,47,48,50,53,56,57,66] showed a moderate risk of bias on the adapted scale by Hoy et al.[23] The remaining 26 studies had low risk of bias. Figure 2 shows the risk of bias assessment of the included studies. See Appendix 2 for an overview of the criteria used to assess the risk of bias. Seven studies [36,37,41,44,45,65,66] did not include an appropriate sample frame. No study

has used random probabilistic sampling as a recruitment method. Only two studies [45,59] provided a sample size calculation or explanation of the obtained sample size. Five studies [30,38,52,54,65] provided a detailed description of the participants (i.e., age, disease stage, and comorbidities). The authors decided to mark all included studies as unclear whether data analyses were conducted with sufficient coverage of the identified sample. Seven studies were either unclear [30,31,34,45,46] or did not use valid methods [48,57] for the measurement of pain. Three studies [30,31,55] were unclear as to whether the measurement was performed in a standardized and reliable manner. All the included studies performed an appropriate statistical analysis. Seven studies [30,31,47,48,50,53,56] did not have an adequate response rate or managed it appropriately.

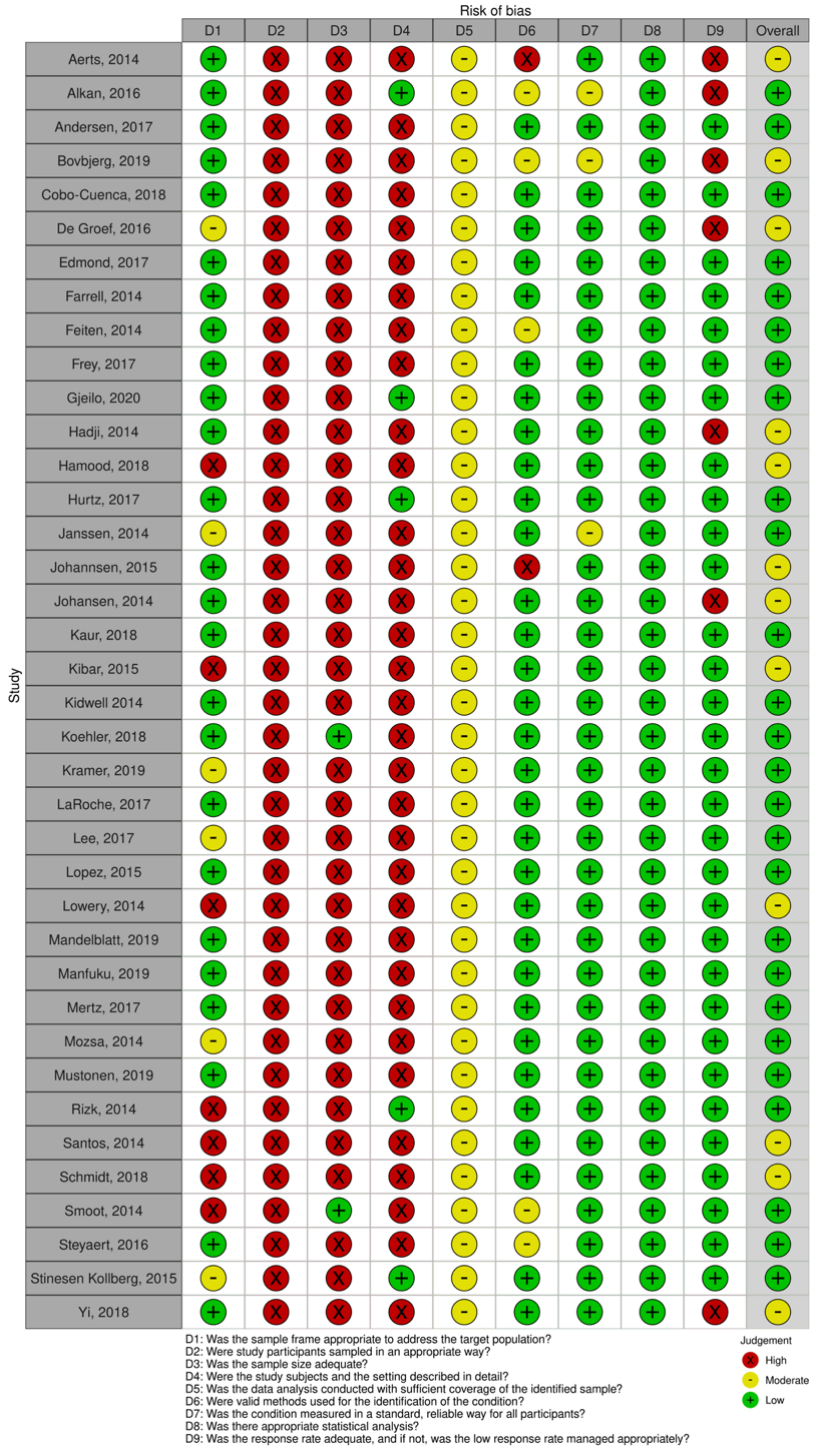

Figure 2. Risk of bias assessment

Prevalence of pain after cancer treatment

Using the highest reported pain prevalence rates, our meta-analysis resulted in a pooled pain prevalence of 47% (95% CI 39 - 55%) with a heterogeneity of (I^2=98.99%) (Figure 3). Pain prevalence rates per population are shown in Figure 3.

The meta-regression analyses for the variable cancer type, treatment location, pain measurement and follow-up time showed no significant influence (p = 0.6209, p = 0.8999, p = 0.3305 and p = 0.8823 respectively) on the high amount of heterogeneity (I^2=98.99%) (Table 2).

Table 2. Meta-regression outcome. NRS/VAS=Numeric Rating Scale/Visual Analogue Scale

Covariate	**ß (95% CI)**	***P-value***	***R^2***
Cancer type		0.5267	
Breast (n = 30)	0.7710 (0.6912 - 0.8508)	< 0.0001	
Gynecological (n = 3)	0.0381 (-0.2324 - 0.3087)	0.7824	0%
Lung (n = 3)	-0.0911 (-0.3548 - 0.1726)	0.4985	
Prostate (n = 1)	-0.3689 (-0.8158 - 0.0780)	0.1057	
Rectal (n = 1)	0.0388 (-0.4245 - 0.5021)	0.8696	
Treatment strategy		0.6503	
Localized	0.7151 (0.5168 - 0.9134)	< 0.0001	0%
Localized and systemic	0.0491 (-0.1633 - 0.2616)	0.6503	
Pain measurement		0.5437	
Combination	0.7175 (0.5350 - 0.9001)	<0.0001	
Not specified	0.0631 (-0.2472 - 0.3734)	0.6903	
Not-pain specific	-0.0408 (-0.2631 - 0.1815)	0.7193	0%
NRS/VAS	0.0819 (-0.1884 - 0.3521)	0.5526	
Pain specific	0.0951 (-0.1347 - 0.3248	0.4173	
Study specific	0.2320 (-0.1257 - 0.5896)	0.2036	
Follow-up time		0.7153	
>3 months	0.6931 (0.4934 - 0.8928)	< 0.0001	
>6 months	0.1446 (-0.1168 - 0.4059)	0.2783	
>12 months	0.0985 (-0.1651 - 0.3620)	0.4640	0%
>24 months	-0.0196 (-0.2646 - 0.3039)	0.8924	
>36 months	0.1570(-0.1242 -0.4381)	0.2738	
>48 months	-0.0435 (-0.3254 - 0.2385)	0.7626	
>60 months	-0.0216 (-0.2789 - 0.3222)	0.8878	

NRS= Numeric rating scale, VAS= Visual analogue scale

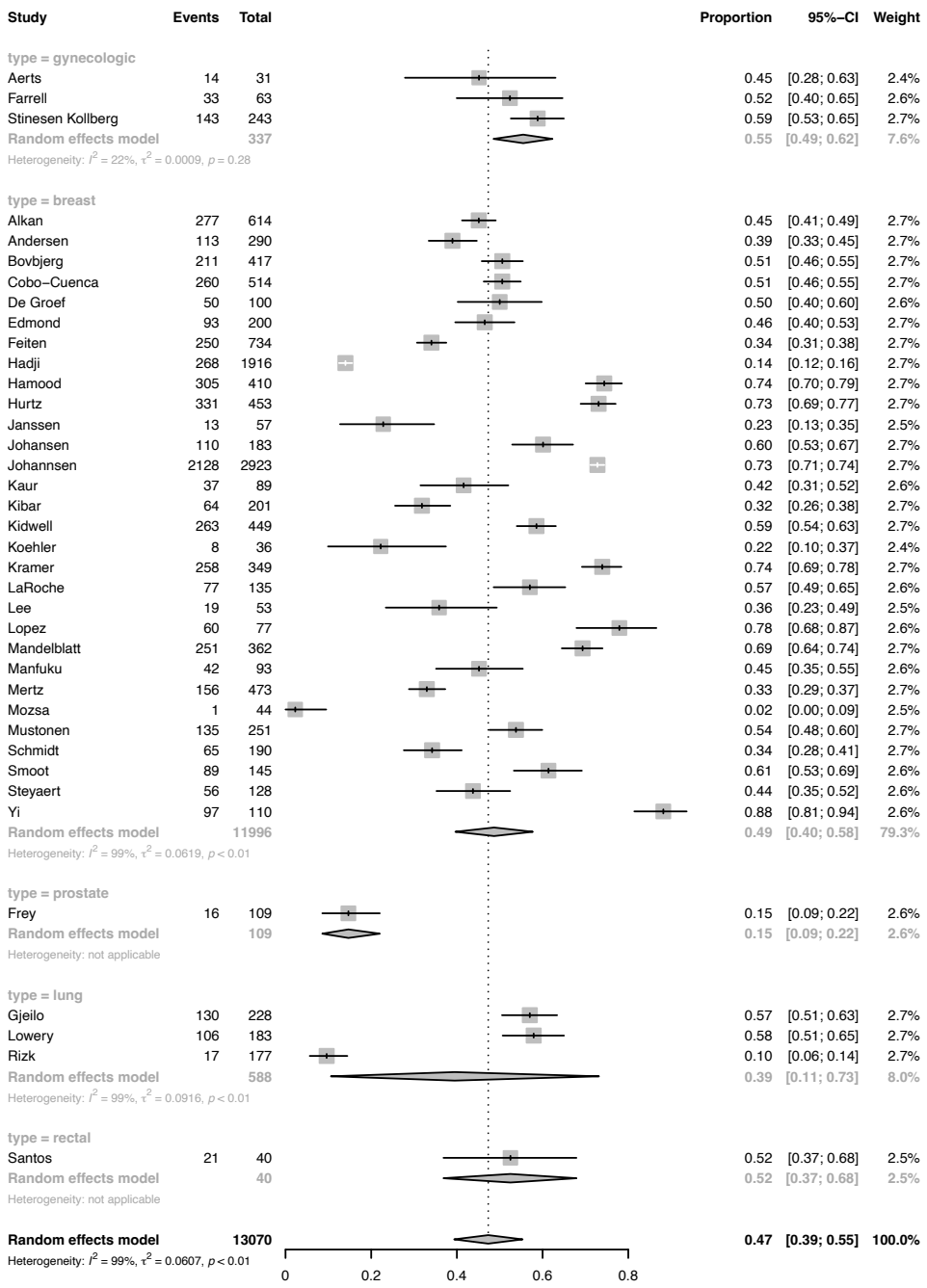

Figure 3. Forest plot of the highest reported pain prevalence rates, subgrouped by cancer type.

Pain characteristics and measurements

Different **types of pain** were used to summarize or assess pain symptoms. In breast cancer survivors the most used and best-defined pain types were *shoulder pain* (n=2), *arthralgia* (n=4) and *arm-shoulder pain* (n=3). [39,40,53,56–60] *Post-mastectomy pain syndrome* or *breast pain* was used by seven studies but each study termed it differently (e.g. *post-mastectomy pain syndrome, chronic postmastectomy pain, persistent breast pain*).[30,31,33,43,46,49,68] Six studies did not specify which type of pain the authors assessed, or failed to describe it.[41,44,47,52,62,66]

Regarding the assessment of **pain mechanisms** (*nociceptive, neuropathic, nociplastic or mixed pain*), only three studies assessed for neuropathic pain using the Douleur Neuropathique en 4 Questions (DN4), the Neuropathic Pain Symptom Inventory (NPSI) and ID Pain Questionnaire.[46,60,68] Mustonen and colleagues assessed neuropathic pain clinically in breast cancer survivors through a subjective examination and a somatosensory testing protocol as proposed by Finnerup et al.[64,69] Andersen et al. also assessed sensory dysfunction using quantitative sensory testing in breast cancer survivors but ascribing neuropathic pain was not in the scope of their study.[49] No other studies have utilized different pain mechanisms as a descriptors for pain assessment.

Although all studies used questionnaires to assess pain, numerous types of pain measurement tools have been used. The most frequently used questionnaires were the BPI (n=9)[31,33,41,42,47,52,60,64,65] VAS (n=8)[37,40,44,50,59–61,68], followed by the pain subscale of the European Organization for Research and Treatment for Cancer Quality of Life Questionnaire (EORTC-QLQ-C30) (n=3)[43,44,66] (Appendix 3). Three studies did not specify which type of questionnaire they used [30,34,62], and two studies used a self-developed study specific questionnaire to assess pain [38,57]. Six studies used a combination of different questionnaires which most of the time consisted of a VAS in combination with a general health or disability questionnaire [37,44–46,59].

Sixteen studies did not report pain severity, or merely reported the presence of pain without quantifying its severity.[30,34–36,38,41,42,45,48,53,57,60,62,65] The remaining 22 studies reported the average pain, pain severity ranging from mild to severe pain, or moderate to severe pain.[30,34–36,38,41,42,45,48,53,57,58,60–62,65] Mild pain is pain defined as 1-4 on the NRS from 0 to 10, whereas moderate pain ranges from 5-6 on the NRS and severe pain ranges from 7 to 10 on the NRS.[9]

Discussion

Main findings

This systematic review aimed to summarize the prevalence rates of pain after curative treatment for different solid cancer types. If available, the prevalence rates of different pain mechanisms, pain characteristics, and assessment methods for pain were presented. Based on a meta-analysis, **47%** (95% CI 39 - 55%) of cancer survivors experience pain after completing cancer treatment. The meta-analysis showed high heterogeneity (I^2=98.99%) among the included studies, and none of the selected covariates seemed to have a significant influence on the heterogeneity of the meta-analysis.

Looking at the different cancer types separately, we could conclude that pain was present in 49% (95% CI 40 - 58%) of breast cancer survivors, 39% (95% CI 11 - 73%) of lung cancer survivors, and 55% (95% CI 49 - 62%) of gynecological cancer survivors. Due to the lack of studies, we were not able to draw conclusions on the presence of pain in survivors of rectal and prostate cancer. We hypothesized that different cancer types would present with different prevalence rates of pain. However, breast and lung cancer survivors seem to have similar rates of pain, whereas survivors of gynecological cancer tend to show higher pain prevalence rates. This comparison needs to be viewed with caution since only three studies on gynecological cancer were included in our review.[38,48,51]

In this review, we also aimed to present the prevalence rates of different pain mechanisms. Unfortunately, only three studies explicitly assessed neuropathic pain

whereas the other included studies did not mention any of the different pain mechanisms described by the IASP.[46,60,68]There is a lack of studies investigating the presence of these pain mechanisms in cancer survivors. Our narrative description concluded that in cancer studies, different types of pain assessment methods are used together with different types and definitions of pain. Due to the lack of studies and heterogeneous pain assessment methods and pain definitions, we were not able to draw conclusions from our narrative description.

This review adds to the growing body of evidence on the presence of pain after curative cancer treatment. Clinicians should routinely screen for pain during follow-up visits to improve pain management and QoL after cancer treatment. We would recommend that future studies either use proposed guidelines [17] and/or other simple, validated, and recommended questionnaires to assess pain in cancer survivors.[70] Further research is urgently required to examine the prevalence of different pain mechanisms in cancer survivors and to investigate more effective interventions for pain after cancer treatment.

Risk of bias

Examining the general risk of bias assessment, we noticed that most studies had difficulties in providing proper sampling of participants, sample size calculation, or description of the subjects. In addition, we chose to mark all studies as unclear for the question “Was the data analysis conducted with sufficient coverage of the identified sample?”. Assessing coverage bias was complicated due to the lack of information in most studies; therefore, we marked all studies as unclear. Although only 31.5% of the included studies had a moderate risk of bias, future studies on prevalence need to consider these biases.

Strengths and limitations

The first strength of this review is that the authors used the JBI manual for systematic reviews of prevalence and incidence.[71] Two other strengths of this review are the clear-cut eligibility criteria and a quality appraisal of the included studies with an

endorsed and frequently used quality appraisal tool.[72] Another strength is the meta-analysis used to estimate the prevalence of pain after curative cancer treatment: a Freeman-Tukey double arcsine transformation was performed to approximate a normal distribution and to stabilize the variance[25]. Most of the studies included in our review showed either a low or moderate risk of bias (Figure 2). Finally, we screened articles written in English, French, German, and Dutch, thus limiting language bias.

This study has some limitations. Several studies were excluded when the data were unclear or missing, or when the authors did not respond to our questions (Figure 1). Cancer survivors had to have completed treatment for at least three months which creates a selection bias. Cancer survivors who had completed treatment for less than three months were excluded. Concurrently, we did not include patients with cancer in an advanced or palliative stage, with metastases, or undergoing non-curative treatment. We were not able to control the coverage bias of the included studies, as defining a sufficient coverage proportion for the different types of solid cancers was not feasible. For the assessment of pain, we only noted the questionnaires utilized, as this was the most common practice in the studies. However, some studies used clinical examinations such as somatosensory testing to evaluate pain, which we did not include in our data extraction and review. Most of the included studies conducted their research in high-income countries; therefore, generalizability is limited to these types of countries. Furthermore, it is known that persistent pain prevalence rates continue to increase worldwide and that 19% of adult Europeans suffer from chronic non-cancer related pain.[73,74] It is not known whether the cancer survivors included in our review were already suffering from non-cancer-related pain (e.g., low back pain), and whether studies made a distinction between the assessment of cancer-related pain and non-cancer-related pain. Therefore, by not making this distinction, pain prevalence rates could be overstated. Six studies, reporting an average of 59.8% pain prevalence rate altogether, failed to specify which type of pain they assessed, therefore scrutiny of these prevalence rates is

warranted.[41,44,47,52,62,66] Regarding the severity of pain, 17 studies did not report this.[30,34–36,38,41,42,45,48,53,57,58,60–62,65] It is therefore difficult to conclude if patients had clinically significant pain, defined as 30/100 on a VAS.[33,68,75] If patients scored less than 30/100 and were classified as having pain, this could have overestimated the pain prevalence rates.

Breast cancer was overly represented (12 to 1 ratio) in this systematic review, which affects the pooled prevalence and limits generalizability towards other solid cancers. Not all solid cancer types were included in this review, again limiting generalizability (e.g., head and neck and gastrointestinal cancers). Finally, we did not include gray or unpublished articles in our systematic search. This could exclude more recent findings and/or negative or inconclusive data.

Conclusion

Evidence with a low risk of bias suggests that 47% of cancer survivors who finished curative treatment at least three months ago experience pain. No conclusions could be drawn regarding the influence of cancer type, treatment strategy, pain measurement, or follow-up time on this pain prevalence rate. In addition, we could not provide information on the prevalence of the different types of pain mechanisms in cancer survivors. These results must be carefully weighed because a high amount of unexplained heterogeneity is present. Generalizability towards other solid cancer types is limited due to the disproportionate inclusion of breast cancer studies. Further research is necessary to explore pain prevalence rates, the presence of different pain mechanisms, and pain severity not only in breast cancer but also in other types of cancer.

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Appendices

Appendix 1

A1.1 Eligibility criteria.

Table A1.1. Eligibility criteria

Inclusion criteria	Exclusion criteria
Original studies	Conference proceedings, editorials and letters, reviews, case studies, congress reports and secondary analyses.
Studies set in primary care or the general population	Studies focusing on breakthrough cancer pain
Studies published between 2014 and 2020	Studies reporting on pain without differentiating between patients with and without cancer
Studies where prevalence data on cancer pain can be extracted or calculated	Studies about pain in childhood cancer
Adult study population (mean age greater than 18 years)	Studies performed at pain clinics including only patients with pain
Studies published in English, Dutch, French or German	

A1.2 Search strategy

Table A1.2.1. Keywords included in the search strategy for all four databases

Pain term	pain
	AND
Study type term	epidemiology **OR** prevalence
	AND
Patient term	Cancer **OR** neoplasm **OR** neoplastic **OR** tumor **OR** tumour **OR** tumoral **OR** tumoural **OR** tumourous **OR** tumorous **OR** metastatic **OR** metastasis **OR** oncology **OR** oncological **OR** oncologic

Table A1.2.2. Database specific subject heading terms

	Medline – MeSH Headings
Pain term	Pain
Study type term	prevalence epidemiology
Patient term	neoplasms neoplasm metastasis

A1.3 Database specific search strategies

Table A1.3.1. Pubmed – limit to human; adult; Dutch, English, French, German; 2014–current

Pain term	Keywords searched for in all fields	"Pain"
		OR
	MeSH headings	"Pain"
		AND
Study type term	Keywords searched for in all fields	"epidemiolog*" OR "prevalence"
		OR
	MeSH headings	"prevalence" OR "epidemiology"
		AND
Disease term	Keywords searched for in all fields	"cancer" OR cancer s" OR "cancerated" OR "canceration" OR "cancerization" OR "cancerized" OR "cancerous" OR "cancers" **OR** "neoplasm" OR "neoplasm s" OR "neoplasms" OR "neoplastic" **OR** "tumor" OR "tumor s" OR "tumors" OR "tumour" OR "tumour s" OR "tumours" OR "tumoral" OR "tumoural" OR "tumorous" OR "tumourous" **OR** "oncology" OR "oncology s" OR "oncologic" OR "oncologically" OR "oncological" OR "oncologics" **OR** "metastasi" OR "metastasis" OR "metastatically" OR "metastatics" OR "metastatic" OR "neoplasm metastasis" **OR**
	MeSH headings	"neoplasms" OR "neoplasm metastasis"

Table A1.3.2. Scopus – limit to human; adult; Dutch, English, French, German; 2014–current; excluded: Medline

Pain term	Keywords searched for in title, abstract and keywords	"Pain"
		AND
Study type term	Keywords searched for in title, abstract and keywords	"epidemiology" OR "epidemiological" OR "prevalence"
		AND
Disease term	Keywords searched for in title, abstract and keywords	"cancer" OR "cancerated" OR "canceration" OR "cancerization" OR "cancerized" OR "cancerous" OR "cancers" **OR** "neoplasm" OR "neoplasms" OR "neoplastic" **OR** "tumor" OR "tumors" OR "tumour" OR "tumours" OR "tumoral" OR "tumoural" OR "tumorous" OR "tumourous" **OR** "oncology" OR "oncologic" OR "oncologically" OR "oncological" OR "oncologics" **OR** "metastasi" OR "metastasis" OR "metastatically" OR "metastatics" OR "metastatic" OR "neoplasm metastasis"

Table A1.3.3. Web of Science – limit to human, English, French, German; 2014–current; document type: articles

Pain term	Keywords searched for in title, abstract and keywords	"Pain"
		AND
Study type term	Keywords searched for in title, abstract and keywords	"epidemiology" OR "epidemiological" OR "prevalence"
		AND
Disease term	Keywords searched for in title, abstract and keywords	"cancer" OR "cancerated" OR "canceration" OR "cancerization" OR "cancerized" OR "cancerous" OR "cancers" **OR** "neoplasm" OR "neoplasms" OR "neoplastic" **OR** "tumor" OR "tumors" OR "tumour" OR "tumours" OR "tumoral" OR "tumoural" OR "tumorous" OR "tumourous" **OR** "oncology" OR "oncologic" OR "oncologically" OR "oncological" OR "oncologics" **OR** "metastasi" OR "metastasis" OR "metastatically" OR "metastatics" OR "metastatic" OR "neoplasm metastasis"

Table A1.3.4. Embase – limit to human; adult; Dutch, English, French, German; 2014–current; Embase database

Pain term	Keywords searched for in title, abstract and keywords	"Pain"
		AND
Study type term	Keywords searched for in title, abstract and keywords	"epidemiology" OR "epidemiological" OR "prevalence"
		AND
Disease term	Keywords searched for in title, abstract and keywords	"cancer" OR "cancerated" OR "canceration" OR "cancerization" OR "cancerized" OR "cancerous" OR "cancers" **OR** "neoplasm" OR "neoplasms" OR "neoplastic" **OR** "tumor" OR "tumors" OR "tumour" OR "tumours" OR "tumoral" OR "tumoural" OR "tumorous" OR "tumourous" **OR** "oncology" OR "oncologic" OR "oncologically" OR "oncological" OR "oncologics" **OR** "metastasi" OR "metastasis" OR "metastatically" OR "metastatics" OR "metastatic" OR "neoplasm metastasis"

Table A1.3.5. Cochrane Trials – limit to English, French, German; 2014–current

Pain term	Keywords searched for in title, abstract and keywords	"Pain"
		AND
Study type term	Keywords searched for in title, abstract and keywords	"epidemiology" OR "epidemiological" OR "prevalence"
		AND
Disease term	Keywords searched for in title, abstract and keywords	"cancer" OR "cancerated" OR "canceration" OR "cancerization" OR "cancerized" OR "cancerous" OR "cancers" **OR** "neoplasm" OR "neoplasms" OR "neoplastic" **OR** "tumor" OR "tumors" OR "tumour" OR "tumours" OR "tumoral" OR "tumoural" OR "tumorous" OR "tumourous" **OR** "oncology" OR "oncologic" OR "oncologically" OR "oncological" OR "oncologics" **OR** "metastasi" OR "metastasis" OR "metastatically" OR "metastatics" OR "metastatic" OR "neoplasm metastasis"

A1.5 Full search strategy performed on 17 April 2020

A1.5.1 PUBMED

(("pain"[MeSH Terms] OR "pain"[All Fields]) AND (("epidemiology"[MeSH Subheading] OR "epidemiolog*"[All Fields]) OR "prevalence"[All Fields]) OR "prevalence"[MeSH Terms]) AND (((((((("cancer s"[All Fields] OR "cancerated"[All Fields]) OR "canceration"[All Fields]) OR "cancerization"[All Fields]) OR "cancerized"[All Fields]) OR "cancerous"[All Fields]) OR "cancer"[All Fields]) OR "cancers"[All Fields]) OR (((((("neoplasm s"[All Fields]) OR "neoplasms"[MeSH Terms]) OR "neoplasms"[All Fields]) OR "neoplasm"[All Fields]) OR "neoplastic"[All Fields]) OR ((((((((("tumor s"[All Fields]) OR "tumoral"[All Fields]) OR "tumorous"[All Fields]) OR "tumour"[All Fields]) OR "tumor"[All Fields]) OR "tumour s"[All Fields]) OR "tumoural"[All Fields]) OR "tumourous"[All Fields]) OR "tumours"[All Fields]) OR "tumors"[All Fields]) OR (((((("oncology"[All Fields] OR "oncology s"[All Fields]) "oncologic"[All Fields]) OR "oncological"[All Fields]) OR "oncologically"[All Fields]) OR "oncologics"[All Fields]) OR ((((((("metastasi"[All Fields] OR "neoplasm metastasis"[MeSH Terms]) OR "metastasis"[All Fields]) OR "neoplasm metastasis"[All Fields]) OR "metastatically"[All Fields]) OR "metastatics"[All Fields]) OR "metastatic"[All Fields])))

+ FILTER: Human, Adult (19+), English, Dutch, French, German

+ YEAR: 2014-2020

A1.5.2 SCOPUS

(TITLE-ABS-KEY (pain) AND TITLE-ABS-KEY (epidemiology OR epidemiolog OR prevalence OR epidemiological) AND TITLE-ABS-KEY ("cancer" OR "cancerated" OR "canceration" OR "cancerization" OR "cancerized" OR "cancerous" OR "cancers" OR "neoplasm" OR "neoplasms" OR "neoplastic" OR "tumor" OR "tumors" OR "tumour" OR "tumours" OR "tumoral" OR "tumoural" OR "tumorous" OR "tumourous") OR TITLE-ABS-KEY ("oncology" OR "oncologic" OR "oncologically" OR "oncological" OR "oncologics") OR TITLE-ABS-KEY ("metastasi" OR "metastasis" OR “metastases” OR "metastatically" OR "metastatics" OR "metastatic" OR "neoplasm metastasis")) AND PUBYEAR > 2013 AND NOT INDEX (medline) AND (LIMIT-TO (LANGUAGE , "English") OR LIMIT-TO (LANGUAGE , "French") OR LIMIT-TO (LANGUAGE , "German"))

A1.5.3 WEB OF KNOWLEDGE

TS=(pain AND (epidemiology OR epidemiolog OR epidemiological OR prevalence) AND ("cancer” OR “cancerated” OR “canceration” OR “cancerization” OR “cancerized” OR “cancerous” OR “cancers” OR “neoplasm” OR “neoplasms” OR “neoplastic” OR “tumor” OR “tumors” OR “tumour” OR “tumours” OR “tumoral” OR “tumoural” OR “tumorous” OR “tumourous” OR “oncology” OR “oncologic” OR “oncologically” OR “oncological” OR “oncologics” OR “metastasi” OR “metastasis” OR “metastases” OR “metastatically” OR “metastatics” OR “metastatic” OR “neoplasm metastasis”)) NOT TS=(animal* AND model* OR mouse OR mice)

Timespan: 2014-2020.

+ FILTER: Articles

+ Languages: English, French, German

A1.5.4 EMBASE

pain:ab,ti,kw AND (epidemiology:ab,ti,kw OR epidemiolog:ab,ti,kw OR epidemiological:ab,ti,kw OR prevalence:ab,ti,kw) AND ('cancer':ab,ti,kw OR 'cancerated':ab,ti,kw OR 'canceration':ab,ti,kw OR 'cancerization':ab,ti,kw OR 'cancerized':ab,ti,kw OR 'cancerous':ab,ti,kw OR 'cancers':ab,ti,kw OR 'neoplasm':ab,ti,kw OR 'neoplasms':ab,ti,kw OR 'neoplastic':ab,ti,kw OR

'tumor':ab,ti,kw OR 'tumors':ab,ti,kw OR 'tumour':ab,ti,kw OR 'tumours':ab,ti,kw OR 'tumoral':ab,ti,kw OR 'tumoural':ab,ti,kw OR 'tumorous':ab,ti,kw OR 'tumourous':ab,ti,kw OR 'oncology':ab,ti,kw OR 'oncologic':ab,ti,kw OR 'oncologically':ab,ti,kw OR 'oncological':ab,ti,kw OR 'oncologics':ab,ti,kw OR 'metastasi':ab,ti,kw OR 'metastasis':ab,ti,kw OR 'metastases':ab,ti,kw OR 'metastatically':ab,ti,kw OR 'metastatics':ab,ti,kw OR 'metastatic':ab,ti,kw OR 'neoplasm metastasis':ab,ti,kw) AND [2014-2020]/py AND [embase]/lim AND ([dutch]/lim OR [english]/lim OR [french]/lim OR [german]/lim) AND [adult]/lim AND [humans]/lim

A1.5.5 COCHRANE TRIALS

(pain AND (prevalence OR epidemiolog OR epidemiology OR epidemiological) AND (cancer OR cancers OR tumor OR tumors OR tumour OR tumours OR tumoral OR tumoural OR tumourous OR tumorous OR neoplasm OR neoplasms OR neoplastic OR metastasis OR metastases OR metastatic OR metastatic OR oncological OR oncology OR oncologic OR oncologics))

with Publication Year from 2014 to 2020, with Cochrane Library publication date from Jan 2014 to May 2020, in Trials (Word variations have been searched)

#2 "accession number" near pubmed

#3 "accession number" near embase

#4: #1 NOT (#2 OR #3)

Appendix 2

D1: Was the sample frame appropriate to address the target population?	
Yes	Age and disease stage following the eligibility criteria
No	Age and disease stage not following the eligibility criteria
Unclear	Age and disease stage not reported
D2: Were study participants sampled in an appropriate way?	
Yes	Random probabilistic sampling
No	No random probabilistic sampling or not reported
D3: Was the sample size adequate?	
Yes	Sample size calculation reported
No	No sample size calculation reported or less than 80% of power with the current amount of participants included
D4: Were the study subjects and the setting described in detail?	
Yes	Age, disease stage and morbidities reported
No	Age, disease stage and morbidities not reported
D5: Was the data analysis conducted with sufficient coverage of the identified sample?	
Yes	Certain age range, disease stage and morbidities equal represented
No	Certain age range, disease stage and morbidities equal represented
Unclear	Response rates for the three primary characteristics not reported
D6: Were valid methods used for the identification of the condition?	
Yes	Validated questionnaires for measuring pain within a cancer population
No	Questionnaires not validated for measuring pain or for measuring pain within a cancer population
Unclear	Unclear if questionnaire is also validated for measuring pain within a cancer population
D7: Was the condition measured in a standard, reliable way for all participants?	
Yes	Measurements conducted in the same way by all the participants
No	Measurements not conducted in the same way by all the participants
Unclear	Unclear if measurements were conducted in the same way / not reported
D8: Was there appropriate statistical analysis?	
Yes	Statistical analysis reported
No	No statistical analysis reported
D9: Was the response rate adequate? If not, was the low response rate managed appropriately?	
Yes	Response rate higher than 80% or reported reasons for drop-out
No	Response rate lower than 80% and reason of drop-out not reported

Appendix 3

First Author, Year Study design	Continent	Sex	Mean age (±SD) [range]	Sample size (n)	Type of cancer	Cancer stage
Aerts, 2014 Prospective cohort study	Europe	F	46.81 (±10.34) [29 - 73]	31	Cervical cancer	Stage IA: 9.7% Stage IB: 90.3%
Alkan, 2016 Cross-sectional	Asia	F	54.4 (±10.1)	614	Breast cancer	Stage I: 21.7% Stage II: 56.6% Stage III: 21.5%
Andersen, 2017 Prospective cohort study	Europe	F	60 [50 - 67]	290	Breast cancer	Stage I-II
Bovbjerg, 2019 Cross-sectional	North America	F	59.4 (± 11.2)	417	Breast cancer	Stage I 61.9% Stage II 25.7% Stage III 11.8%

	Cancer treatment	Pain measurement	Pain measurement timing	Pain prevalence	Pain definition	Pain severity (low, moderate, severe)
	Abdominal radical hysterectomy 47.3% Laparoscopic radical hysterectomy 51.6%	The Short Sexual Functioning Scale (SSFS) - entry dyspareunia (ED) - deep dyspareunia (DP) - abdominal coital pain (ACP)	6, 12 and 24 months after surgery	6 / 12 / 24 months: - ED: 26% / 44% / 33% - DP: 13% / 22% / 33% - ACP: 6% / 0% / 33%	Entry dyspareunia, deep dyspareunia, abdominal pain during intercourse	Not reported
	65.2% ME 34.8% LE RT 2.8% CT 23.6% CRT 64.8% HT 9%	Interview and questionnaires Not specified	Minimum 6 months of interval after operation	PMPS 45.1%	PMPS = post mastectomy pain syndrome	Not reported
	ME 70% LE 30% SLNB 66% ALND 34% RT 81% CT 53% HT 81% Trastuzumab 10%	Questionnaire: NRS Quantitative Sensory Testing (QST)	1 year after surgery	39% new or worse pain 13% moderate-severe pain at rest 8% moderate-severe pain during movement	PPBCS was defined as an increase of 1 NRS in any of the 4 predefined anatomical locations from the preoperative questionnaire to the 12-month questionnaire.	See Pain prevalence
	LE 100% RT 93.8% CT 44.1% HT 78.2%	Questionnaire: BPI	First surveillance mammography examination at 6–15 months - 10.3 (±1.9) months post-surgery	Persistent breast pain 50.6% Clinically significant breast pain 21.8% Clinically significant PBP 17.3%	Significant Pain ≥ 3 Duration ≥ 6 months	Not reported

Appendix 3. Continued

First Author, Year Study design	Continent	Sex	Mean age (±SD) [range]	Sample size (n)	Type of cancer	Cancer stage
Cobo-Cuenca, 2018 Cross-sectional	Europe	F	46.34 (±8.28) [21 - 66]	514	Breast cancer	Stage I-III
De Groef, 2016 Cohort	Europe	F	60.5 (± 9.7)	100	Breast cancer	DCIS: 6% Stage I 68% Stage II 24% Stage III 2%
Edmond, 2017 Cross-sectional	North America	F	59.29 (± 11.56)	200	Breast cancer	Stage I 56.3% Stage II 27.4% Stage III 16.3%
Farrell, 2014 Cohort	Oceania	F	63 [31 - 89]	63	Gynecological cancer (squamous cell carcinoma of the vulva)	Stage IB 45% Stage II 32% Stage III 23%
Feiten, 2014 Cross-sectional	Europe	F	65 [30 - 91]	734	Breast cancer	Stage I 46% Stage II 42% Stage III 12%

	Cancer treatment	Pain measurement	Pain measurement timing	Pain prevalence	Pain definition	Pain severity (low, moderate, severe)
	LE 37.9% ME 41.7% Bilateral ME 16.7% RT 2.3% CT 5.8% HT 4.9% RT+CT 12.2% RT+HT 8.8% CT+HT 12.5% RT+CT+HT 49.4%	Questionnaire: Questionnaire on Women's Sexual Function	4.05 ± 5.226 years since diagnosis	50.6%	Penetration pain	Penetration pain: - Severe: 9.7% - Moderate: 40.9% - No: 49.4%
	ME 41% LE 59% SLNB 100% RT 71% CT 28% HT 82%	Questionnaire: "Pain during past week? (y/n)" VAS	12 months after SLNB	50%	Pain at the upper limb	Classification not reported. Mean score VAS 20.9/100 (total group) Mean score VAS 43.7/100 for group with pain
	LE 100% SLNB 90% ALND 23% RT 94.8% CT 51.1% HT 79.0%	Questionnaire: BPI	6 to 15 months after breast cancer surgery: Average 10.12 (±2.25) months after surgery	46.5% breast pain 28.5% (clinically significant breast pain)	≥3 out of 10 = clinically significant breast pain 'Breast pain'	Classification not reported. Mean NRS: 1.63 (±1.73)/10
	Groin surgery: 45% unilateral; 55% bilateral RT 17%	Questionnaire: NRS	18 months or more after surgery (92%)	53%	'Leg pain'	Mild: 28% Moderate: 18% Severe 7%
	ME 22% LE 78% SLNB 55% ALND 43% RT 85% CT 49% HT 85%	Questionnaire Not specified	38 (±16) months after diagnosis	34%	'Operation site pain'	Not reported

Appendix 3. Continued

First Author, Year Study design	Continent	Sex	Mean age (±SD) [range]	Sample size (n)	Type of cancer	Cancer stage
Frey, 2017 Cross-sectional	Europe	M	71 [57 - 81]	109	Prostate cancer	Stage I: 20.1% Stage II: 36.7% Stage III: 29.4% Unknown: 13.8%
Gjeilo, 2020 Cohort	Europe	58% M / 42% F	65.8 (± 8.5) [30 - 87]	228	Lung cancer: - Adenocarcinoma: 56% - Squamous-cell carcinoma: 31%	Stage IA: 32.7% Stage IB: 29.9% Stage II: 18.4% Stage III: 16.8%
Hadji, 2013 Cohort	Europe	F	65 (± 8)	1916	Breast cancer	HR+ early breast cancer
Hamood, 2017 Cross-sectional	Asia	F	66.4 (± 13.4)	410	Breast cancer	Early-stage or regionally advanced invasive breast cancer

	Cancer treatment	Pain measurement	Pain measurement timing	Pain prevalence	Pain definition	Pain severity (low, moderate, severe)
	EBRT: 100% ADT: 81%	Questionnaire: Erection Hardness Scale (EHS)	Median time since final EBRT: 50 months (range = 4 - 71)	Orgasm-associated pain: 15% Painful erection 6%	Orgasm-associated pain Painful erection	Not reported
	Lobectomy 69% Bilobectomy 7% Pulmonectomy 9% Wedge resection 9% VATS 5%	Questionnaire: BPI	5 months, 9 months, and 12 months after surgery	56% at 5 months, 57% at 9 months, 55% at 12 months.	Not reported	5 months: 47.4% (no pain), 24.8% (mild), 19.6% (moderate), 8.2% (severe) 9 months: 44.4% (no pain), 29.3% (mild), 16.7% (moderate), 9.6% (severe) 12 months: 45% (no pain), 24.1% (mild), 24.6% (moderate), 6.3% (severe)
	Surgery 100% RT and/or CT. Specifics not reported.	Questionnaire: Rheumatoid Arthritis Symptom Questionnaire (RASQ)	3, 6, and 9 months (visits 1, 2, and 3) after start of anastrozole therapy	3 months: 14% 6 months: 11% 9 months: 9%	Arthralgia	Not reported
	LE 76% ME 23% RT 75,1% CT 100% HT 100%	Survey – questionnaire SF-36	8.64 (± 3,3) years after diagnosis	74.4%	Chronic pain	Not reported

Appendix 3. Continued

First Author, Year Study design	Continent	Sex	Mean age (±SD) [range]	Sample size (n)	Type of cancer	Cancer stage
Hurtz, 2017 Cohort	Europe	F	57.0 [30 - 79]	453	Breast cancer	Stage I: 26.0% Stage II: 44.4% Stage III: 15.7% Unknown: 13.9%
Janssen, 2014 Cohort	Europe	F	69.0 [45 - 92]	74-57-25 (1-2-4 years follow-up)	Breast cancer	DCIS 3% Stage I 56% Stage II 39% Stage III/IV 0%
Johansen, 2014 Cohort	Europe	F	55 [30 - 75]	183	Breast cancer	Stage II 62% Stage III 37%

	Cancer treatment	Pain measurement	Pain measurement timing	Pain prevalence	Pain definition	Pain severity (low, moderate, severe)
	Surgery 100%: - LE 66% - non-LE 28.7% - unknown 5.3% RT 78.1% CT: -12.8% neoadjuvant -87.2% adjuvant HT 62%	Survey – questionnaire MaTox questionnaire ('specifically developed based on a review of the literature and an expert survey on potential long-term impairments after breast cancer treatment.')	6 months, 18 months, and 3 years after start of systemic CT (after surgery, before RT)	73% muscle pain 67% pain at the operated site	'pain in arm/shoulder /chest wall' 'muscle pain' 'joint pain'	Reported in Figure 3
	LE 100% CT 24% (before RT) RT: 100%	Common Terminology Criteria for Adverse Events version 4	1 (n=74), 2 (n=57) and 4 (n=25) years post RT	1 year: 13% (grade 1: 9%, ≥ grade 2: 4%) 2 years: 15% (grade 1: 11%, ≥ grade 2: 4%) 4 years: 8% (grade 1)	Late toxicity (assessed according to Common Terminology Criteria for Adverse Events version 4)	One year: 13% (grade 1: 9%, ≥ grade 2: 4%) 2 years: 15% (grade 1: 11%, ≥ grade 2: 4%) 4 years: 8% (grade 1)
	LE 31% ME 69% CT 78% RT 100% HT 82%	Questionnaire: KAPS (Kwan's Arm Problem Scale) & Likert scale	42 months (29-58) after RT	60%	'Arm pain'	38% little 16% some 5% substantial 1% severe

Appendix 3. Continued

First Author, Year Study design	Continent	Sex	Mean age (±SD) [range]	Sample size (n)	Type of cancer	Cancer stage
Johannsen, 2015 Cohort	Europe	F	56.5 [27.3 - 71.2]	2923	Breast cancer	Grade I (26.9%), Grade II (36.4%), Grade II (17.3%), Non-ductal (19.7%)
Kaur, 2018 Cross-sectional	Asia	F	47.4	89	Breast cancer	Stage I 13.5% Stage II 44.5% Stage III 42%

	Cancer treatment	Pain measurement	Pain measurement timing	Pain prevalence	Pain definition	Pain severity (low, moderate, severe)
	ME 50.7% LE 49.3% SLNB 69.9% ALND 22.9% CT 82.3% (pre-menopausal) 14.3% (post-menopausal) RT 79.3% HT 67.4% (pre-menopausal) 64.3% (post-menopausal)	Questionnaire Pain experience during last month at the arm/shoulder of the operated side and the surgical area: no pain(0), a few times a month(1), a few times a week(2), almost every day(3), several times every day(4), and all the time(5). Degree of pain burden: 'minimally(0), a little(1), some(2), much(3), and very much(4)	15 months & 7-9 years post-surgery	15 months: 72.8% reported pain during the last month 59.1% in surgical area 60.6% in arm/shoulder 7-9yrs: 43.4% in surgical area 49.2% in arm/shoulder on operated side	'Pain experience during last month at two body locations (the arm/shoulder of the operated side and the surgical area)'	Severity: not reported Frequency: Surgical area: (15m/7-9yrs) - no pain: 40.9%/56.6% - monthly: 23.0%/23.5% - weekly: 16.0%/9.0% - daily: 10.5%/6.2% - several times daily: 6.0%/2.6% - constant: 3.5%/2.1% Arm/shoulder: - no pain: 39.4%/50.8% - monthly: 17.4%/20.1 - weekly: 14.6%/11.5% - daily: 12.5%/9.6% - several times daily: 10.6%/4.6% - constant: 5.5%/3.5%
	LE 11% ME 89% CT 91% RT 87% HT 48%	Questionnaire: NPSI, VAS	At least 3 months after surgery	41.4%	'Postmastectomy chronic pain'	19.5% moderate to severe pain (VAS ≥ 3/10) 80.5% VAS < 3/10

Appendix 3. Continued

First Author, Year Study design	Continent	Sex	Mean age (±SD) [range]	Sample size (n)	Type of cancer	Cancer stage
Kibar, 2015 Cross-sectional	Europe	F	52.5 (± 10.4)	201	Breast cancer	Not specified
Kidwell, 2014 Prospective clinical trial	North America	F	59 [38 - 83]	449	Breast cancer	DCIS 6% Stage I 52.3% Stage II 32% Stage III 9.6%
Koehler, 2018 Cohort	North America	F	56.0	36	Breast cancer	Early stage
Stinesen Kollberg, 2015 Cross-sectional	Europe	F	Mean/Median not reported [29 - 80]	243	Gynecological cancer: - cervical: 28% - endometrial: 53% - ovarian: 8% - sarcoma: 6% - tubal: 2% - vaginal 3% - vulvar: 1%	Stage I-II (84%)

	Cancer treatment	Pain measurement	Pain measurement timing	Pain prevalence	Pain definition	Pain severity (low, moderate, severe)
	ME 94.53% LE 5.47% ALND 100% RT breast-chest 57.8% RT axilla 33.8% CT 47.2%	Interview & questionnaire: VAS, SF-36	47.9 (± 48.7) months after treatment, minimum 6 months after treatment	31.8%	3/10 VAS = pain Pain = an upper extremity impairment	Not reported
	Surgery 100% CT 44.5% RT 79.4% HT 36.5%	Questionnaire: BCPT *(Breast cancer prevention trial symptom checklist)*	Average 7 months after surgery (range: 0-109 months)	58.6%	Joint pain severity	Not reported
	LE 50% ME 31% Contralateral prophylactic ME 19% SLNB 78% ALND 22% RT 61% CT 44%	Questionnaire: DASH, VAS	12 weeks and 18 months after breast cancer surgery	12 weeks: 22% 18 months: 28%	VAS ≥ 3/10 = physical impairment	Pain severity: not reported Average VAS at 12w: 17/100 (6.8 - 27.6) Average VAS at 18m: 17.15/100 (5.6 - 27.6)
	Hysterectomy, Salpingo-oophorectomy, lymph oophorectomy: 89% Vulvar surgery: 1% Other: 2% No surgery: 8% RT: 100% Brachytherapy: 81% CT: 33%	Questionnaire by Lind et al.	78 months (7 years) after treatment (range: 30 - 180 months)	59%	Dyspareunia (deep / superficial or both)	Not specified

Appendix 3. Continued

First Author, Year Study design	Continent	Sex	Mean age (±SD) [range]	Sample size (n)	Type of cancer	Cancer stage
Kramer, 2019 Cross-sectional	Africa	F	60.05 (± 10.32)	349	Breast cancer	Grade I 18.91% Grade II 43.84% Grade III 19.48% Missing 17.77%
Laroche, 2017 Cohort	Europe	F	61.5 (± 7.1)	135	Breast cancer	Early-stage breast cancer (I-II)
Lee, 2014 Cohort	Oceania	F	52.0	53	Breast Cancer	Stage I 8% Stage II 49% Stage III 43%
Lopez, 2015 Cross-sectional	Europe	F	60.8 (± 7.1) [44 - 77]	77	Breast cancer	Grade I 31.2% Grade II 49.4% Grade III 16.9% Unknown 2.6%
Lowery, 2014 Cross-sectional	North America	M 36.1% / F 63.9%	69 (± 9.9)	183	Lung cancer	Stage IA 68.3% Stage IB 31.7%
Mandelblatt, 2019 Cohort	North America	F	65.3 (± 5.7) [60 - 98]	362	Breast cancer	Stage 0 (DCIS) 7.8% Stage I 50.7% Stage II 33.3% Stage III 8.2%

	Cancer treatment	Pain measurement	Pain measurement timing	Pain prevalence	Pain definition	Pain severity (low, moderate, severe)
	ME 0% MME 73.35% LE 18.34% ALND 78% SLNB 13% CT 72.78% RT 63.32% HT 70.49%	Questionnaire: SPADI	6.52 (± 2.43) yrs since surgery (2 - 17 years)	74%	Shoulder pain	26% no pain 46% mild pain 14% moderate pain 14% severe pain
	Not reported	Questionnaire: BPI, DN4, VAS	1, 3, 6 and 12 months after start of AI treatment	57%	Joint pain 36%, Diffuse pain 22%, Tendinitis 22%, Neuropathic pain 9% and Mixed pain 11%	Not reported
	ME 53% LE 47% ALND 72% SLNB 26% RT 85% HT 79% CT: 100%	Questionnaire: VAS	6 months after completion of CT	35.8%	VAS ≥ 1	Average VAS 3.7 (± 2.0)
	Surgery 97.4% CT 40% RT 89.6%	Questionnaire: VAS	2.5 (± 1.09) yrs since start AI treatment	78%	Arthralgia	47% mild 46% moderate Average VAS: 3.8/10
	Surgical resection with curative intent	Questionnaire: BPI	2.9 (± 1.2) years since surgery (range 1-6 years)	57.9 %	Not reported	Not reported
	LE: 55.2% ME: 44.8% RT 52.3% (LE only) CT 27.3% (with or without HT) HT only: 68.8%	Survey not specified	Baseline (before systemic therapy), 6, 12, 24 and 36 months after starting systemic therapy	1 year: 60.65% 2 years: 66.35% 3 years: 69.4%	Not reported	Not reported

Appendix 3. Continued

First Author, Year Study design	Continent	Sex	Mean age (±SD) [range]	Sample size (n)	Type of cancer	Cancer stage
Manfuku, 2019 Cross-sectional	Asia	F	56.3 (± 10.6)	93	Breast cancer	Stage 0-I 55% Stage II-III 45%
Mertz, 2017 Cross-sectional	Europe	F	Median 60 (IQR 14)	473	Breast cancer	DCIS (stage 0)
Mozsa, 2014 Cohort	Europe	F	62.6 [47 - 77]	44	Breast cancer	Stage I-II 100%
Mustonen, 2019 Cohort	Europe	F	60.7 (± 5.8)	251	Breast cancer	Stage I 20.8%, Stage II 40.3%, Stage III 38.9%
Rizk, 2014 Cohort	North America	M 41.3% /F 58.7%	67.9 [22 - 88]	177-146-120 (4-, 8- and 12-months follow-up)	Lung cancer	Stage IA 76% Stage IB 24%
Santos, 2014 Cross-sectional	South America	F/M Percentage not reported	53.7 (±15.4) [35 - 74]	40	Rectal cancer	Stage I 23% Stage IIa 34.2% Stage IIb 2.6% Stage IIIb 23% Stage IIIc 15.8%

	Cancer treatment	Pain measurement	Pain measurement timing	Pain prevalence	Pain definition	Pain severity (low, moderate, severe)
	LE 68.8% ME 31.2% SLNB 71% ALND 29% RT 72% CT 36.6% HT 28%	Questionnaire: BPI	1.6 (± 0.8) years after surgery	65.1%	Not defined	Not reported
	ME & SLNB 30% LE & SLNB & RT 33% LE & RT 32%	Questionnaire: EORTC-QLQ-C30	12-36 months after surgery: Median 24 (±13), range 12 - 36	33%	Not defined. Pain in breast, side of chest, axilla, or arm.	12% moderate to severe pain 21% mild pain 67% no pain
	LE 100%: SLNB 90.1% ALND 9.9% RT 100% CT 6.8% (before RT) HT 95.5 % (before RT)	Questionnaire: RTOG/EORTC early and late radiation morbidity scoring schemes	5 years after RT	2%	Late radiation side effects	45.5% mild (grade 1) 54.5% no pain (grade 0)
	LE 36% ME 64% SLNB 10.2% ALND 89.8% RT 67.1% CT 87.6% HT 84.5%	Questionnaire BPI Quantitative Sensory Testing	4 to 9 years after surgery	53.8%	Chronic postsurgical neuropathic pain	22% moderate to severe pain
	Surgery: - 33% thoracotomy - 67% VATS	Questionnaire: BPI	4, 8 and 12 months after surgery (thoracotomy/VATS)	9.6%	Clinically significant pain (≥ 4/10)	Not reported
	Surgery 100% (anterior rectal dissection or abdominoperineal amputation) (Neo)adjuvant CRT	Interview & questionnaire: EORTC-QLQ-C30, VAS	28.7 (± 18.7) months after surgery	52.5%	Not defined	Average pain intensity: 3.8 (±2.4)

Appendix 3. Continued

First Author, Year Study design	Continent	Sex	Mean age (±SD) [range]	Sample size (n)	Type of cancer	Cancer stage
Schmidt, 2018 Cohort	Europe	F	59 (± 9.0)	190	Breast cancer	Stage 0 4.7% Stage I 50.5% Stage II 33.7% Stage III 11.1%
Smoot, 2014 Cross-sectional	Europe	F	56.24 (±9.4)	145	Breast cancer	Stage I-III
Steyaert, 2015 Cross-sectional	Europe	F	56.5 (± 12.4)	128	Breast cancer	Stage I 21% Stage II 60% Stage III 19%
Yi, 2018 Cross-sectional	Asia	F	53.56 [38 - 69]	110	Breast cancer	Stage 0-I 51% Stage II 36%

F=Female, M=Male, SSFS=The Shot Sexual Functional Scale, ED=Entry Dyspareunia, DP=Deep Dyspareunia, ACP=Abdominal Coital Pain, ME=Mastectomy, MME=Modified Mastectomy, LE=Lumpectomy, RT=Radiotherapy, CT=Chemotherapy, CRT=Chemoradiotherapy, HT=Hormone Therapy, SLNB=Sentinel Lymph Node Biopsy, ALND=Axillary Lymph Node Dissection, QST=Quantitative Sensory Testing, NRS=Numeric Rating Scale, PMPS=Post Mastectomy Pain Syndrome, PPBCS=Persistent Pain after Breast Cancer Surgery, BPI=Brief Pain Inventory, DCIS=Ductal Carcinoma In Situ, VAS=Visual Analogue Scale, EBRT=External Beam Radiotherapy, ADT=Androgen Deprivation Therapy, EHS=Erection Hardness Scale, VATS=Video-Assisted Thoracoscopic Surgery, HR+=Hormone Receptor positive, RASQ=Rheumatoid Arthritis Symptom Questionnaire, SF-36=36-Item Short Form Health Survey, KAPS=Kwan's Arm Problem Scale, NPSI=Neuropathic Pain Symptom Inventory, BCPT=Breast Cancer Prevention Trial Symptom Checklist, DASH=Disability of the Arm, Shoulder and Hand Questionnaire, SPADI=Shoulder Pain And Disability Index,

	Cancer treatment	Pain measurement	Pain measurement timing	Pain prevalence	Pain definition	Pain severity (low, moderate, severe)
	Surgery 100% CT & RT 53% RT 41% CT 6% HT 77.4%	Questionnaire: EORTC-QLQ-C30	5 years post-diagnosis (4.9 ± 0.7 yrs: 3.4 - 6.7 yrs)	34%	Not reported	No Little Some Much (Figure 2)
	Not reported	Questionnaire: Breast Symptoms Questionnaire (BSQ), NRS	At least 6 months after completion of treatment	61%	Not reported	Not reported
	ME & ALND 100% RT 60.2% CT 64.8% HT 82.8%	Questionnaire: *'Our questionnaire was based on the one used by Gärtner et al[1]and the one used by Li and Kong[10], in 2 recent studies on prevalence of chronic pain after breast cancer treatment & ID Pain Questionnaire'*	4-9 years after surgery: 80 ± 18.5 months	43.8%	48.2% neuropathic pain (ID Pain Q) 'chronic postmastectomy pain'	12.3% severe pain
	ME 40% LE 59% CT 62% RT 62% HT 100%	Questionnaire: BPI	≥ 3 months after breast surgery	88.2%	Not reported	None 13.6% Mild 61.8% Moderate 20% Severe 4.5% Average: 28.83/100 (±24.03)

DN4=Douleur Neuropathique en 4 Questions, AI=Aromatase Inhibitor, EORTC-QLQ-C30= European Organization for Research and Treatment for Cancer Quality of Life Questionnaire, RTOG/EORTC= Radiation Therapy Oncology Group/European Organization for Research and Treatment of Cancer

Chapter 2

Continuum of somatosensory profiles in breast cancer survivors with and without pain, compared to healthy controls and patients with fibromyalgia.

Continuum of somatosensory profiles in breast cancer survivors with and without pain, compared to healthy controls and patients with fibromyalgia

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Abstract

Context: The prevalence of persistent pain among breast cancer survivors (BCS) is high and it is unclear what distinguishes those with persistent pain from those without. Research suggests that differences in somatosensory function, evaluated by quantitative sensory testing (QST) may be responsible.

Objectives: This study first aimed to describe the somatosensory profiles in terms of loss and gain in function of BCS with and without persistent pain using reference data from healthy controls. Second, QST parameters of BCS with and without pain were compared with those of healthy controls (i.e., a negative control group) and patients suffering from fibromyalgia (i.e., a positive control group).

Methods: Hundred twenty-eight participants were divided into four equal groups: healthy controls, BCS with persistent pain, BCS without persistent pain, and patients with fibromyalgia. Nine QST parameters were evaluated at the trunk and at a remote location. Somatosensory profiles were determined using z-score transformation of the QST data by using normative data of healthy controls.

Results: At the trunk and compared to healthy controls, BCS with persistent pain showed a significant difference across five out of seven QST parameters. Pain-free BCS showed a significant difference across four QST parameters in comparison to healthy controls. Temporal summation and conditioned pain modulation were not found to be significantly different between groups.

Conclusion: Aberrations in the peripheral, but not in the central somatosensory nervous system are likely present in BCS with and without persistent pain when compared to healthy controls and participants with fibromyalgia.

Key words: Cancer-related pain, breast cancer, conditioned pain modulation, temporal summation

Introduction

Approximately 47% of breast cancer survivors (BCS) experience persistent pain after finishing primary cancer treatments, making this a commonly reported symptom.[1] Persistent pain is known to negatively impact emotional and physical functioning and quality of life in this population.[2,3]

Although scientific research into the pathophysiology of persistent pain after breast cancer treatment has improved our understanding of persistent pain after breast cancer treatment, it is still unclear why some BCS experience pain while others do not. It has been proposed that BCS with persistent pain exhibit impairments in nociceptive processing within the peripheral and central somatosensory nervous system.[4–10]

Quantitative sensory testing (QST) can be used to evaluate differences in somatosensory function of the peripheral and central nervous system by assessing hyper- or hypoesthesia in response to standardized stimuli under controlled conditions.[11–13] Hyperesthesia is defined as an increase in sensitivity to stimulation, whereas hypoesthesia is defined as a decrease in sensitivity to stimulation. So far, a number of studies have investigated somatosensory functioning in BCS with persistent pain after breast cancer surgery.[4–10] In general, these studies showed the presence of hypoesthesia[4,6,7], and hyperesthesia (hyperalgesia, allodynia) in the treated area and remote areas in comparison to pain-free BCS [4,5,8,9] and healthy controls.[6,10] Hypoesthesia was mainly present for the detection of thermal and mechanical stimuli locally, whereas hyperalgesia was found for pressure pain thresholds (PPTs) locally and remotely. In addition, aberrations in dynamic QST paradigms were found (e.g., decreased conditioned pain modulation (CPM) and exaggerated temporal summation (TS) of pain).[4,5,8,9] Unfortunately, studies either lacked a healthy control group [4,5,8,9] or a control group consisting of pain-free BCS, limiting general conclusions on the nociceptive processing within the somatosensory nervous system.[6,10] Furthermore, previous studies have never used a control group with clear evidence of aberrations in the central processing of nociceptive

signals.[14,15] Patients with fibromyalgia are known are known to suffer from chronic widespread pain and show impairments in the inhibitory descending pathways evaluated by CPM or increased facilitation of endogenous nociceptive pathways evaluated by TS.[14] Besides impairments in central nociceptive processing, these patients demonstrate local hyperesthesia (hyperalgesia) in PPT, thermal and mechanical pain thresholds.[14–16] Patients suffering from fibromyalgia are considered a positive control group while healthy individuals are considered a negative control group.[15]

The goal of this study is to compare QST data, describe the somatosensory profiles of BCS with and without persistent pain, and compare them with the somatosensory profiles of patients with fibromyalgia and healthy controls using dynamic and static QST paradigms. We hypothesized that BCS with persistent pain will show hypoesthesia for the detection of thermal and mechanical stimuli in the area of breast cancer treatment, and hyperalgesia in PPT locally and remotely compared to healthy controls. This information may contribute to our understanding of persistent pain after breast cancer.

Methods

Participants

Participants were recruited between May 2020 and December 2022 as part of a larger cross-sectional study at the University of Leuven and University of Antwerp. This larger study investigated different mechanistic pain descriptors using different assessment methods in cancer survivors with pain (clinicaltrail.gov: NCT03981809) and received approval from the Ethical Committee of the University Hospitals Leuven (s62584) and the University Hospital of Antwerp (B322201940289). Participants were recruited consecutively from the larger study and provided written informed consent prior to enrollment. The study is reported following the Strengthening the Reporting of Observational studies in Epidemiology (STROBE) statement.[17]

First, a group of BCS with persistent pain was recruited with the following inclusion criteria: (1) ≥ 18 years, (2) completed primary treatment for primary breast cancer at least three months ago, and (3) complete remission. Ongoing hormonal treatment and targeted immunotherapy were permitted. BCS experiencing persistent pain needed to report mean pain intensity during activity ≥ 3/10 on the numeric rating scale (NRS) during the past week with 0 meaning no pain and 10 being the worst pain imaginable.[18,19] The NRS was conducted via telephone prior to inclusion. BCS experiencing persistent pain related to the treatment of breast cancer were recruited via the oncology department of the University Hospitals Leuven and University Hospital Antwerp (Belgium). Persistent pain related to the treatment of breast cancer was defined based on its location and timing of onset. Pain in the area of breast or axillary surgery, area of radiation therapy, or the shoulder and upper limb was considered to be related to breast cancer treatment if it occurred concurrently or after its completion.

Second, a group of BCS without pain was recruited. The same inclusion criteria were used. In addition, they did not report a mean pain intensity during activity of ≥ 3/10 on the NRS during the past week. Pain-free BCS were recruited via national and local cancer survivorship organizations and via the research database of the Department of Rehabilitation Sciences of the KU Leuven, University of Leuven.

Third, patients with fibromyalgia were recruited. Patients with fibromyalgia were diagnosed by rheumatologists, rehabilitation physicians, or pain physicians and had painful symptoms for at least three months. Subsequently and prior to participating, patients with fibromyalgia were screened using the 2010 American College of Rheumatology (ACR) criteria.[20] Patients with fibromyalgia were recruited via patient organizations, the Center for Algology and Pain Management of the University Hospitals Leuven, and the Pain Center of the University Hospital Antwerp.

Fourth, a reference group with healthy female controls was included if they did not have a history of cancer and no mean pain intensity during activity of ≥ 3/10 on the

NRS during the past week. Healthy controls were recruited via local organizations and peers at the University Hospitals Leuven, KU Leuven, and University of Antwerp.

For all groups, participants were excluded if they had (1) any active metastasis, (2) a palliative status, (3) recurrence of cancer, (4) bilateral cancer, (5) pregnancy or breastfeeding, (6) inability to speak and read Dutch, and (7) physical and mental inability to complete the assessment.

Data collection

The following descriptive data for all participants were obtained via questionnaires: age, body mass index, hand dominance, and analgesic use. Data on breast cancer treatment were obtained via questionnaires and by consulting the electronic health records: type of breast surgery and axillary surgery, side of surgery, tumor size and lymph node stage, and type of (neo-)adjuvant treatment (radiotherapy, chemotherapy, and/or hormonal therapy). In addition, for each participant, three questionnaires assessing psychosocial factors were administered prior to the assessment. Participants accessed the questionnaires via REDcap, an online platform for electronic data capturing.[21] The following questionnaires were administered: 1) **Pain catastrophizing** was evaluated using the pain catastrophizing scale (PCS). This self-report questionnaire consists of 13 questions evaluating thoughts and feelings of previous painful experiences on a scale from 0 (not at all) to 4 (all the time). The total score ranges from 0 to 52 (with higher scores indicating a greater level of catastrophizing). In addition to the total sum of scores, three dimensions are present within the PCS: (1) rumination, defined as irrationals thoughts regarding pain (score range from 0 to 16); (2) magnification, defined as the increased threat value of pain (score range from 0 to 12); (3) helplessness, defined as the inability to handle perceptions of suffering (score range from 0 to 24).[22,23] 2) **Depression, anxiety, and stress** over the past week were evaluated using the Depression, Anxiety, and Stress Scale (DASS-21). The DASS-21 contains 21 questions (7 for each subscale: depression, anxiety, stress) with scores ranging from 0 (did not apply to me at all) to 3 (applied

to me very much, or most of the time).[24,25] 3) The central sensitization inventory (CSI) is a self-report questionnaire that evaluates **health-related symptoms that may be related to the neurophysiological state, termed central sensitization**. The CSI contains 25 questions, each scaled from 0 (not at all) to 4 (all the time). The total score ranges from 0 to 100, with a score of 40 or higher score indicating the suspected presence of central sensitization.[26,27] In accordance with the 2010 ACR criteria for fibromyalgia, patients with fibromyalgia filled out the widespread pain index (WPI) and the symptom severity scale (SSS). Both questionnaires are a self-report measure for the **assessment of pain distribution** (WPI) and the **severity of symptoms** of fatigue, waking unrefreshed and cognitive symptoms (SSS).[20] The WPI assesses the presence of pain over the past week in 19 specific areas of the body, with each affected area presenting one point (0-19).[20] The SSS uses a scale from 0 (no problem) to 3 (severe) for each symptom category, with total scores ranging from 0 to 12.[20] Patients with fibromyalgia were eligible for inclusion when (1) pain was present for at least 3 months, (2) the patients did not have a disorder that could explain their pain symptoms, (3) the WPI score was greater or equal to 7 and SSS was greater or equal to 5, or WPI score was between 3 and 6 and SSS was greater or equal to 9.[20]

QST was performed in a quiet room at temperatures between 21°C and 23°C. Standardized test instructions were provided for each QST method before testing. Nine QST parameters were evaluated using five QST methods. The examiner was not blinded during the comprehensive assessment. Participants were seated on a chair. The total duration of testing approximated 2 hours with an interval between each test varying between 2 and 3 minutes.

Static QST parameters were evaluated at the lateral trunk and the upper part of the opposite tibialis anterior muscle, four fingers below the tibial tuberosity. When chemotherapy-induced peripheral neuropathy or pain in the lower leg was reported, the location of symptoms were evaluated. When neuropathy or pain presented at the upper part of the tibialis anterior muscle, a non-painful location was chosen

nearby or on the other leg. In the breast cancer population, the lateral trunk was assessed at the affected side. The lateral trunk was defined as the area innervated by the lateral intercostal nerve and marked by placing four fingers under the armpit fold at the lateral side of the trunk on the anterior axillary line.[28] The side of the lateral trunk in the fibromyalgia population and healthy controls was chosen using simple randomization (odd and even numbers). To facilitate reading of the paper, the chosen side in the fibromyalgia and healthy control groups is called the 'affected side' throughout the manuscript. CPM was evaluated at both forearms, and the TS of pain was evaluated only at the upper part of the opposite tibialis anterior.

The nine QST parameters were evaluated in the following order.

1. Pressure pain threshold (PPT)

A digital pressure algometer (Wagner FDX, Greenwich CT, USA) with a flat round rubber tip and a probe area of 1 cm^2 was used. The **PPT** was defined as the amount of pressure at which the sensation of pressure was first perceived as unpleasant and was determined by two series of ascending pressure at a rate of approximately 0.1 kgf/s.[13] The final threshold was the arithmetic mean of two trials (kgf/cm^2).[8]

2. Mechanical thresholds

Mechanical detection and pain thresholds (MDT and MPT) were evaluated using a standardized set of 12 von Frey monofilaments (Optihair2, Marstock Nervtest, Germany) exerting forces between 0.25 and 512 mN. The monofilaments were applied at a rate of 2 seconds on and 2 seconds off, in an ascending and descending order respectively, starting with an 8 mN monofilament.[12,13]

For the assessment of **MDT** (e.g., the lowest mechanical force felt), the participants kept their eyes closed and verbally indicated when a force was detected. Similarly, for the assessment of **MPT** (e.g., the lowest mechanical force perceived as painful), the participants kept their eyes closed and verbally indicated when a force was experienced as unpleasant. To decrease guessing, two consecutive forces required detection (MDT) or needed to be perceived as painful (MPT) by the participant. The

geometric mean of the ascending (first detected, or painful stimulus) and descending (last detected, or painful stimulus) sequence was calculated (mN).[12,13]

3. Thermal thresholds

Thermal thresholds were evaluated using a computer-controlled thermode system (Advanced Thermosensory Stimulator TSA-2, Medoc, Ramat Yishai, Israel) with a Peltier thermode (3 × 3 cm). The participant was instructed to push a computer-controlled button when he/she experienced a change from a 122hermos-neutral state to a distinct warm, or cold sensation (warmth and cold detection threshold respectively, **WDT**, **CDT**).[12,13] Thermal pain thresholds were evaluated by instructing the participant to push the computer-controlled button when the sensation of warmth (heat pain threshold, **HPT**) or cold (cold pain threshold, **CPTh**) was experienced as unpleasant.[12,13] The baseline temperature was 32°C and the temperature was decreased or increased at a rate of 1°C/s. The temperature was limited to 50°C for heat and 0°C for cold. The final thermal detection and pain thresholds were defined as the arithmetic mean of three consecutive measurements.[12,13]

4. Temporal summation (TS) of pain

Temporal summation (**TS**) of pain was measured only at the upper part of tibialis anterior muscle, opposide to the side of the assessed trunk, by applying a train of pinprick stimuli using a von Frey monofilament with a stimulation force of 256mN (Optihair2-Set, Marstock Nervtest, Germany). After the first stimulus, a train of stimuli was delivered during 30 seconds at a rate of 1 stimulation/s. Participants were asked to score the pain after the first stimulus on a 0-10 NRS and immediately after the series of stimuli.[29,30] The difference between the NRS after the last stimulus and the NRS after the first stimulus was used.[8,28]

5. Conditioned pain modulation (CPM)

The **CPM** protocol was performed using the same computer-controlled thermode system (Advanced Thermosensory Stimulator TSA-2; Medoc, Ramat Yishai, Israel).

First, the intensity of the stimulus was individualized for each subject, that is, the Pain4 Temperature. A Peltier thermode (3x3 cm) was applied first on the volar side of the forearm of the non-affected side.[28,31] The temperature required to evoke a painful sensation with a rating of 4 on a 0-10 NRS (Pain4) was determined by administering a series of heat stimuli to the unaffected forearm. The baseline temperature was 32°C, which increased at a rate of 2°C/s and decreased at a rate of 1°C/s. During the first stimulation, temperature rose to 43°C. If a score above or below 4/10 on the NRS was given, the temperature of the next stimulation was decreased or increased by 1°C respectively. A maximum of five stimulations was administered to search for the Pain4 temperature. The minimum and maximum temperatures of the test stimulus were 39 and 46°C, respectively. After determining the Pain4 test stimulus, a parallel CPM paradigm was introduced. The Pain4 test stimulus was administered to the volar side of the affected forearm for 45 seconds (Phase A, Figure 1). Participants were asked to verbally rate the intensity of the test stimulus at 10, 20, 30, and 40 seconds using a 0-10 NRS. A 120 second break followed, after which the conditioning stimulus was administered to the volar side of the unaffected forearm for 65 seconds (Phase B, Figure 1). The conditioning stimulus was set 0.5 °C warmer than the Pain4 test stimulus. Twenty seconds after the initiation of the conditioning stimulus, the Pain4 test stimulus was applied parallel to the volar side of the affected forearm. Verbal ratings of pain intensity for the affected forearm were obtained at 10, 20, 30, and 40 seconds of stimulation (0-10 NRS). The arithmetic means of the four NRS scores during phases A and B were calculated. The mean NRS score of Phase B was subtracted by the mean NRS score of Phase A. A negative score indicated the presence of efficient CPM.[31] CPM results were presented together with QST data measured at the opposite tibialis anterior muscle.

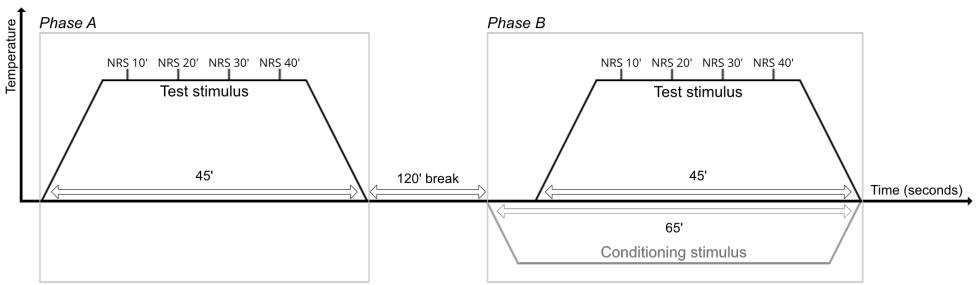

Figure 1: A schematic overview of the CPM protocol sequence.
Phase A: application of Pain4 heat on the affected forearm, Phase B: application of Pain4 + 0.5˚C heat (conditioning stimulus) on the non-affected forearm for 65 seconds and concurrently the application of Pain4 heat (test stimulus) on the affected forearm for 45 seconds. NRS= Numeric rating scale.

The QST protocol was found to be reliable in breast cancer survivors with pain, with the exception of CPM. Intra and inter rater reliability (absolute and relative) ranged from moderate to excellent for most paradigms. Intra and inter rater reliability of CPM ranged from weak to moderate.[28]

Statistical analysis

Data analysis was performed using IBM SPSS Statistics for Macintosh, Version 28.0.[32] All graphs were made using GraphPad Prism for Macintosh, Version 9.4.1.[33]

Descriptive statistics for non-normally distributed and continuous variables were presented as median and interquartile range (IQR), and normally distributed variables were presented as mean and standard deviation (SD). Categorical variables were presented as frequencies and proportions (%).

All QST data with the exception of HPT, CPTh, TS and CPM were transformed into decadic logarithms to achieve normal distributions.[13,34] HPT and CPTh were not transformed as this was not recommended by Rolke et al., whereas TS and CPM contained negative scores which did not allow for logarithmic transformation.[13,34] For comparison of QST data between groups, we used log-transformed and raw QST data. The Kruskal-Wallis test was used for continuous, non-normally distributed variables, and analysis of variance (ANOVA) was used for continuous, normally

distributed variables. Dunn's post hoc multiple comparison tests with Bonferroni multiple-comparison correction were performed to evaluate differences between the different groups. The χ^2 test with Bonferroni multiple comparison correction was used for categorical variables. Statistical significance was defined as $p < 0.05$.

Furthermore, the QST data were z-transformed using the mean and standard deviation of the healthy control data as follows: *Z-score = (mean single participant – mean controls) / SD*. To ensure clear data presentation, the algebraic sign of the Z-score was adjusted to align with the participants' sensitivity to the parameters being tested. A positive Z-score represented hyperesthesia, whereas a negative Z-score represented hypoesthesia. A Z-score of zero was defined as the mean of healthy controls. Z-scores outside the 95% confidence interval (CI) of the healthy controls data were considered as somatosensory aberrations.[6,35]

Results

Participants

The participant characteristics and breast cancer treatment-related factors are summarized in Table 2. The participants had a similar BMI ($p = 0.133$) but differed significantly in age ($p < 0.001$); BCS with persistent pain were significantly older than healthy controls ($p = 0.008$) and patients with fibromyalgia ($p < 0.001$). In addition, the pain-free BCS group was significantly older than the fibromyalgia group ($p < 0.001$).

Patients with fibromyalgia reported a mean of 12.6 ± 3.0 on the WPI, and a mean of 10.1 ± 1.6 on the SSS (Table 2). Participants with persistent pain (BCS with pain and fibromyalgia) reported a mean VAS score of over 50/100 for pain during the past seven days. In addition, psychosocial factors differed significantly between the groups ($p < 0.001$). Post hoc comparison revealed that participants with persistent pain (BCS and fibromyalgia) reported significantly higher scores regarding psychosocial factors (i.e., worse psychosocial functioning) than pain-free BCS and healthy controls: DASS-21, $p < 0.001$; PCS, $p < 0.001$; CSI, $p < 0.01$. Furthermore, the

BCS with persistent pain group exhibited significantly lower CSI scores than the fibromyalgia group ($p < 0.01$).

Table 2. Participant demographics. Values are reported as mean ± standard deviation and median (IQR), unless mentioned otherwise.

Characteristics	Healthy controls (n=32)	Pain-free BCS (n=32)	BCS pain (n=32)	Fibromyalgia (n=32)	p-value
Age † (y)	47.6 ± 8.7[a] 49 (13)	54.9 ± 8.5[b] 55 (11.5)	56.7 ± 10.4[a] 56.0 (10.3)	43.8 ± 11.8 [ab] 44.5 (15.8)	< **0.001**
Sex: female, n (%)	32 (100%)	32 (100%)	32 (100%)	29 (90.6%)	
Body Mass Index †	24.0 ± 3.6 23.82 (4.5)	25.1 ± 4.4 24.0 (4.8)	26.3 ± 4.9 25.7 (6.8)	26.6 ± 5.5 25.3 (8.5)	0.133
Dominant side: right, n (%)	30 (93.8%)	28 (82.4%)	30 (93.8%)	29 (90.6%)	
"Affected" side: right, n (%)	15 (45.5%)	12 (37.5%)	14 (43.8%)	15 (46.9%)	
Mean VAS pain: past week (0-100)	5.5 ± 7.9 2.0 ± 7.0	7.4 ± 7.2 6.5 (11.3)	52.3 ± 14.4 51.3 (17.9)	54.7 ± 11.3 52.3 (16.4)	
Duration pain (months)	n/a	n/a	59.7 ± 83.4 24.0 (55.5)	118.7 ± 92.3 90 (114)	
Location of pain, n (%) Chest and lateral trunk Arm, shoulder, and axilla Chest, lateral trunk, arm, shoulder, and axilla Widespread pain			 24 (75.0%) 3 (9.4%) 5 (15.6%)	 32 (100%)	
Presence of CIPN, n (%)	n/a	0%	4 (12.5%)	n/a	
Presence of concurrent lower leg pain, n (%)	0%	0%	1 (3.1%)	6 (18.8%)	
Pain medication: type, n (%) *- Tricyclic antidepressants, gabapentinoids or SNRI* *- NSAID, acetaminophen, or mild opioid* *No medication*	0%	0%	 3 (9.4%) 14 (43.8%) 15 (46.9%)	 15 (46.8%) 17 (53.1%) 0 (0%)	
Breast surgery type LE ME	n/a	 5 (15.6%) 27 (84.4%)	 12 (37.5%) 20 (62.5%)	n/a	
Axillary surgery type ALND SLNB	n/a	 16 (50.0%) 16 (50.0%)	 15 (46.9%) 17 (53.1%)	n/a	
Chemotherapy: yes, n (%)	n/a	26 (86.7%)	18 (56.3%)	n/a	
Radiotherapy: yes, n (%)	n/a	27 (84.3%)	29 (90.6%)	n/a	
Endocrine therapy: yes, n (%)	n/a	24 (75.0%)	24 (75.0%)	n/a	
Date since diagnosis (months)	n/a	73.0 ± 64.9 51.5 (21.8)	84.8 ± 82.2 61.5 (55.3)	n/a	

Table 2. Continued

Widespread Pain Index (0-19)	n/a	n/a	n/a	12.6 ± 3.0 13.0 (5.0)	
Symptom Severity Scale (0-9)	n/a	n/a	n/a	10.1 ± 1.6 11.0 (1.3)	
Pain Catastrophizing Scale ‡ (0-52)	6.6 ± 5.2[a] 6.0 (7.3)	6.0 ± 6.0[b] 3.5 (8.3)	23.1 ± 10.3[ab] 23.0 (13.5)	25.3 ± 13.1[ab] 27.5 (19.8)	**< 0.001**
DASS-21 ‡ (0-84): Depression (0-28)	2.4 ± 3.6[a] 2.0 (2.5)	2.9 ± 4.9[b] 0 (4.0)	9.0 ± 10.9[ab] 4.0 (11.0)	14.1 ± 10.7[ab] 13.0 (17.0)	
Anxiety (0-28)	1.8 ± 3.5[a] 0 (2.0)	2.1 ± 3.6[b] 0 (2.5)	7.4 ± 7.7[ab] 5.0 (11.5)	12.7 ± 7.8[ab] 13.0 (11.0)	**< 0.001**
Stress (0-28)	4.9 ± 5.2[a] 0.0 (8.0)	65.5 ± 8.2[b] 0 (8.5)	12.7 ± 10.0[ab] 12.0 (13.5)	16.1 ± 9.9[ab] 15.0	
Central Sensitization Inventory † (0-100)	20.4 ± 9.6[a] 18.0 (13.3)	27.8 ± 12.2[b] 29.0 (17.0)	43.6 ± 15.8[abc] 45.5 (22.8)	64.1 ± 8.7[abc] 65.5 (11.8)	**< 0.001**

† Analysis of variance (ANOVA) for Age, Body Mass Index and Central Sensitization Inventory.
‡ Kruskal-Wallis test for Pain Catastrophizing Scale and DASS-21.
Post hoc tests: a, b, c: same letters marking the values of categories within a given row denote mutually statistically different groups. Significant p-values ($p < 0.05$) are indicated in bold.
VAS= Visual Analogue Scale, SNRI= Serotonin and norepinephrine reuptake inhibitors, NSAID= Non-steroidal anti-inflammatory drugs, CIPN= Chemotherapy-induced peripheral neuropathy, LE= Lumpectomy, ME= Mastectomy, SLND= Sentinel lymph node biopsy, ALND= Axillary lymph node dissection, DASS-21= Depression, anxiety, stress scale.

Quantitative sensory testing (Table 3, 4, 5 and Figure 2, 3, 4, 5)

Comparison of QST results

The QST results are presented in Table 3. In Table 4, the overall p-value for the comparison of QST parameters between groups (Kruskal-Wallis) is given together with the results of the post hoc analyses of the parameters that were found to be significant.

1. Pressure pain threshold (PPT)

The **PPTs** at the *opposite tibialis anterior muscle* and *trunk* differed significantly between the groups ($p < 0.001$).

Post hoc tests revealed that patients with fibromyalgia had significantly lower PPTs at the *opposite tibialis anterior* than healthy controls ($p = 0.01$), pain-free BCS ($p < 0.001$), and BCS with pain ($p = 0.003$). There were no significant differences between

the healthy controls and the BCS (with or without pain) in PPTs at the *opposite tibialis anterior*.

At the *trunk*, pain-free BCS showed significantly higher **PPTs** than BCS with pain ($p < 0.001$) and patients with fibromyalgia ($p = 0.003$) in post hoc analysis. In addition, PPTs of BCS with pain were significantly lower than the **PPTs** of healthy controls ($p = 0.005$), in contrast to the PPTs of pain-free BCS, which did not show a significant difference compared to healthy controls ($p = 0.072$).

2. Mechanical thresholds

Overall, a significant difference was found between the groups concerning **MDT** at the *opposite tibialis anterior* ($p < 0.001$) and **MDT** at the *trunk* ($p < 0.001$).

Post hoc analyses revealed that BCS with and without persistent pain had significantly higher **MDTs** in comparison to healthy controls (respectively, $p < 0.001$ and $p = 0.004$) at the *opposite tibialis anterior*. In addition, BCS with pain also had a significantly higher **MDTs** than patients with fibromyalgia ($p = 0.012$). Concerning **MDT** measured at the *trunk*, all four groups differed significantly from each other, except for the comparison between the two BCS groups. All patient groups had significantly higher **MDT** scores than healthy controls: pain-free BCS ($p < 0.001$), BCS with pain ($p < 0.001$), and fibromyalgia ($p = 0.022$). Both BCS groups showed significantly higher **MDTs** than the fibromyalgia group: pain-free BCS ($p < 0.001$) and BCS with pain ($p = 0.003$).

The **MPT** was significantly different between the groups at the *opposite tibialis anterior* ($p = 0.010$) and *trunk* ($p < 0.001$). Post hoc analyses revealed that the fibromyalgia group had significantly lower **MPTs** than healthy controls ($p = 0.007$) and pain-free BCS ($p = 0.026$) groups at the *opposite tibialis anterior*. At the *trunk*, fibromyalgia participants showed significantly lower **MPTs** than healthy controls ($p < 0.001$) and pain-free BCS ($p = 0.001$).

3. Thermal thresholds

Regarding the thermal thresholds measured at the *opposite tibialis anterior*, only **CPTh** differed significantly between the groups (p = 0.002). Post hoc testing revealed that the **CPTh** of pain-free BCS differed significantly (p < 0.001) in patients with fibromyalgia.

Thermal thresholds (**WDT, CDT, HPT, CPTh**) measured at the *trunk* differed significantly between the groups (p < 0.001 (WDT), p < 0.001 (CDT), p < 0.001 (HPT), and p = 0.002 (CPTh)). Both BCS groups differed significantly from the healthy controls and fibromyalgia group in terms of WDT, CDT, and HPT, with p < 0.001 for each [70]thermal threshold. BCS without pain generally showed lower CDT/CPTh and higher WDT/HPTs. Pain-free BCS also exerted lower CDTs and higher WDTs; however, pain-free BCS exerted higher CPTh and lower HPT. Regarding CPTh, only the pain-free BCS group had significantly higher thresholds than did the fibromyalgia group (p < 0.001).

4. Temporal summation of pain

The **TS** of pain was measured only at the *opposite tibialis anterior* and differed significantly between groups (p < 0.001). Post hoc tests revealed significantly higher scores for patients with fibromyalgia than for healthy controls (p = 0.007) and pain-free BCS (p = 0.001). In addition, BCS with pain exerted higher TS of pain than pain-free BCS (p = 0.021).

5. Conditioned pain modulation (CPM)

No significant differences were found in **CPM** between the groups; however, a trend was observed (p = 0.051). Post hoc tests revealed a significant difference between healthy controls and patients with fibromyalgia. Missing data was present in the following groups: pain-free BCS (n=5), BCS with pain (n=3), and fibromyalgia (n=7). For the majority of BCS with missing CPM data, determination of the Pain4 temperature was not possible because the heat stimulus was not perceived as unpleasant (VAS 4/10). For the patients with fibromyalgia (n=7), data is missing as the baseline heat of 43˚C caused excessive pain.

Table 3. Quantitative sensory testing results in healthy controls, pain-free BCS, BCS with persistent pain, and patients with fibromyalgia. All data are presented as mean ± standard deviation.

		Healthy controls		Pain-free BCS			BCS pain			Fibromyalgia		
	QST parameter	Raw	Log	Raw	Log	Z-score	Raw	Log	Z-score	Raw	Log	Z-score
Tibialis anterior muscle	**PPT (kgf)**	3.60 ± 1.54	0.52 ± 0.17	4.21 ± 1.47	0.60 ± 0.14	-0.47 ± 0.85	3.67 ± 1.59	0.52 ± 0.21	0.02 ± 1.28	2.62 ± 1.56	0.36 ± 0.21	0.97 ± 1.27
	MDT (mN)	2.69 ± 2.01	0.31 ± 0.35	14.11 ± 31.83	0.72 ± 0.62	-1.18 ± 1.79	23.96 ± 28.51	1.03 ± 0.63	-2.07 ± 1.81	7.26 ± 11.45	0.56 ± 0.53	-0.71 ± 1.53
	MPT (mN)	441.26 ± 123.19	2.62 ± 0.17	423.25 ± 146.05	2.58 ± 0.23	0.23 ± 1.40	413.25 ± 146.21	2.58 ± 0.20	0.25 ± 1.23	316.53 ± 171.95	2.42 ± 0.28	1.19 ± 1.71
	WDT (˚C)	37.98 ± 2.61	1.58 ± 0.03	39.02 ± 3.81	1.59 ± 0.04	-0.37 ± 1.41	39.14 ± 3.74	1.59 ± 0.04	-0.41 ± 1.36	38.25 ± 4.09	1.58 ± 0.05	-0.05 ± 1.65
	CDT (˚C)	29.28 ± 1.31	1.47 ± 0.02	29.26 ± 1.44	1.47 ± 0.02	-0.02 ± 1.10	27.71 ± 3.78	1.44 ± 0.07	-1.45 ± 3.75	29.34 ± 1.46	1.47 ± 0.02	0.04 ± 1.13
	HPT (˚C)	45.34 ± 2.09	-	45.51 ± 2.81	-	-0.06 ± 1.34	45.41 ± 3.20	-	-0.03 ± 1.53	44.41 ± 3.33	-	0.44 ± 1.59
	CPTh (˚C)	14.95 ± 11.44	-	9.28 ± 10.50	-	-0.50 ± 0.92	14.12 ± 10.93	-	-0.07 ± 0.95	19.47 ± 10.88	-	0.39 ± 0.95
	TS (0-10)	1.59 ± 1.78	-	1.19 ± 1.15	-	-0.23 ± 0.65	2.66 ± 2.24	-	0.60 ± 1.26	2.81 ± 1.84	-	0.69 ± 1.04
Trunk	**PPT (kgf)**	1.74 ± 0.94	0.19 ± 0.22	2.65 ± 1.69	0.34 ± 0.29	-0.71 ± 1.31	1.18 ± 1.09	-0.08 ± 0.37	1.22 ± 1.68	1.48 ± 0.74	0.13 ± 0.19	0.27 ± 0.89
	MDT (mN)	1.33 ± 1.56	-0.14 ± 0.47	173.85 ± 202.16	1.63 ± 0.96	-3.71 ± 2.02	173.69 ± 221.62	1.45 ± 1.15	-3.34 ± 2.41	4.88 ± 4.90	0.43 ± 0.54	-1.18 ± 1.13
	MPT (mN)	420.33 ± 132.18	2.59 ± 0.22	408.97 ± 136.64	2.58 ± 0.17	0.02 ± 0.79	332.33 ± 159.15	2.45 ± 0.29	1.15 ± 1.22	268.58 ± 160.79	2.31 ± 0.39	0.67 ± 1.20
	WDT (˚C)	36.51 ± 2.25	1.56 ± 0.02	42.50 ± 5.52	1.62 ± 0.06	-2,57 ± 2.32	43.27 ± 5.82	1.63 ± 0.06	-2.88 ± 2.42	37.27 ± 2.59	1.57 ± 0.03	-0.35 ± 1.19
	CDT (˚C)	28.82 ± 5.44	1.42 ± 0.27	21.19 ± 10.56	1.18 ± 0.50	-0.91 ± 1.82	16.54 ± 12.83	0.90 ± 0.67	-1.94 ± 2.46	29.61 ± 1.69	1.47 ± 0.03	0.17 ± 0.10
	HPT (˚C)	43.25 ± 3.25	-	46.57 ± 3.20	-	-1.02 ± 0.98	46.72 ± 3.69	-	-1.07 ± 1.13	42.66 ± 2.79	-	0.18 ± 0.86
	CPTh (˚C)	15.49 ± 9.11	-	6.04 ± 9.84	-	-1.04 ± 1.08	5.40 ± 8.82	-	-1.11 ± 0.97	21.48 ± 8.44	-	0.66 ± 0.93

Forearm	CPM Phase A: Mean NRS (0-10)	2.90 ± 1.71 (raw)	3.50 ± 1.64 (raw)		4.07 ± 2.20 (raw)		3.41 ± 1.24 (raw)	
	CPM Phase B: Mean NRS (0-10)	2.23 ± 1.72 (raw)	2.75 ± 1.99 (raw)	-0.08 ± 0.73	3.28 ± 2.56 (raw)	-0.14 ± 1.41	2.82 ± 1.48 (raw)	0.07 ± 0.87
	Phase B - Phase A Mean NRS (0-10)	-0.66 ± 1.04 (raw)	-0.75 ± 0.76 (raw)		3.04 ± 2.25 (raw)		-0.59 ± 0.91 (raw)	

The mean original data ± SD are shown for CPTh, HPT, TS, and CPM. All other QST parameters are presented as log-transformed and raw data. The QST parameters that showed a significant ($p < 0.05$) difference between groups based on the Kruskal-Wallis test are indicated in bold.

BCS= Breast cancer survivor, PPT= Pressure pain threshold, MDT= Mechanical detection threshold, MPT= Mechanical pain threshold, WDT= Warm detection threshold, CDT= Cold detection threshold, HPT= Heat pain threshold, CPTh= Cold pain threshold, TS= Temporal summation, CPM= Conditioned pain modulation.

Table 4. Comparison of QST results between healthy controls, breast cancer survivors with and without persistent pain, and patients with fibromyalgia, using a Kruskal-Wallis test and Dunn's post hoc multiple comparisons test.

	QST Parameter	P_{KW}-value	HC - $BCS_{pain\text{-}free}$	HC - FM	HC - BCS_{pain}	$BCS_{pain\text{-}free}$ - FM	$BCS_{pain\text{-}free}$ - BCS_{pain}	BCS_{pain} - FM
			P_{bonf} (Z-statistic)	P_{bonf} (Z-statistic)	P_{bonf} (Z-statistic)	P_{bonf} (Z-statistic)	P_{bonf} (Z-statistic)	P_{bonf} (Z-statistic)
Tibialis anterior muscle	PPT	**< 0.001**	0.256 (-1.721)	**0.010** (2.939)	1.000 (-0.349)	**< 0.001** (4.660)	0.510 (1.372)	**0.003** (-3.288)
	MDT	**< 0.001**	**0.004** (-3.191)	0.109 (-2.092)	**< 0.001** (-4.965)	0.816 (1.099)	0.228 (-1.775)	**0.012** (-2.873)
	MPT	**0.010**	1.000 (0.434)	**0.007** (3.060)	1.000 (0.676)	**0.026** (2.626)	1.000 (0.241)	0.051 (-2.384)
	WDT	0.800						
	CDT	0.284						
	HPT	0.689						
	CPTh	**0.002**	0.116 (2.068)	0.267 (-1.700)	1.000 (0.352)	**< 0.001** (-3.768)	0.258 (-1.717)	0.121 (2.051)
	TS	**< 0.001**	1.000 (0.513)	**0.007** (-3.054)	0.087 (-2.185)	**0.001** (-3.567)	**0.021** (-2.698)	1.000 (0.870)
Trunk	PPT	**< 0.001**	0.072 (-2.257)	0.891 (1.043)	**0.005** (3.135)	**0.003** (3.300)	**< 0.001** (5.391)	0.109 (2.091)
	MDT	**< .001**	**< 0.001** (-6.626)	**0.022** (-2.684)	**< 0.001** (-5.937)	**< 0.001** (3.942)	1.000 (0.690)	**0.003** (-3.252)
	MPT	**< 0.001**	1.000 (0.315)	**< 0.001** (3.899)	0.080 (2.218)	**0.001** (3.585)	0.171 (1.903)	0.278 (-1.681)
	WDT	**< 0.001**	**0.001** (-4.558)	1.000 (-0.920)	**< 0.001** (-4.993)	**< 0.001** (3.638)	1.000 (-0.435)	**< 0.001** (-4.073)
	CDT	**< 0.001**	**0.001** (4.382)	1.000 (0.291)	**< 0.001** (5.282)	**< 0.001** (-4.091)	1.000 (0.900)	**< 0.001** (4.991)
	HPT	**< 0.001**	**0.001** (-3.517)	1.000 (0.697)	**< 0.001** (-3.785)	**< 0.001** (4.214)	1.000 (-0.268)	**< 0.001** (-4.482)
	CPTh	**0.002**	0.116 (2.068)	0.267 (-1.700)	1.000 (0.352)	**< 0.001** (-3.768)	0.258 (-1.717)	0.121 (2.051)

Forearm	CPM	0.051	0.061 (-2.248)	**0.040** (-2.474)	0.329 (-1.390)	0.398 (-0.263)	0.398 (0.864)	0.398 (1.114)

The mean original data ± SD are shown for CPTh, HPT, TS, and CPM. All other QST parameters were log transformed.
P_{KW} = Kruskal-Wallis p-value, $Z_{Dunn's}$ = Dunn's post hoc test z-statistic, P_{Bonf} = Bonferroni p-value. Significant p-values ($p < 0.05$) are indicated in bold.

HC= Healthy controls, $BCS_{pain\text{-}free}$= Breast cancer survivors without persistent pain, BCS_{pain}= Breast cancer survivors with persistent pain, FM= patients with fibromyalgia, BCS= Breast cancer survivor, PPT= Pressure pain threshold, MDT= Mechanical detection threshold, MPT= Mechanical pain threshold, WDT= Warm detection threshold, CDT= Cold detection threshold, HPT= Heat pain threshold, CPTh= Cold pain threshold, TS= Temporal summation, CPM= Conditioned pain modulation.

Comparison of somatosensory profiles

Somatosensory profiles using the Z-scores for both BCS groups and patients with fibromyalgia are presented in Figure 2 and 4 for the opposite tibialis anterior and trunk, respectively.

At the **opposite tibialis anterior**, no somatosensory aberrations exceeding the 95% CI were observed, except for BCS with persistent pain, showing hypoesthesia in **MDT** (Figure 2). Group comparison using the proportion of somatosensory aberrations revealed a significant difference between the groups for PPT ($p = 0.018$) (Figure 3, Table 5). Post hoc tests revealed a significant difference in hyperesthesia between the pain-free BCS group and fibromyalgia group for **PPT** (Table 5). No other significant differences across groups were found. (Table 5).

At the **trunk**, the somatosensory profiles of both BCS groups were similar for most QST parameters, overall presenting hypoesthesia in these parameters (Figure 4). Nevertheless, both groups differed in **PPT**, with the pain-free BCS showing a limited hypoesthesia and the BCS with persistent pain in contrast, showing hyperesthesia (Figure 4, Table 5). Comparing the proportions of somatosensory aberrations, a significant difference was found between the groups for all QST parameters, with the exception of **CPTh** (Figure 5, Table 5). BCS with pain showed a significantly higher proportion of hyperesthesia in **PPT** than the pain-free BCS and fibromyalgia groups ($p < 0.001$). Both BCS groups showed a similar frequency of hypoesthesia in **MDT** and were significantly different from the fibromyalgia group ($p < 0.001$). In contrast, the fibromyalgia group showed a significantly higher frequency of hyperesthesia in **MPT** compared to both BCS groups, which had similar frequencies of hyperesthesia (Table 5). Regarding the thermal thresholds (**WDT, CDT, HPT** – not **CPTh**), both BCS groups showed similar proportions of hypoesthesia, and both were significantly different from the fibromyalgia group ($p < 0.001$).

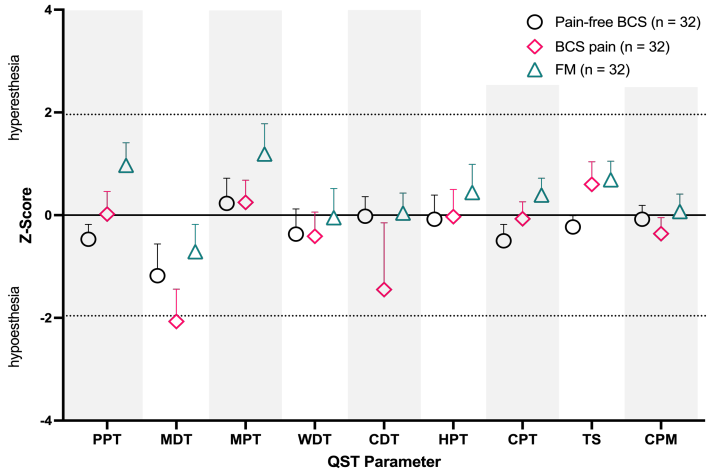

Figure 2. Quantitative sensory testing profiles of pain-free BCS, BCS with persistent pain, and patients with fibromyalgia in comparison to healthy normative data were measured at the *opposite tibialis anterior* muscle.

Presented mean Z-scores ± 95% confidence interval. Z-scores outside the 95% confidence interval of healthy control data (dotted line) were considered aberrant. Gain of function or hyperesthesia, loss of function or hypoesthesia.

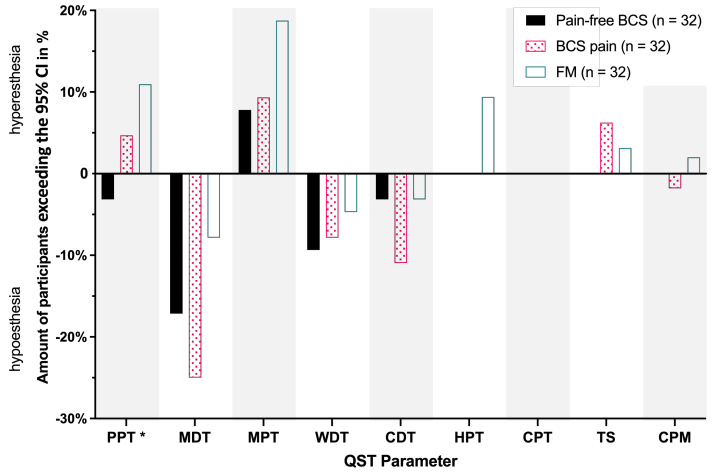

Figure 3. The frequency of QST parameters exceeding the 95% confidence interval measured at the opposite tibialis anterior muscle. Gain of function or hyperesthesia, loss of function or hypoesthesia.

** QST parameters showing a significant difference ($p < 0.05$) between groups based on the $\chi 2$ test.*

PPT= Pressure pain threshold, MDT= Mechanical detection threshold, MPT= Mechanical pain threshold, WDT= Warmth detection threshold, CDT= Cold detection threshold, HPT= Heat pain threshold, CPT= Cold pain threshold, TS= Temporal summation, CPM= Conditioned pain modulation

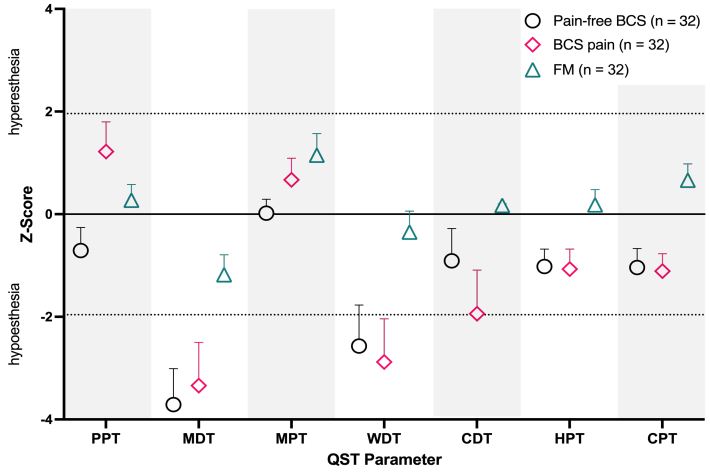

Figure 4. Quantitative sensory testing profiles of pain-free BCS, BCS with persistent pain, and patients with fibromyalgia in comparison to healthy normative data measured at the trunk.

Presented mean Z-scores ± 95% confidence interval. Z-scores outside the 95% confidence interval of healthy control data (dotted line) were considered aberrant. Gain of function or hyperesthesia, loss of function or hypoesthesia.

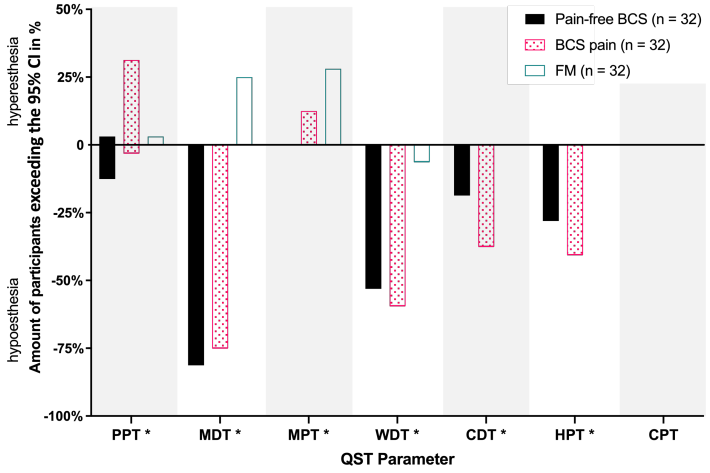

Figure 5. Frequency of QST parameters exceeding the 95% confidence interval, measured at the *trunk*. Gain of function or hyperesthesia, loss of function or hypoesthesia.

** QST parameters showing a significant difference ($p < 0.05$) between groups based on the $\chi 2$ test.*

PPT= Pressure pain threshold, MDT= Mechanical detection threshold, MPT= Mechanical pain threshold, WDT= Warmth detection threshold, CDT= Cold detection threshold, HPT= Heat pain threshold, CPT= Cold pain threshold, TS= Temporal summation, CPM= Conditioned pain modulation

Table 5. Summary of QST aberrations (e.g., hypoesthesia or loss of function, hyperesthesia or gain of function) across all groups and locations.

QST parameter		Tibialis anterior muscle			p-value χ2 value	Trunk			p-value χ2 value
		Pain-free BCS	BCS pain	FM		Pain-free BCS	BCS pain	FM	
PPT	Normal	30 (93.7%)	29 (90.6%)	23 (71.9%)	**p = 0.018**	27 (84.3%)	21[a] (65.6%)	31[a] (96.9%)	**p < 0.001**
	Gain	0[a]	3 (9.4%)	8[a] (25.0%)		1[a] (3.1%)	10[ab] (31.3%)	1[b] (3.1%)	
	Loss	2 (6.3%)	0	1 (3.1%)	χ2= 11.958	4 (12.6%)	1 (3.1%)	0	χ2= 20.624
MDT	Normal	17 (53.1%)	14[a] (43.8%)	25[a] (78.1%)	p = 0.058	6[a] (18.7%)	8[b] (25.0%)	24[ab] (75%)	**p < 0.001**
	Gain	2 (6.3%)	1 (3.1%)	1 (3.1%)		0	0	0	
	Loss	13 (40.6%)	17[a] (53.1%)	6[a] (18.8%)	χ2= 9.131	26[a] (81.3%)	24[b] (75%)	8[ab] (25.0%)	χ2= 25.437
MPT	Normal	27 (84.4%)	26 (81.3%)	20 (62.5%)	p = 0.086	32[a] (100%)	28 (87.5%)	23[a] (71.9%)	**p = 0.004**
	Gain	5 (15.6%)	6 (18.7%)	12 (37.5%)		0[a]	4 (12.5%)	9[a] (28.1%)	
	Loss	0	0	0	χ2= 4.917	0	0	0	χ2= 10.854
WDT	Normal	26 (81.3%)	27 (84.3%)	27 (84.4%)	p = 0.658	15 (46.9%)	13 (40.6%)	30 (93.7%)	**p < 0.001**
	Gain	0	0	1 (3.1%)		0	0	0	
	Loss	6 (18.7%)	5 (15.7%)	4 (12.5%)	χ2= 2.425	17[a] (53.1%)	19[b] (59.4%)	2[ab] (6.3%)	χ2= 22.563
CDT	Normal	30 (93.7%)	25 (78.1%)	30 (93.7%)	p = 0.077	26[a] (81.2%)	20[b] (62.5%)	32[ab] (100%)	**p < 0.001**
	Gain	0	0	0		0	0	0	
	Loss	2 (6.3%)	7 (21.9%)	2 (6.3%)	χ2= 5.134	6[a] (18.7%)	12[b] (37.5%)	0[ab]	χ2= 14.769
HPT	Normal	26 (81.2%)	24 (75%)	24 (75%)	p = 0.446	23[a] (71.9%)	19[b] (59.4%)	32[ab] (100%)	**p < 0.001**
	Gain	3 (9.4%)	4 (12.5%)	7 (21.9%)		0	0	0	
	Loss	3 (9.4%)	4 (12.5%)	1 (3.1%)	χ2= 3.715	9[a] (28.1%)	13[b] (40.6%)	0[ab]	χ2= 15.686
CPTh	Normal	32 (100%)	32 (100%)	32 (100%)		32 (100%)	32 (100%)	32 (100%)	
	Gain	0	0	0	-	0	0	0	-
	Loss	0	0	0		0	0	0	

Table 5. Continued

QST parameter		Tibialis anterior muscle			p-value χ2 value	Trunk			p-value χ2 value
		Pain-free BCS	BCS pain	FM		Pain-free BCS	BCS pain	FM	
TS	Normal	32 (100%)	28 (87.5%)	30 (93.7%)	p = 0.118				
	Gain	0	4 (12.5%)	2 (6.3%)					
	Loss	0	0	0	χ2= 4.267				
CPM	Normal	27 (100%)	27 (96.4%)	24 (96%)	p = 0.649				
	Gain	0	0	1 (4%)					
	Loss	0	1 (3.6%)	0	χ2= 4.202				

-values represent comparisons between the three groups using the χ2 test. Post hoc tests: a, b, c: same letters marking the values of categories within a given row denote mutually statistically different groups. Significant p-values ($p < 0.05$) are indicated in bold.

PPT= Pressure pain threshold, MDT= Mechanical detection threshold, MPT= Mechanical pain threshold, WDT= Warmth detection threshold, CDT= Cold detection threshold, HPT= Heat pain threshold, CPTh= Cold pain threshold, TS= Temporal summation, CPM= Conditioned pain modulation.

Discussion

This study aimed to compare QST data and describe somatosensory profiles between BCS with and without persistent pain by comparing them to each other and to reference data from healthy controls (i.e., negative control group) and patients with fibromyalgia (i.e., positive control group).

Looking at the comparison of QST parameters, our study found that BCS with persistent pain had significantly lower **PPTs** (hyperesthesia: hyperalgesia) at the *trunk* compared to healthy controls and pain-free BCS. BCS with and without persistent pain had significantly higher **MDTs** (hypoesthesia) at both the *opposite tibialis anterior* muscle and *trunk* compared to healthy controls and at the *trunk* compared to the fibromyalgia group. Regarding **MPT**, patients with FM showed significantly higher thresholds than healthy controls and pain-free BCS. Thermal thresholds (**WDT**, **CDT**, **and HPT**) measured at the *trunk* were significantly different in BCS with and without persistent pain compared to healthy controls and patients with fibromyalgia, indicating hypoesthesia for thermal stimulation. Regarding **CPTh**, only the pain-free BCS and patients with fibromyalgia differed significantly from each other at both locations, with the pain-free BCS showing lower **CPThs**. We did not find any significant differences in **CPM** across the four groups, however, BCS with persistent pain showed a significantly higher score for TS of pain than pain-free BCS. When comparing somatosensory profiles and the proportion of somatosensory aberrations at the *opposite tibialis anterior*, no differences were found between both BCS groups. Patients with fibromyalgia showed a higher proportion of aberrant hyperesthesia (hyperalgesia) in **PPT**. At the *trunk*, BCS with and without persistent pain in general showed similar hypoesthesia for most QST parameters, apart from **PPT**. BCS with persistent pain exhibit a higher proportion of hyperesthesia (hyperalgesia) in **PPT** than pain-free BCS. Age and psychosocial burden was significantly different between groups. Sensitivity analyses however did not find a significant influence of age or psychosocial burden on QST outcomes. Differences in

QST outcomes between groups are unlikely to be attributed to variations in age or psychosocial burden.

Our findings are in line with previous research and suggest the presence of aberrant peripheral nociceptive processing at the *trunk*, affirming our hypothesis.[4,6,7] Changes such as the presence of hypoesthesia indicate a lesion in the peripheral somatosensory nervous system.[36] The underlying cause of hypoesthesia in the trunk area remains unclear, with previous research failing to ascribe the handling of the intercostobrachial nerve during axillary lymph node dissection as potential a contributor.[6] In the trunk area, nerves such as the long thoracic nerve, the lateral cutaneous branches of the intercostal nerves and the thoracodorsal nerve are also susceptible to peri- and postoperative injury.[37] In our study, BCS with persistent pain exhibited higher proportions of aberrant hyperesthesia in **PPT** (i.e., lowered PPT, hyperalgesia) at the treated area than in all other groups. These findings are in line with previous studies and suggest the presence of hyperalgesia or allodynia at the treated area of the breast.[4,6] Both BCS groups had an equal amount of ALND, whereas a lower percentage of BCS with persistent pain received a mastectomy (84.4%) in comparison to the pain-free group (62.5%). Previous studies have demonstrated that BCS who received a mastectomy presented with lower PPT, and more frequently demonstrated persistent pain in the area of the breast.[7,38] In contrast to other studies, **PPT** at the opposite tibialis anterior did not significantly differ from the other groups, suggesting absence of widespread mechanical hyperalgesia.[6,39] Further prospective studies using QST are needed to understand the causal factors of these sensory changes and pain in BCS.

Besides aberrations in the peripheral somatosensory nervous system, we explored whether BCS also exert impairments in the inhibitory descending pathways or exert increased facilitation of endogenous nociceptive pathways. Previous research indicates that impairments in the central processing of nociceptive signals are present in BCS.[4,5,8] These studies have solely compared BCS with pain to pain-free BCS, without including healthy controls for comparison.[4,5,8] First, we did not find any

significant differences in **CPM** across the four groups. Edwards et al., who performed a CPM paradigm using a cold pressor test in BCS with and without persistent pain found decrements in CPM in BCS that developed pain after cancer treatment, decreased inhibition of nociceptive signals by descending pathways.[8] The fact that we did not find any changes in CPM in the current study could be due to limitations in our CPM methodology (i.e., modality of conditioning stimulus, lack of spatial summation, a two-thermodes protocol instead of a single stimulus protocol[31]), simplified responder analysis based on Z-scoring instead of the methodology suggested by Kennedy et al. [40], and the amount of missing data due to pain or the absence of unpleasantness during testing. These limitations might be debatable, as we found a significant difference between the healthy control group and the fibromyalgia group, suggesting that our CPM methodology is able to detect decreased inhibition of nociceptive signals. Second, regarding **TS** of pain measured at the opposite tibialis anterior muscle, BCS with persistent pain showed a significantly higher score for TS of pain than pain-free BCS. However, when comparing somatosensory profiles and the proportion of somatosensory aberrations, we found no significant differences between the groups. Previous research on TS of pain measured at remote locations is inconclusive. Edwards et al. found significant differences between BCS with and without pain, whereas Schreiber et al. found no differences.[8,9] By using the opposite tibialis anterior muscle as a remote test location for TS of pain, we aimed to provide evidence for widespread increased responsiveness of nociceptive neurons.[41] Even though we could not acknowledge the presence of increased facilitation of endogenous nociceptive pathways in BCS with persistent pain, we did find that BCS with persistent pain exhibited significantly higher PCS scores, higher DASS-21 scores, and higher CSI scores than healthy controls and pain-free BCS. BCS with persistent pain had similar scores to those of patients with fibromyalgia, with the exception that patients with fibromyalgia showed even worse CSI scores. These psychosocial factors are

associated with changes in the central somatosensory nervous system and persistent pain following breast cancer surgery.[9,26,42]

The results of our study add to the body of evidence that BCS exert somatosensory aberrations in the treated area. These results acknowledge earlier research in BCS with and without pain and also indicates that further research into the assessment of central somatosensory processing of nociceptive signals in BCS remains needed.[4–10]

Strengths and limitations

This study offers several strengths, including the presence of healthy controls acting as a negative control group and patients with fibromyalgia acting as a positive control group. This is the first study of its kind to incorporate both a negative and positive control group. Furthermore, the use of two measurements locations, made it possible to evaluate nociceptive processing within the peripheral and central somatosensory nervous system, creating a comprehensive sensory profile.

The limitations of this study include a lack of control over pain medication use. Participants with pain self-reported the use of pain medication but were not asked to stop their medication prior to testing. Tricyclic antidepressants, gabapentinoids or serotonin and norepinephrine reuptake inhibitors (SNRIs) may influence QST outcomes. Second, due to limited access and time constraints, we deviated from the German Research Network on Neuropathic Pain (DFNS) QST protocol regarding the MPT and TS.[13] Instead of the recommended pinprick stimulation, we used von Frey monofilaments to assess MPT. This deviation in MPT methodology makes it difficult to compare the results with those of other studies. Additionally, only one train of TS was performed using the spherical end of a von Frey filament rather than pinprick stimulation, which could have limited the difference in scores between the pain and pain-free participants. Moreover, the study did not assess other QST parameters, such as mechanical pain sensitivity and thermal sensory limen, owing to limited access to material and time.[13] Third, the overall small sample size and relative youth

of the healthy controls and patients with fibromyalgia compared with the BCS cohorts is a limitation of this study. As healthy controls tend to exert a high variability in QST a bigger sample size would increase reliability.[13] We believe that the use of conservative statistical measures, such as non-parametric testing and correcting for multiple testing, took these limitations into account. Finally, we did not perform an a priori sample size calculation.

Conclusion

Our study found differences and similarities in the somatosensory profiles of BCS with and without persistent pain compared to a healthy control group and patients with fibromyalgia. These findings further confirm that BCS with pain exert impairments in peripheral nociceptive processing, such as hypoesthesia for thermal and mechanical stimuli, hyperesthesia (hyperalgesia) to pressure, and furthermore increased psychosocial burden. BCS with pain also showed increased facilitation of nociceptive processing, similar to patients with FM. Even though our findings are in line with those of previous research, further longitudinal research is needed to improve our understanding of somatosensory functioning in relation to pain in BCS. Improved understanding of this relationship can contribute to the improvement of pain management strategies for BCS dealing with persistent pain.

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Chapter 3

Concurrent validity of dynamic bedside quantitative sensory testing paradigms in breast cancer survivors with persistent pain.

Concurrent validity of dynamic bedside quantitative sensory testing paradigms in breast cancer survivors with persistent pain.

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Abstract

Background: Studies on the concurrent validity of clinically applicable testing protocols for conditioned pain modulation (CPM) and temporal summation (TS) in breast cancer survivors (BCS) with persistent pain are lacking.

Objectives: This study investigated the concurrent validity of two bedside protocols for CPM and TS in comparison to a respective reference protocol. The participants' preferences for bedside CPM and TS protocols were assessed.

Methods: Thirty BCS experiencing persistent pain were included in this study. For CPM, a cold pressor test (CPTe) and blood pressure cuff (BPC) were used as conditioning stimulus. The test stimulus was elicited in parallel by pressure pain threshold after 45 and 90 seconds of conditioning at the lower limb. TS was elicited using a von Frey monofilament (256 mN) and an algometer at the affected upper limb and the opposite lower limb. The CPM reference test consisted of parallel heat stimuli at the forearms using the Advanced Thermosensory Stimulator. The TS reference test consisted of heat stimuli at the affected upper limb, and opposite lower limb.

Results: The two bedside CPM protocols were strongly correlated ($r=0.787$-0.939, $p<0.005$). A strong correlation was found between the BPC protocol and reference test using the relative effect magnitude ($r=0.541$-0.555, $p<0.005$). The bedside TS protocols were moderately correlated with each other only at the lower limb using absolute change scores ($r=0.455$, $p=0.012$). No significant correlation was found between the bedside and reference TS protocols.

Conclusion: Bedside protocols for CPM and TS are significantly and strongly or moderately correlated with each other, and thus interchangeable. Clinicians are able to choose which bedside protocol they utilize; however, participants preferred the use of a BPC and algometer for the evaluation of CPM and TS.

Key words: Breast cancer survivor, cancer-related pain, quantitative sensory testing

Introduction

Breast cancer remains the most prevalent cancer type (11.7%) with 2.3 million new cases reported worldwide in 2020.[1] Breast cancer survivors (BCS) can experience a myriad of side-effects of cancer treatment.[2] Over one-third of women (35%) experience persistent pain, of whom one in four (24%) experience moderate-to-severe pain.[3] These symptoms can have a significant adverse impact on emotional and physical functioning and quality of life.[2]

Persistent pain is often related to a dysfunction of the somatosensory system.[4] Aberrations in central somatosensory functioning can be evaluated using dynamic quantitative sensory testing (QST), such as conditioned pain modulation (CPM) and temporal summation (TS).[5] CPM relates to the reduction of pain intensity for a test stimulus after or during the application of a conditioning stimulus to a different part of the body. In doing so, CPM evaluates the endogenous inhibitory descending pathways.[6] TS is a psychophysical measurement in which "a high frequency of action potentials in the presynaptic neuron elicits postsynaptic potentials that overlap and summate with each other", thereby evaluating the endogenous facilitatory nociceptive pathways (e.g., TS of pain).[7,8] Previous studies in persistent pain after breast cancer treatment reported decreased CPM effects and presence of exaggerated TS of pain.[9,10] Several experimental methods for CPM and TS have been investigated in patients with chronic musculoskeletal pain[11,12], neuropathic pain[13,14], osteoarthritis[15] and in healthy individuals[16]. These studies have used either sophisticated laboratory equipment or simplified bedside alternatives, defined as bedside tests. Previous studies investigating CPM and TS in BCS have primarily used laboratory-based protocols with computer-controlled thermode systems or computer-controlled cuff algometry.[10,17] Although these protocols are considered the gold standard because of their standardization and control of stimuli, they are mostly unfeasible for use in clinical practice owing to cost, inaccessibility, and required training. Since assessing the somatosensory system and its function is

suggested to improve pain management, research into bedside QST methods is needed warranted.[18–20]

Currently, bedside tests for the assessment of CPM and TS in clinical practice exist, but they have not been investigated in a breast cancer population nor have their concurrent validity, which refers to their ability to produce consistent results when compared to a gold standard protocol, been determined.[11,14,15,20] In addition, patients were never involved in the development of bedside QST protocols even though they are at the receiving end and can provide valuable information concerning the application of such protocols in clinical practice. Therefore, aim of this study was to investigate the concurrent validity of two bedside protocols for CPM and TS in BCS experiencing persistent pain by comparing them with each other and with a laboratory-based reference test. Furthermore, participants' preferences for bedside CPM and TS protocols were assessed.

Methods

Participants

Participants were recruited between November 2020 and August 2022 from a cohort of cancer survivors participating in a larger cross-sectional study at the University of Leuven and University of Antwerp. This larger study investigated different mechanistic pain descriptors using different assessment methods in cancer survivors with pain (clinicaltrial.gov NCT03981809) and received approval from the Ethical Committee of the University Hospitals Leuven (s62584) and the University Hospital of Antwerp (B322201940289). All patients provided written informed consent prior to enrollment. The study is reported following the Strengthening the Reporting of Observational studies in Epidemiology (STROBE) statement.[21]

To be eligible for inclusion, women aged ≥ 18 years had to be treated for primary breast cancer at least three months ago and be in complete remission. Ongoing hormonal treatment and targeted immunotherapy were permitted. BCS experiencing persistent pain needed to report mean pain intensity during activity ≥

3/10 on the numeric rating scale (NRS) during the past week, with 0 indicating no pain and 10 indicating the worst pain imaginable.[22,23] The NRS was conducted via telephone prior to inclusion. Persistent pain related to breast cancer treatment was defined based on the location and timing of onset. Pain in the area of the chest, lateral trunk, axilla, arm, or shoulder was considered to be related to breast cancer treatment if it occurred concurrently or after its completion. Patients were excluded if they had (1) any active metastasis, (2) palliative status, (3) cancer recurrence, (4) bilateral cancer, (5) pregnancy, or (6) inability to speak and read Dutch. Participants were recruited via the oncology departments of University Hospitals Leuven and University Hospital Antwerp.

Study design

For each participant, a reference test and two bedside alternatives for both TS and CPM were performed. The measurements were performed in a quiet room with an approximate temperature of 21–23 °C with the participant in a seated position. An overview of these protocols is shown in Figure 1. Between each test, an average wash-out period of at least two minutes was foreseen.[24] The order of testing was chosen to minimize overlap between tests, maximize the washout period, and improve practicality and time needed to perform the whole protocol.

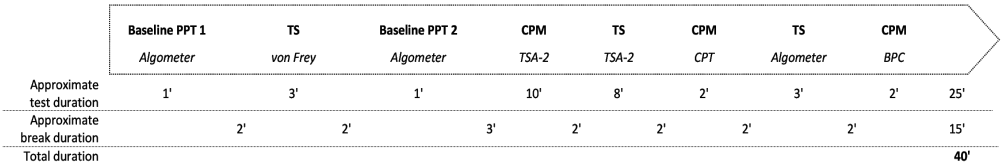

Figure 1. Measurement protocol. PPT= pressure pain threshold, TS= Temporal Summation, CPM= Conditioned pain modulation, CPTe= Cold pressor test, BPC= Blood pressure cuff, TSA-2= Advanced Thermosensory Stimulator. The duration is reported in minutes (').

Conditioned pain modulation protocols

1. Conditioned pain modulation reference test

The reference CPM protocol was performed using the Advanced Thermosensory Stimulator TSA-2 (Medoc, Ramat Yishai, Israel). First, the intensity of the stimulus was individualized for each participant. A Peltier 30 × 30 mm contact thermode was applied on the volar side of the unaffected forearm.[25,26] The temperature required to evoke an unpleasant sensation with a rating of 4 on the 0-10 NRS was determined by administering a series of heat stimuli to the unaffected forearm (Pain4). During the first stimulation, the temperature increased to 43 °C, starting from a baseline temperature of 32 °C. The temperature increased at a rate of 2 °C/s and decreased at a rate of 1 °C/s. After each stimulus, participants were asked to verbally rate the intensity of pain using the NRS. If a score above or below 4/10 on the NRS was given, the temperature of the next stimulation was decreased or increased by 1 °C. A maximum of five stimulations were administered in search of the Pain4 temperature. The minimum and maximum temperatures of the test stimulus were 39 °C and 46 °C, respectively. After determining the Pain4 test stimulus, a parallel CPM paradigm was introduced. The Pain4 test stimulus was administered to the volar side of the affected forearm for 45 seconds. Participants were asked to verbally rate the intensity of the test stimulus at 10, 20, 30, and 40 seconds using a 0-10 NRS. A 120 second break followed, after which the conditioning stimulus was administered to the volar side of the unaffected forearm for 65 seconds. The conditioning stimulus was set 0.5 °C warmer than the Pain4 test stimulus. Twenty seconds after applying the conditioning stimulus, the Pain4 test stimulus was applied in parallel to the volar side of the affected forearm. Verbal ratings of pain intensity for the affected forearm were obtained at 10 seconds, 20 seconds, 30 seconds, and 40 seconds of stimulation (0-10 NRS).

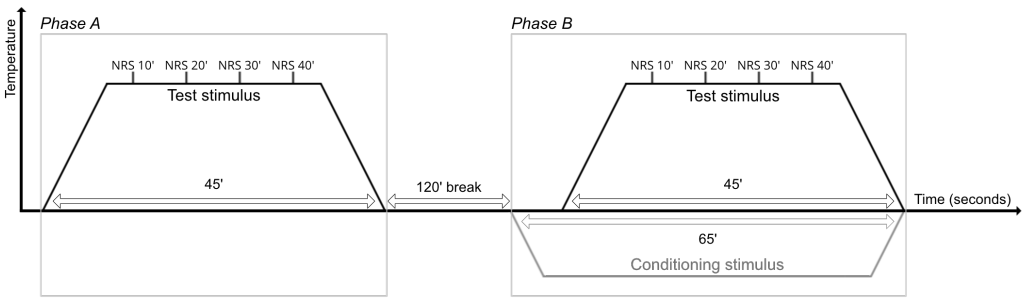

Figure 2. Schematic overview of the reference CPM protocol sequence using the TSA-2. NRS= Numeric rating scale.
Phase A: application of Pain4 heat on the affected forearm, Phase B: application of Pain4 + 0.5˚C heat (conditioning stimulus) on the non-affected forearm for 65 seconds and concurrently the application of Pain4 heat (test stimulus) on the affected forearm for 45 seconds. NRS= Numeric rating scale.

2. Conditioned pain modulation bedside test 1: cold pressor test

Pressure pain threshold (PPT) was used as a test stimulus at the upper part of the tibialis anterior muscle opposite to the affected side. First, a baseline PPT without the presence of a conditioning stimulus was determined using a digital pressure algometer (Wagner FDX, Greenwich CT, USA) with a flat round rubber tip and probe area of 1 cm^2. The PPT was defined as the amount of pressure at which the sensation of pressure was first perceived as unpleasant with a rating of 4 on a 0-10 NRS, and was determined by two series of ascending pressure at a rate of approximately 0.1 kgf/s.[27] The final threshold was the arithmetic mean of two trials (kgf).[10] Participants were blinded to the algometer's screen, making them uninformed of the imposed pressure.[28,29]

The conditioning stimulus used in this first bedside CPM protocol consisted of a cold pressor test (CPTe) in which the participants' unaffected hand was submerged in a cold-water bath of approximately 12 °C. Tap water was brought to this target temperature by cooling for approximately 45 minutes using simple household cold packs. The participants' hand was then placed in a cold water bath until the wrist crease. After 30 seconds participants were asked to verbally rate the intensity of pain

in the hand on a 0-10 NRS. PPT was performed at 45 and 90 seconds respectively, providing two PPT outcomes during the presence of a conditioning stimulus. Ascending pressure at a rate of 0.1 kgf/s was used until the participant verbally indicated that the pressure was unpleasant (4 on the 0-10 NRS).[27]

3. Conditioned pain modulation bedside test 2: blood pressure cuff occlusion

This protocol consisted of the same PPT test stimulus as the bedside CPM test with CPTe. For the second bedside CPM test, a single, 8,5-cm-wide chamber blood pressure cuff (BPC) (Boso Profitest, Jungingen, Germany) exerted pressure on the unaffected arm, 2 cm superior to the cubital fossa. The occlusion cuff was inflated manually by the examiner via hand squeeze (approximately 20 mmHg per squeeze). After each squeeze, the participant was asked to rate the intensity of the pain on a 0-10 NRS. The occlusion cuff was inflated until the participant experienced 5/10 on the NRS for pain or until 220 mmHg was exerted by the BPC. Arm ischemia was not intended to happen.[30] PPT measurements were performed at the same timepoints (45 and 90 seconds) and rate of pressure as the CPM protocol using CPTe.[8]

Temporal summation protocols

1. Temporal summation reference test

TS was measured at the most painful site (chest, lateral trunk, axilla, arm, or shoulder) and the upper part of the opposite tibialis anterior muscle by applying a series of heat stimuli utilizing the TSA-2 (Medoc, Ramat Yishai, Israel) with a 30 × 30 mm Peltier thermode. The intensity of the heat stimuli was individualized for each subject using the Pain4 temperature assessed in the CPM reference protocol. The participants received a series of 30 heat stimuli, starting from a baseline temperature of 38 °C. The peak temperature was set at an individualized Pain4 temperature. Thermal TS was executed with an increase in temperature at a rate of 13 °C/s, 0.8 seconds at peak stimulus, and a return rate of 13 °C/s to baseline temperature. The inter-stimulus interval was set to 1 second.[31] Participants were asked to verbally rate

the intensity of pain immediately after the first and last heat stimulus on the 0-10 NRS.[32]

2. Temporal summation bedside test 1: von Frey monofilament

The TS was measured at the same locations by applying a series of stimuli using a von Frey monofilament with a stimulation force of 256mN (Optihair2-Set, Marstock Nervtest, Germany). After the first stimulus, a series of stimuli was delivered for 30 seconds at a rate of 1 stimulation/s. Participants were asked to score the pain after the first stimulus on a 0-10 NRS and immediately after the series of stimuli.[26]

3. Temporal summation bedside test 2: algometer

For the second bedside TS test, a digital pressure algometer with a stimulation frequency of 1 kgf/s (Wagner FDX, Greenwich, CT, USA) was used at both locations. Amounts of repetitions, and instructions to the patient were the same as the bedside TS test with the von Frey monofilament.[8,33]

Patients' experience and preference

After completion of the testing protocol, participants were given a purpose-designed questionnaire regarding their experiences and bedside test preferences. The questionnaire contained two questions (yes or no): (1) testing was comfortable, and (2) instructions were clear. In addition, participants were asked to indicate their preference for one of the bedside protocols for CPM and TS at the most painful site and the opposite tibialis anterior muscle (Supplementary Methods S1).

Statistical analysis

Data analysis was performed using R statistical software version 3.6.2.[34] Normal distribution of the data was checked by visual inspection of the QQ plots and a Shapiro-Wilk test.[35] Descriptive statistics for non-normally distributed and continuous variables are presented as median and interquartile range (IQR), and normally distributed variables are presented as means and standard deviations (SD). Categorical variables were presented as frequencies and proportions (%).

First, concurrent validity between the different bedside and reference CPM and TS protocols was examined by calculating correlations between the test effects of the different protocols, that is, the absolute and relative CPM or TS effects at different time points. Using the NRS for pain, zero values were present, therefore 0.01 was added making relative calculations possible and allowing an additional approach to explore validity of the different protocols.[36] Spearman's rank (rho) coefficients were calculated [37,38] and interpreted as follows: < 0.3 weak, 0.3-0.5 moderate, 0.5-0.7 good and > 0.7 very good.[39] Correlation coefficient of > 0.7 are considered to show sufficient evidence of validity.[40]

Second, concurrent validity was explored by comparing the proportion of responders to the different test protocols using Fisher's exact test based on absolute or relative effect magnitude. Regarding the CPM protocol, we calculated a meaningful CPM effect by determining the ± 2 SEm (standard error of measurement) method proposed by Kennedy et al..[41] For the reference CPM protocol, the SEm was calculated using the NRS scores at the different time points during Phase A (Figure 2): *SEm = (pooled SD of NRS scores* during *Phase A) * √(1-ICC)*. The interclass correlation coefficient (ICC) was calculated from the mean NRS scores during *Phase A*.[41] Using the +/- 2SEm method, participants were classified into three groups of responders: (1) anti-nociceptive = decrease in NRS of at least 2 SEm during *Phase B*; (2)pro-nociceptive = increase in NRS during *Phase B of at least 2 SEm*; and (3) non-response = no change in NRS or change smaller than 2 SEm. We applied the same methodology for bedside CPM protocols, using baseline PPT values instead of NRS as the outcome. For these bedside protocols, the baseline PPT values were logarithmically transformed to normalize the data distribution, after which the ICC was calculated. Using the ± 2 SEm method for bedside protocols, participants were grouped similarly (anti-nociceptive = increase in overall PPT at 45s and 90s of at least 2 SEm, pro-nociceptive = decrease in PPT at 45s and 90s of at least 2 SEm, and non-response = no change in PPT or change smaller than 2 SEm). For all CPM protocols, the ± 2 SEm method was used for both absolute and relative effect magnitudes in

the CPM. The relative effect magnitude was calculated by dividing the 2 SEm by the median baseline PPT or NRS scores during Phase A.

Regarding TS, defining responders is less straightforward because the cutoff values are less clearly described for the presence of exaggerated TS of pain. We therefore used the minimal clinically important difference of more than 2 points on the NRS for absolute change and 33% for the relative change to determine the presence or absence of exaggerated TS of pain as recommend by the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT group).[42–44]

Correction for multiple testing was performed using a Bonferroni correction by dividing the alpha (0.05) by the number of tests performed. Patient experiences and preferences were summarized descriptively.

Results

Subjects

A total of 30 consecutive participants were included, with a median (IQR) age of 52 (10.5) years. Patient characteristics are summarized in Table 1. A comprehensive overview of the patient characteristics is provided in Supplementary Results S1.

Table 1. Demographic characteristics of the participants (frequency (%) unless specified otherwise) (n = 30)

Age (years), Median (IQR)	52.0 (10.5) [44-70]
BMI (kg/m²), Median (IQR)	25.1 (7.0) [17-34.4]
Pain intensity, Median (IQR)	
- VAS at rest	31.0 (29.0) [3-80]
- VAS during activity	43.5 (34.3) [8-80]
- Maximum VAS	71.0 (15.8) [50-100]
- Minimum VAS	23.0 (20.8) [0-65]
- Mean VAS	45.5 (26.8) [0-88]
Location of the most painful site	
- Chest and lateral trunk	11 (36.7%)
- Arm, shoulder, and axilla	12 (40.0%)
- Chest, lateral trunk, arm, shoulder, and axilla	7 (23.3%)

Table 1. Continued

Pain medication: type, n (%)	
- Tricyclic antidepressants, gabapentinoids or SNRI	2 (6.7%)
- NSAID, acetaminophen, or mild opioid	16 (53.3%)
- No medication	12 (40%)

NRS= Numeric rating scale, IQR= Interquartile range, VAS= Visual analogue scale, SNRI= Serotonin and norepinephrine reuptake inhibitors, NSAID= Non-steroidal anti-inflammatory drugs

Conditioned pain modulation

One participant was unable to perform the reference CPM protocol because of pain during the application of the conditioning stimulus (46.5 °C). Another participant was not able to keep her hand submerged for 90 seconds during the CPTe due to intolerable pain, and one participant did not experience unpleasant pressure during the BPC test and reached the BPC's limits. The CPM data are listed in Table 2.

Table 2. Conditioned pain modulation (CPM) data. The median (IQR) is provided, unless mentioned otherwise.

			CPM CPTe	**CPM BPC**	**CPM TSA-2**
		Temperature test stimulus (˚C)	-	-	42.00 (2.00)
		Pooled SD	2.23	2.23	2.05
		2 SEm	1.30 (47.6%)	1.30 (47.6%)	1.74 (43.5%)
		NRS during Phase A	-	-	4.00 (2.50)
		NRS during Phase B	-	-	3.00 (2.00)
		Cuff pressure (mmHg)	-	130.00 (40.00)	-
		NRS 0-10 Pain H_20	4.00 (3.75)	-	-
		Baseline PPT (kg/cm^2)	2.73 (2.59)	2.73 (2.59)	-
		PPT with conditioning at 45' (kg/cm^2)	3.62 (3.37)	3.40 (2.49)	-
		PPT with conditioning at 90' (kg/cm^2)	3.29 (3.45)	2.98 (0.28)	-
Absolute CPM effect		Reference test (NRS)	-	-	-1.00 (1.00) (n=29)
		Bedside test at 45' (kg/cm^2)	+0.29 (1.87) (n=30)	+0.27 (2.29) (n=29)	-
		Bedside test at 90' (kg/cm^2)	+0.27 (2.19) (n=29)	+0.04 (2.31) (n=29)	-
	Responder analysis n(%)	Pro-nociceptive 45'	4 (13.3%)	5 (17.2%)	1 (3.4%)
		90'	4 (13.8%)	6 (20.7%)	
		Anti-nociceptive 45'	9 (30.0%)	9 (31.0%)	4 (13.8%)
		90'	8 (27.6%)	8 (27.6%)	
		Non-responder 45'	17 (56.7%)	15 (51.7%)	24 (82.8%)
		90'	17 (58.6%)	15 (51.7%)	

Table 2. Continued

Relative CPM effect		Reference test (NRS)	-	-	0.78 (0.33) (n=29)
		Bedside test at 45' (kg/cm²)	+1.14 (0.71) (n=30)	+1.07 (0.73) (n=29)	-
		Bedside test at 90' (kg/cm²)	+1.15 (0.82) (n=29)	+1.02 (0.79) (n=29)	-
	Responder analysis n(%)	Pro-nociceptive 45'	2 (6.7%)	3 (10.3%)	4 (13.8%)
		90'	2 (6.9%)	2 (6.9%)	
		Anti-nociceptive 45'	11 (36.7%)	9 (31.0%)	3 (10.3%)
		90'	9 (31.0%)	8 (27.6%)	
		Non-responder 45'	17 (56.7%)	17 (58.6%)	22 (75.9%)
		90'	18 (62.1%)	19 (65.5%)	

CPM= Conditioned pain modulation, CPTe= Cold pressor test, BPC= Blood pressure cuff occlusion, TSA-2= Advanced Thermosensory Stimulator, PPT= Pressure pain threshold, NRS= Numeric rating scale, SD= Standard deviation. Pooled SD of NRS or PPT during test stimulus are given for the calculation of 2 SEm: *SEm = (pooled SD of NRS scores* during *Phase A) * √(1-ICC)*.

The correlations between CPM protocols are presented in Table 3. The bedside CPM protocols were significantly and strongly correlated at each time point, using both absolute and relative CPM effects (Table 3). No other significant correlations were found after correction for multiple testing.

Table 3. Correlation (Spearman's rho) between CPM protocols using *absolute* and *relative* CPM effects.

		Absolute CPM effect				*Relative* CPM effect			
		BPC 90	**CPTe 45**	**CPTe 90**	**TSA-2**	**BPC 90**	**CPTe 45**	**CPTe 90**	**TSA-2**
BPC 45	p-value	**< 0.005**	**< 0.005**	**< 0.005**	0.145	**< 0.005**	**< 0.005**	**< 0.005**	0.119
	rho	**0.910†**	**0.877†**	**0.822†**	0.283	**0.939†**	**0.839†**	**0.795†**	0.301
	n		29	28	28		29	28	28
BPC 90	p-value		**< 0.005**	**< 0.005**	0.0325*		**< 0.005**	**< 0.005**	0.041
	rho		**0.840†**	**0.888†**	0.4051		**0.860†**	**0.812†**	0.389
	n		29	28	28		29	28	28
CPTe 45	p-value		1	**< 0.005**	0.1981		1	**< 0.005**	0.134
	rho		1	**0.787†**	0.2461		1	**0.856†**	0.285
	n			29	29			29	29
CPTe 90	p-value			1	0.233			1	0.395
	rho			1	0.233			1	0.167
	n				28				28

CPM= Conditioned pain modulation, CPTe= Cold pressor test, BPC= Blood pressure cuff occlusion, TSA-2= Advanced Thermosensory Stimulator; * $p < 0.05$; †p-value < Bonferroni corrected threshold: 0.05 / 10 = 0.005

Second, 2 SEm values were calculated to explore meaningful CPM effects. The 2 SEm for the reference CPM protocol was 1.74 (43.5%) on the NRS. The 2 SEm for the bedside CPM protocols using baseline PPT was 1.30 (47.6%) kg/cm^2 (Table 2). The proportions of BCS with anti-nociceptive, pro-nociceptive, and no response are shown in Table 2, while the statistical comparison of these frequencies between test protocols is shown in Table 4. Fisher's exact tests showed no significant differences between the proportions of CPM responses with regard to all CPM protocols using either absolute or relative effect magnitudes, indicating good concurrent validity (Table 4).

Temporal summation

Missing data were highest for the bedside TS protocol with the algometer at the most painful site (n=11). Eleven participants were unable to withstand a pressure of 1 kgf/cm^2 at this location due to excessive pain. In addition, two and three participants declined TS with the von Frey monofilament and TSA-2, respectively, as they expected a very painful reaction at the most painful site (Table 5).

Table 4. Comparison (Fisher's exact test) of the proportion of responders between the different CPM protocols.

		Absolute CPM effect			*Relative* CPM effect		
		CPTe 45	**CPTe 90**	**TSA2**	**CPTe 45**	**CPTe 90**	**TSA-2**
BPC 45	p-value	0.850	1	0.218	0.938	0.878	0.056
	n	29	28	28	29	28	28
BPC 90	p-value	0.834	1	0.245	0.827	0.827	*0.035**
	n	29	28	28	29	28	28
CPTe 45	p-value			0.058			0.112
	n			29			29
CPTe 90	p-value			0.109			0.131
	n			28			28

CPM= Conditioned pain modulation, CPTe= Cold pressor test, BPC= Blood pressure cuff occlusion, TSA-2= Advanced Thermosensory Stimulator; * $p < 0.05$; †p-value Bonferroni corrected threshold: 0.05 / 10 = 0.005

The presence of exaggerated TS of pain was highest when the stimulus was administered with the von Frey monofilament (36.7-39.3% for absolute NRS change, 70.0-75.0% for relative NRS change) (Table 5). TS remained modest when it was

applied with the TSA-2 (0-3.7% for absolute NRS change, 3.3-3.7% for relative NRS change) (Table 5).

No correlation was found between the reference TS protocol and bedside TS protocols at the most painful site or the opposite tibialis anterior muscle (Table 6). A significant and moderate correlation was found between the two bedside TS tests (von Frey monofilament versus algometer) at the tibialis anterior muscle using the absolute (p = 0.012, rho = 0.455) and relative changes (p = 0.039, rho = 0.379) in the NRS (Table 6). However, corrected for multiple testing, the p-value calculated using the relative change in NRS exceeded the Bonferroni adjusted significance threshold, indicating insignificant concurrent validity.

Table 5. Temporal summation data. Median (IQR) unless mentioned otherwise

	von Frey		**Algometer**		**TSA-2**	
	MPS (n=28)	TAM (n=30)	MPS (n=19)	TAM (n=30)	MPS (n=27)	TAM (n=30)
NRS (0-10) *first stimulus*	2.50 (3.00)	2.00 (3.75)	1.00 (2.00)	0.00 (2.00)	5.00 (3.00)	4.00 (2.75)
NRS (0-10) *last stimulus*	5.50 (3.00)	4.00 (3.75)	3.00 (3.00)	1.00 (3.75)	2.00 (4.00)	2.00 (375)
Absolute change [Exaggerated TS of pain %]	2.00 (3.00) [39.3%]	2.00 (2.00) [36.7%]	1.00 (2.50) [31.6%]	0.00 (1.75) [20.0%]	-2.00 (3.00) [3.7%]	-2.00 (1.75) [0%]
Relative change [Exaggerated TS of pain %]	1.75 (1.66) [75.0%]	1.67 (1.74) [70.0%]	1.60 (3.30) [73.7%]	1 (1.37) [43.3%]	0.71 (0.63) [3.7%]	0.37 (0.66) [3.3%]

TS= Temporal summation, TSA-2 = Advanced Thermosensory Stimulator, TAM= Tibialis anterior muscle, MPS= Most painful site, NRS= Numeric rating scale

Table 6. Correlation (Spearman's rho) for the absolute and relative TS effects of the different test protocols.

			Absolute change in NRS		*Relative* change in NRS	
			Algometer	**TSA-2**	**Algometer**	**TSA-2**
Most painful site	**von Frey**	p-value	0.433	0.313	0.976	0.157
		rho	0.191	-0.210	0.008	-0.292
		n	19	25	19	25
	Algometer	p-value		0.701		0.086
		rho		-0.101		-0.429
		n		17		17
Tibialis anterior muscle	**von Frey**	p-value	***0.012*†**	0.685	0.039*	0.321
		rho	0.455	0.077	0.379	0.188
		n	30	30	30	30
	Algometer	p-value		0.850		0.321
		rho		-0.036		0.188
		n		30		30

TSA-2 = Advanced Thermosensory Stimulator, NRS= Numeric rating scale; * $p < 0.05$; †p-value < Bonferroni corrected threshold: 0.05 / 3 = 0.017

Second, at both locations, Fisher's exact tests showed a significant difference between the reference protocol and bedside protocols in the proportion of participants showing an exaggerated TS for both absolute and relative effects after correction for multiple testing, indicating low concurrent validity (Table 7).

Table 7. Comparison (Fisher's exact test) of the proportion of responders between the different TS protocols.

		Absolute change in NRS		*Relative* change in NRS	
		Algometer	**TSA-2**	**Algometer**	**TSA-2**
Most painful site	**von Frey**	0.759	***0.002*†**	1.000	**< 0.001†**
	n	19	25	19	25
	Algometer		***0.015*†**		**< 0.001†**
	n		17		17
Tibialis anterior muscle	**von Frey**	0.252	**< 0.001†**	0.067	**< 0.001†**
	n	30	30	30	30
	Algometer		*0.024**		**< 0.001†**
	n		30		30

TSA-2= Advanced Thermosensory Stimulator, NRS= Numeric rating scale; * $p < 0.05$; †p-value < Bonferroni corrected threshold: 0.05 / 3 = 0.017

Participants' experience and bedside test preference

All participants (1) perceived the testing as comfortable, (2) thought the instructions were clear, and (3) appreciated the positioning during testing. The participants' preferred bedside method for CPM was the test with BPC as the conditioning stimulus (n=23, 76.7%).

For TS at the tibialis anterior muscle, 73.3% (n=22) of the participants preferred the algometer over the von Frey monofilament (10.0%, n=3) (Figure 3). For TS at the most painful site, 11 (36.7%) participants indicated that TS using the algometer was too painful and was, therefore, not included in the bedside test preference count (Figure 3). Of the remaining participants, 33.3% (n=10) preferred the algometer to the von Frey monofilament (n=6, 20.0%) (Figure 3). Five (16.7%) and three (10.0%) participants remained undecided for testing their preference (Figure 3).

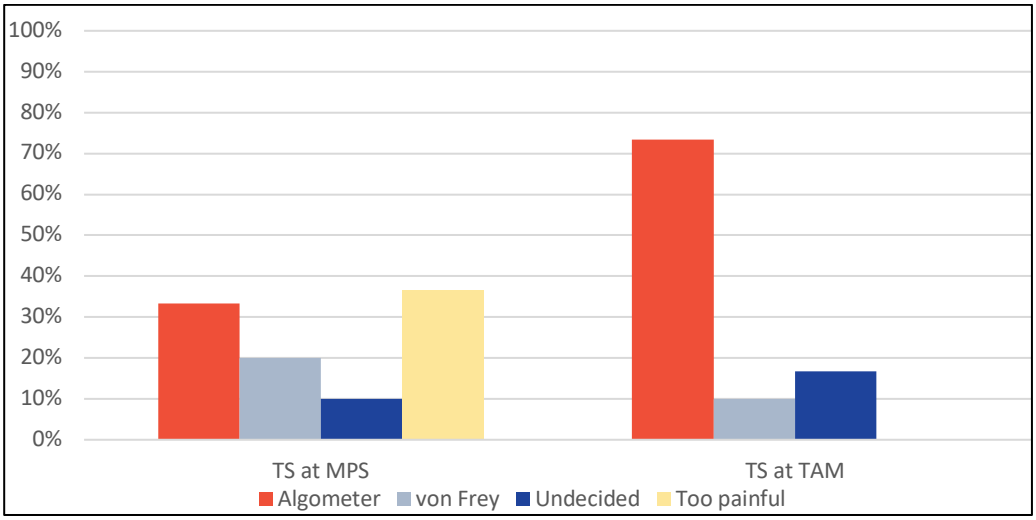

Figure 3. Participants' test preferences for bedside temporal summation (TS). TAM= Tibialis anterior muscle, MPS= Most painful site.

Discussion

This study aimed to explore the concurrent validity of clinically applicable CPM and TS protocols in BCS with persistent pain. We examined CPM and TS using absolute and relative effects and the corresponding proportions of responders. In general, the highest correlations were found between the two bedside CPM protocols, both for the absolute and relative effects, and at both the 45 and 90 second time points. No correlation was found between bedside CPM protocols and the reference protocol. However, looking at the proportion of responders to the different CPM protocols using the 2 SEm-method, no significant differences were found between the bedside protocols and the reference test, pointing towards some agreement in concurrent validity. A significant and moderate correlation was found between the two bedside TS tests at the tibialis anterior muscle using the absolute, but not the relative, change in NRS. No significant correlations were found between bedside TS protocols and the reference tests. The presence of exaggerated TS of pain was significantly higher for the bedside TS protocols than for the reference protocols at both locations, confirming limited validity. Furthermore, the participants favored the bedside CPM test using the BPC and algometer as a bedside TS test. TS with an algometer at the most painful site was too painful for 11 participants (36.7 %); therefore, a remote body location was preferred.

The lack of correlation between bedside and reference protocols may be due to the reference protocols used in this study. At this moment, no protocol has been validated as 'the reference protocol', probably owing to the variability and complexity of TS and CPM protocols in addition to the lack of standardization in research paradigms.[45,46] For the CPM, the last recommendation by Yarnitsky and colleagues dates back from 2014 and acknowledges that currently there is insufficient data to identify a specific CPM protocol as most preferred.[47] We utilized the TSA-2 by Medoc for its practicality in standardization and controlling thermal stimuli, and its previous use in studies.[26,31,48] The reference CPM protocol was based on a prior protocol in young healthy subjects [25], however it recently showed limited

reliability in BCS in a study by Dams et al.[26] The authors suggested that reliability was limited possibly due to the limited contact area of the conditioning stimulus (9 cm^2) and duration of the test stimulus.[25] These factors not only influence reliability, but can also influence the magnitude of CPM effect and in turn its validity. We utilized a parallel CPM protocol rather than a sequential CPM protocol to limit the time required to perform all protocols. Although sequential protocols have been suggested as they limit distraction, parallel protocols do not seem to differ in CPM effect.[49] Furthermore, in our study, not only did the type of stimulus differ between protocols (heat vs. cold vs. pressure), but the location of the conditioning and test stimuli also differed. It has been shown that the CPM effect can be influenced by its location on the body as different body sites have different distributions of sensory receptors.[48]

Looking for alternative reference tests, the CPTe may be interesting since it is a well-established and recommended protocol used for the assessment of the endogenous pain-inhibitory systems in different pain population and BCS experiencing pain.[10,47,50] If we would consider the CPTe as a reference test in our study as well, our results point towards good validity for the BPC test in BCS with persistent pain.[40] In addition, the use of a BPC as a conditioning stimulus has also been frequently used in non-cancer populations.[30,51]

Regarding TS, protocol recommendations are also lacking. The reference method selected for our study was thermal TS with the TSA-2 for the same reason it was selected for CPM (i.e., standardization and control of stimuli), but again its validity on its own has not been examined due to protocol variability and lack of gold-standard assessment methods for the wind-up phenomenon of which TS is a surrogate measure.[31] Our reference TS protocol was based on the protocol of Awali et al. who performed thermal TS with a Peltier thermode on young, pain-free, healthy participants.[31] We did however adapt the protocol to suit our pain population with an individualized test intensity set at the NRS for pain of 4/10 (instead of 6 in Awali et al.).[31] Even though this intensity was in line with previous

research and in line with CPM recommendations, it is possible that this pain intensity was too low and/or that the heat stimulus was set too low for thermal wind-up, as less than 5% showed an exaggerated TS of pain at both testing locations.[26,31] Also, the Pain4 temperature was determined at the unaffected forearm, whereas the TS protocol was applied to the most painful site and opposite tibialis anterior muscle. It is possible that differences in sensory receptor distribution between the unaffected forearm and opposite tibialis anterior muscle contributed to the low amount of summation.[48] Regarding the bedside TS protocols, we utilized a von Frey monofilament or an algometer to exert summation and even though prior research has utilized both tools to perform TS, some considerations are needed.[8,26] The spherical tip of the 256 mN von Frey monofilament is not meant to stimulate nociceptors, resulting in several absent pain scores after the first stimulus. Equally, a pressure of 1 kg/cm^2 at the tibialis anterior was often not painful. To assess the wind-up phenomenon, a noxious stimulus should be applied. Individualization of the stimulus at each location can improve responder rates in the bedside and reference protocols. This individualization might also improve the application of TS with the algometer at a painful site, as illustrated by the missing data (n=11) due to pain.

This study is the first to investigate CPM and TS using both absolute and relative effect magnitudes and the corresponding responder analyses in BCS with persistent pain. Until now, most studies have either used the absolute effect magnitude when relying on the NRS because of possible zero ratings or relative effect magnitudes when relying on PPTs, as zero values are uncommon. Solely using the absolute effect to determine the CPM or TS effect has limitations owing to the floor or ceiling effects. To avoid such limitations, we calculated the relative effect magnitudes for the CPM and TS protocols. Responder analysis for CPM showed similar responder rates using both effect magnitudes, whereas for exaggerated TS of pain, responder rates differed substantially between the methods used. The responder rate could be influenced by the intensity of our protocols, but it is also possible that the cutoff value for absolute and relative change does not match (i.e., an absolute change of 2

on the NRS is not always equal to a relative change of 33%).[52] When applying multiple trains of TS, it would be possible to use the 2 SEm method to calculate a meaningful TS of pain. Future studies should investigate this methodology and establish recommendations for its use in the TS protocols.

Strengths and limitations

This study has several strengths. Three different protocols, consisting of one reference protocol and two bedside protocols per paradigm were selected for comparison. In addition, different conditioning and test stimuli were used and compared for CPM. Furthermore, this study offers a conservative statistical analysis and comprehensive assessment of CPM and TS by using absolute and relative changes. A comparison of the proportion of responders in each paradigm provides additional information regarding its concurrent validity. The participants were asked about their experiences and bedside test preferences. In addition, for our analysis, we calculated the absolute and relative changes in all protocols.

This study also has several shortcomings, the first of which is its limited sample size. Recruitment was ongoing when the covid-19 restrictions were introduced. Therefore, we were required to limit the recruitment and use a convenience sample of 30 participants. We did not perform an a priori sample size calculation. Second, during recruitment, we screened BCS based on pain intensity via telephone. BCS were eligible for inclusion if they indicated a mean pain intensity of > 3/10 on the NRS. Eligible participants were asked to fill in several pain ratings using a VAS: minimum, maximum, during activity, during rest and at present. Consequently, depending on the type of pain rating, several participants had close to no pain, whereas others had severe pain. This finding is indicative for the dynamic nature pain holds, resulting in a non-normal distribution of pain scores. It is possible that the inclusion of BCS with nearly no pain skewed our results, however CPM is known to be highly variable, even in healthy groups.[27] Third, we did not systematically control for wash-out times during our comprehensive assessment, nor did we implement a

randomized order of testing. However, the time required to set up each test, together with the instructions, presumably resulted in a sufficient wash-out time between tests.[24] Furthermore, CPM effects are mostly short-lived and therefore should not have influenced other QST outcomes.[47,49] Fourth, it is plausible that peripheral sensitization occurred near the end of the assessment due to repetitive stimulation, especially in the upper part of the tibialis anterior muscle, which in turn could decrease PPTs and decrease CPM effect. Fifth, when participants took pain medication, they were not excluded, nor were they asked to temporarily stop medication. Although only a limited number of participants took tricyclic antidepressants, gabapentinoids, or SNRIs, they may influence QST outcomes.

Clinical implementations

Interest in the evaluation of somatosensory functioning in a clinical setting has grown in the last few years in line with mechanism-based approaches to pain.[18,53] Clinical guidelines have been proposed to provide clinicians with direction in the complexity of pain classification.[5,54] These guidelines propose that quantitative sensory testing (QST), including CPM and TS, can aid in the assessment of somatosensory (dys)function.[54,55] However, the clinical applicability and validity of such guidelines remain uninvestigated. This study showed that bedside CPM protocols and bedside TS protocols when performed at a remote, non-painful site are well correlated with one another. The participants preferred the CPM protocol with the BPC and the TS protocol with the algometer at the tibialis anterior muscle. According to our findings, clinicians should be able to assess CPM using a BPC as a conditioning stimulus for 45 seconds and TS using an algometer at a remote site. From a clinical point of view, we recommend the use of these tools complementary to history taking and patient-reported outcome measures. It remains unclear whether evaluating these paradigms will improve pain management in individual patients. In addition, the feasibility and utility of these protocols among clinicians requires further investigation.

Conclusion

First, in BCS with persistent pain, bedside CPM protocols using a CPTe, or BPC are significantly and strongly correlated with each other but are not correlated with a reference protocol. Bedside protocols for TS were only significantly and moderately correlated with each other at a remote testing location using absolute scores. Similar to CPM protocols, bedside TS protocols were not correlated with the reference protocol. Participants favored the bedside CPM test using the BPC and the algometer as a bedside TS test. These results indicate that healthcare providers should be able to assess CPM using a BPC, PPT, and TS, using an algometer. Further research on the concurrent validity of CPM and TS protocols in cancer is needed to confirm these results.

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Supplementary Methods S1

Supplementary Methods S1 Table. Patient and cancer characteristics. Frequencies are reported, unless mentioned otherwise

Patient and cancer characteristics	n (%)
Social status	
Retired	5 (17.2%)
Unemployed	5 (17.2%)
Partially employed	11 (37.9%)
Fully employed	9 (31.0%)
Time since end of cancer treatment (years), Median (IQR)	2.3 (3.8)
Tumor size (histopathological staging)	
pTx, pTis, pT0	3 (10.0%)
pT1	9 (30.0%)
pT2	9 (30.0%)
pT3	4 (13.3%)
pT4	2 (6.7%)
unknown	3 (10.0%)
Lymph node stage (histopathological staging)	
pNx	0 (0%)
pN0	15 (50.0%)
pN1	9 (30.0%)
pN2	2 (6.7%)
pN3	1 (3.3%)
unknown	1 (3.3%)
Surgery at dominant side	16 (53.3%)
Type of surgery	
Mastectomy & Sentinel lymph node biopsy	3 (10.0%)
Mastectomy & Axillary lymph node dissection	11 (36.7%)
Breast conserving surgery & Sentinel lymph node biopsy	8 (26.7%)
Breast conserving surgery & Axillary lymph node dissection	6 (20.0%)
Axillary lymph node dissection only	2 (6.7%)
Radiotherapy	29 (96.7%)
Chemotherapy	19 (63.3%)
Paclitaxel (Taxol)	
- Epirubicin - Cyclophosphamide	9 (47.4%)
- Doxorubicin - Cyclophosphamide	1 (5.3%)
Docetaxel (Taxotere)	
- Cyclophosphamide	6 (31.6%)
- Doxorubicin	1 (5.3%)
- 5 fluorouracil - Epirubicin - Cyclophosphamide	1 (5.3%)
- Epirubicin	1 (5.3%)
Hormonal therapy	
Tamoxifen	7 (23.3%)
Aromatase inhibitors	17 (56.7%)
No hormonal therapy	6 (20.0%)
Target therapy	
Trastuzumab	5 (16.7%)
Pertuzumab	0 (0%)

Supplementary Results S1

Participants' experience

1. The testing was comfortable: yes / no
2. Instructions were clear: yes / no

Participants' test preference

1. Temporal summation at the most painful site

   Algometer vs. von Frey monofilament

2. Temporal summation at the tibialis anterior

   Algometer vs. von Frey monofilament

3. Conditioned pain modulation

   Cold pressor test vs. Blood pressure cuff

Chapter 4

The feasibility, utility, and validity of bedside quantitative sensory testing in cancer survivors with persistent pain: a survey among Dutch-speaking physical therapists.

The feasibility, utility, and validity of bedside quantitative sensory testing in cancer survivors with persistent pain: a survey among Dutch-speaking physical therapists.

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Abstract

Objectives: Altered somatosensory function is common in cancer survivors experiencing persistent pain. Bedside quantitative sensory testing (QST) has been proposed to assess somatosensory (dys)function in clinical practice, but the feasibility, utility, face, and content validity of bedside QST have not been investigated among physical therapists (PTs).

Methods: PTs were invited to watch two videos in which four bedside tests and one questionnaire were presented: (1) Pressure pain threshold (PPT); (2) Cold pain threshold (CPTh) using a cold pack; (3) Temporal summation (TS) with an algometer; (4) Conditioned pain modulation (CPM) with a blood pressure cuff and algometer; and (5) the Douleur Neuropathique 4 (DN4) questionnaire. The participants completed an online survey on feasibility, utility, face, and content validity.

Results: Forty PTs were included. Most tests were considered feasible. DN4 and CPTh were rated as the most utile. For content validity, the DN4 and PPT were rated relevant. Most PTs agreed with the face validity of the tests. In total, 45% of PTs would implement the protocol in clinical practice. Barriers to implementation include lack of time and material.

Conclusion: Although most PTs agreed on the feasibility, utility, face, and content validity of QST, its implementation in clinical practice is low.

Key words: Cancer-related pain, breast cancer survivor, conditioned pain modulation, temporal summation, quantitative sensory testing

Introduction

Breast cancer survivors experience different side effects following their treatment.[1,2] Approximately 46% of breast cancer survivors experience persistent pain, with 27% experiencing moderate-to-severe pain.[3] Prolonged pain, which can have a significant negative impact on emotional and physical functioning, as well as quality of life.[1,2] Therefore, a comprehensive evaluation of pain is warranted as part of optimal pain management for this population.

Dysfunction of the somatosensory nervous system is a common feature in persistent pain conditions, including breast cancer survivors experiencing persistent pain.[4–6] Such dysfunction is characterized by the presence of either sensory gain (e.g., gain of function as in allodynia or hyperalgesia) or sensory loss (e.g., loss of function as in hypoesthesia or hypoalgesia).[7] Quantitative sensory testing (QST) is often used to evaluate the (dys)function of the somatosensory nervous system using a collection of well-established psychophysical and non-invasive assessment techniques consisting of systematically applied and quantifiable sensory stimuli (e.g., thermal or mechanical stimuli such as tactile, pressure, vibration).[8] Using QST, sensory function can be quantified, producing a sensory profile.[6] QST can be divided into a static and dynamic part. The static QST part typically includes the assessment of thresholds (including warm and cold detection, heat and cold pain, mechanical detection and pain, and vibration detection). The dynamic QST part encompasses conditioned pain modulation (CPM) and temporal summation (TS).[8] CPM refers to the decrease in pain intensity for a first test stimulus following or while a second, conditioning stimulus is applied to a different region of the body. CPM is assumed to represent the descending suppression of nociceptive signals which could be used to evaluate endogenous inhibitory descending pathways.[9,10] TS is a psychophysical test that evaluates the facilitative endogenous nociceptive pathways by eliciting high frequency action potentials in the presynaptic neuron, thereby generating postsynaptic potentials that overlap and summate with each other (e.g., TS of pain).[11,12]

Several studies have proposed that evaluating the (dys)function of the somatosensory nervous system in clinical setting allows clinicians to tailor pain management strategies and possibly improve treatment outcomes.[13–15] In research settings, laboratory-based QST protocols are primarily used to assess a wide range of painful conditions, including neuropathies [4] and fibromyalgia [16]. However, laboratory-based QST protocols incur significant costs, demanding specialized equipment and time-intensive procedures that necessitate substantial training.[17] Such factors limit the implementation of QST in routine clinical settings, such as physical therapy. In order to improve implementation in clinical settings, research has proposed clinical bedside QST alternatives using inexpensive materials, requiring less training and less time to perform in healthy controls [18], patients with neuropathic pain [19] and osteoarthritis [20]. Most bedside alternatives have been developed for its use in a non-cancer population [17], whereas research in the cancer population is scarce.[21] Furthermore, while studies have examined the reliability and concurrent validity of these alternatives[22,23], it is crucial to note that despite their reputation as easy-to-use, little research has been performed towards assessing their clinical feasibility, utility and validity within the context of their intended users, such as clinicians. In order to enhance the integration of QST into clinical practice research needs to involve end users, such as clinicians, assessing its feasibility, utility, as well as its face and content validity. Therefore, the aim of this study is to investigate the clinical feasibility, utility, and face and content validity of bedside QST in Dutch-speaking physical therapists for its use in breast cancer survivors with persistent pain.

Methods

Study design

This study was approved by the Ethical Committees of the University Hospitals Leuven (s62584) and the University Hospital of Antwerp (B322201940289). The study was reported following the Strengthening the Reporting of Observational

studies in Epidemiology (STROBE) statement.[21] All respondents read a summary of the study and signed an informed consent form before participating in the study.

Participants were instructed to watch two videos of the bedside QST protocol before completing the survey to evaluate the feasibility and utility and the face and content validity of these bedside tests for solid cancer survivors with persistent pain. A cancer survivor was defined as "patients who have completed their primary treatment, and have no evidence of active disease".[22] The first video contained the theoretical background of the bedside tests, more specific (1) overview of all bedside tests, (2) required material, (3) basic neurophysiological background information of each test including test interpretation, (4) instructions for the clinician and patient. This video lasted for ten minutes. The second video, with a duration of 10 minutes and 40 seconds, demonstrated bedside tests on a fictious breast cancer survivor with persistent pain in the treated area. The first author (VH) provided the theoretical information on the bedside tests in the first video, and performed the demonstration in the second. A fictious breast cancer survivor with persistent pain was played by a researcher with experience in breast cancer survivors (ADG). At the start of both videos, the participants were asked to carefully pay attention to and replay the videos as much as needed.

Previously published questionnaires evaluating the feasibility, utility, and face and content validity of different tools were consulted for the development of the online survey.[23–28] In addition, three PTs (VH, DL, SU) and three postdoctoral researchers (ADG, MM, ND) with extensive clinical and research experience in oncological rehabilitation and pain (> 5 years) further shaped the purpose-developed online survey. The online survey consisted of eight open questions**,** four dichotomous (i.e., Yes or No) questions, and 22 Likert-type questions divided across seven sections: (1) participants' demographics (country of residence, age, and work experience) (questions 1–3); (2) participants' current clinical assessment approach to painful symptoms (questions 4–12); (3) feasibility (questions 13–15); (4) utility (questions 16–25); (5) content validity (questions 26–28); (6) face validity (questions 29–30);

and (7) concluding remarks using one dichotomous and two open-ended questions (questions 31–33). A detailed overview of all the questions is provided in Table 1.

Table 1. Overview of the survey (questions 1-33).

Domain	Question	Answer possibility
Demographics	1. Country of residence 2. Date of birth 3. Work experience	1. Belgium / The Netherlands 2. DD/MM/YYYY 3. Work activity in years
Assessment of painful symptoms	4. How are painful symptoms currently evaluated in your practice?	☐ History taking ☐ Numeric scale pain ☐ Specific pain questionnaire ☐ Clinical neurological assessment ☐ Clinical specific assessment
	Frequency of … 5. History taking 6. Numeric scale 7. Specific pain questionnaire** 8. Clinical neurological assessment (sensory function, strength, and reflexes) 9. Clinical specific assessment**	☐ Every consultation ☐ New intake ☐ Not systematically ☐ Never ☐ No response
	10. Do you have protocols in your practice on the evaluation of painful symptoms?	○ Yes** ○ No
	11. I feel confident about the assessment of painful symptoms. 12. I feel confident in my knowledge of pain and pain physiology.	○ Strongly agree ○ Agree ○ Neutral ○ Disagree** ○ Strongly disagree**
Feasibility	13. The time (11') required for the combination of bedside tests is acceptable. 14. After watching the instructional video, as well as the practical video, I feel able to apply these bedside tests in practice. 15. These bedside tests appear to be safe for my population of cancer survivors.	○ Strongly agree ○ Agree ○ Neutral ○ Disagree** ○ Strongly disagree**
Utility	16. If you would like to carry out these tests as shown in the practical video, would this be possible for you?	○ Yes ○ No**
	17. Which bedside test would you not be able to perform? ○ DN4 questionnaire ○ Pressure pain thresholds with an algometer ○ Cold detection threshold with a cold pack ○ Temporal summation with an algometer ○ Conditioned pain modulation with a blood pressure cuff and algometer	Reason for not being able to perform the bedside test: ☐ Lack of material ☐ Lack of time ☐ Discomfort of the patient ☐ Unsuitable for my patient population ☐ Other: …

Table 1. Continued

	18. The instructions given to the PT are clear 19. The instructions given to the patient are clear. 20. The order of bedside tests as presented makes sense. 21. The administration accompanying these tests is easy. 22. The results of these tests appear to be useful for my patients' record. 23. The required material is easy to obtain. 24. These tests are easy to perform.	○ Strongly agree ○ Agree ○ Neutral ○ Disagree** ○ Strongly disagree**
	25. All components for assessing pain symptoms are covered with the combination of bedside tests.	○ Yes ○ No**
Content validity	26. Relevance of each bedside test* (e.g., how important is this test)	○ Not relevant ○ Somewhat relevant ○ Quite relevant ○ Highly relevant
	27. Essentiality of each bedside test* (e.g., how necessary is this test)	○ Not essential ○ Useful, but not essential ○ Essential
	28. Clarity of each bedside test* (e.g., how clear is the wording)	○ Not clear ○ Items needs some revision ○ Very clear
Face validity	29. The combination of bedside tests measure what they are supposed to measure. 30. The combination of bedside tests seems to be an added value for guiding pain management in cancer patients.	○ Strongly agree ○ Agree ○ Neutral ○ Disagree ○ Strongly disagree
Concluding remarks	31. Would you like to use the combination of bedside tests as shown in your practice?	○ Yes ○ No**
	32. Can you think of some benefits of these bedside tests? 33. Can you think of any disadvantages of these bedside tests?	Open-ended questionnaires

* Content validity was assessed for each bedside test separately. ** Additional information can be provided.

Completion of this online survey took approximately 15 min and was made available via the online platform REDcap electronic data capture tools.[29]

PTs were recruited between November 2021 and September 2022 in the Flemish-speaking part of Belgium and the Netherlands. Recruitment was performed through social media platforms, national and Flemish PT networks, oncological networks for PTs, and purposive sampling by handsearching PTs' websites offering oncological rehabilitation or rehabilitation for cancer-related lymphedema. The inclusion criteria

for the participating PTs were (1) having an active national registration as a PT; (2) being able to speak, write, and read Dutch; and (3) currently working as a PT with cancer survivors in the first (private practice) or second (hospital or nursing home) line in the Flemish part of Belgium or the Netherlands. All Dutch PTs had to have a post-graduate oncological degree, as recognized by the Royal Dutch Society for Physical Therapy. In Belgium, such a postgraduate degree does not exist and is therefore not needed for inclusion. The exclusion criteria were (1) PTs who did not treat cancer survivors with pain, (2) inactive or undergraduate PTs, and (3) other health professionals such as doctors and paramedic staff, including occupational therapists, speech therapists, and nurses.

Bedside testing

After an exploratory literature search and expert consultation, four bedside QST tests were selected: (1) pressure pain threshold (PPT) using an algometer; (2) cold pain threshold (CPTh) using a cold pack; (3) temporal summation (TS) using an algometer; and (4) conditioned pain modulation (CPM) using a blood pressure cuff for conditioning and an algometer for testing. In addition, the Douleur Neuropathique 4 (DN4) questionnaire (42) was added to these four bedside tests to evaluate neuropathic signs and symptoms. These four bedside tests covered the static and dynamic parts of the QST, capturing the (dys)function of the somatosensory nervous system as comprehensively as possible, and were similar to previously published bedside QST protocols.[16,30,31] In addition, these bedside tests seemed most feasible in the daily clinical practice of PTs owing to the limited material and time required to perform. The total time to complete the combination of all bedside tests was 11 minutes.

1. DN4 questionnaire (Duration: 2 min.)

The **DN4 questionnaire** combines seven specific questions concerning the signs and symptoms of neuropathic pain with three questions involving the sensory

examination of hypoesthesia and allodynia using a pin prick and a brush. The DN4 is meant to be administered at the area that is most painful.[32]

2. Pressure pain thresholds with an algometer (Duration: 2 min.)

PPTs were measured in the area indicated as most painful by the patient and at a remote location, such as the opposite tibialis anterior muscle. A digital pressure algometer (Wagner FDX, Greenwich CT, USA) with a flat round rubber tip and a probe area of 1 cm^2 was used. The PPT was defined as the amount of pressure at which the sensation of pressure was first perceived as unpleasant and was determined by two series of ascending pressure at a rate of approximately 0.1 kgf/s.[33] The final threshold was the arithmetic mean of two trials (kgf/cm^2).[34]

3. Cold pain threshold with a cold pack (Duration: 1.5 min.)

For the **CPTh with a cold pack,** a household cold pack wrapped in a soft paper tissue was placed onto the most painful area and then on the opposite tibialis anterior muscle for 10 seconds. Patients were instructed to score the perceived pain on the numeric rating scale (NRS) for pain, with 0 indicating no pain and 10 indicating the worst pain imaginable. In addition, they were instructed to give a second NRS score for cold with 0 meaning no cold experienced and 10 meaning the worst cold imaginable.[16]

4. Temporal summation with an algometer (Duration: 1.5 min.)

TS was evaluated using a digital pressure algometer (Wagner FDX, Greenwich CT, USA) in the area indicated as most painful by the patient and the opposite tibialis anterior muscle. First, a stimulus of 1 kgf/cm^2 was administered, after which the patient was instructed to score the perceived pain on the NRS (0-10). This stimulus was repeated for 30 seconds at a rate of 1 stimulation/s, after which a second score for pain on the NRS was asked. Finally, 15 seconds after the last given stimulus, the patient was instructed to give a third [75]and last NRS score**.**

5. Conditioned pain modulation with a blood pressure cuff and algometer (Duration: 3 min.)

Finally, CPM relates to the reduction in pain intensity for a certain stimulus after or during the application of another stimulus. **CPM** was evaluated using a parallel design with the PPT at the opposite tibialis anterior as the test stimulus. The conditioning stimulus consisted of a blood pressure cuff placed on the unaffected upper arm 2 cm above the cubital fossa, which was inflated until the pressure was appraised as unpleasant (defined as 4/10 on the NRS). The blood pressure cuff was maintained for 90 seconds. During this, PPT was performed at 45 seconds and at 90 seconds.[33–36]

Statistical analysis

All individual responses were exported to Excel after the survey was closed in September 2022. Participant demographics are presented as median and interquartile range (IQR). Frequencies and proportions (%) of the closed-ended and Likert-type questions are presented. For the open-ended questions, the responses were themed and grouped wherever possible.

The Content Validity Index (CVI) and content validity ratio (CVR) were used to estimate the relevance and essentiality, respectively, as part of the content validity.[37–40] The Item level CVI (I-CVI) is calculated by dividing the number of participants judging the item, or in the context of the study the bedside test, as "relevant" (very relevant or fairly relevant) by the total number of participants. When the I-CVI was > 0.79, the item was considered relevant, and the item needs revision when the CVI was between 0.70 and 0.79. Item elimination was considered desirable if the value was less than 0.70. The scale level CVI (S-CVI) is calculated by dividing the sum of I-CVI items equal to 1 by the total number of items.(51) S-CVI ≥ 0.80 is considered as excellent content validity.[37–39] The CVR measures the essentiality of an item and varies between 1 and −1, with a higher score indicating greater agreement among participants.[39] The CVR is calculated using the following

formula: CVR = (Ne – N/2)/ (N/2), where Ne is the number of participants indicating an item as "essential" and N is the total number of participants.[39] The Lawshe table was used to define the critical value of the CVR. This critical value is based on the number of participants.[41]

Results

Demographics respondents (Questions 1 - 3)

Forty Dutch-speaking PTs from Belgium (n=20) and The Netherlands (n=20) participated in this study. The median age of the PTs was 35 (22.3) years, with a median work experience of 11 (21.8) years.

Participants' current clinical assessment of painful symptoms (Questions 4 - 12)

For the assessment of pain (Q4), most participants utilized history taking (n=34, 85%) and rating scales for pain intensity (n=37, 92.5%) (i.e., the numeric rating scale or visual analogue scale). A minority of participants (n=8, 20.0%) used specific questionnaires, such as the DN4 (n=2), the Central Sensitization Inventory (n=3), and the Brief Pain Inventory (n=2) (Table 2). Half of the participants (n=20, 50%) used clinical assessment methods (neurological testing or other specific tests) (Table 2).

Question 5 through 9 asked when different assessment methods were employed. (Figure 1). Most PTs used standard history-taking in new and returning patients, whereas questionnaires were less systematically utilized. Only 17.5% of the included PTs stated that they have a general standardized protocol in their clinic for the assessment of painful symptoms in all patient populations (i.e., systematic use of the NRS for pain intensity) (Q10). Half of the participants (52.5%) agreed with and strongly agreed with their confidence in assessing painful symptoms (Q11). Fifty-five percent felt confident about their knowledge of pain physiology (agreed or strongly agreed) (Q12).

Table 2. Participants' current clinical assessment of painful symptoms (Q4), n (%)

History taking	34 (85.0%)
Numeric scales (i.e., NRS or VAS)	37 (92.5%)
Specific pain questionnaires**	8 (20.0%)
- DN4	2 (5.0%)
- Central Sensitization Inventory	3 (7.5%)
- Brief Pain Inventory	2 (5.0%)
Clinical assessment: neurological tests	21 (52.5%)
Clinical assessment: specific tests**	20 (50.0%)
- Pain provocation tests	6 (15%)
- Test dependent of diagnosis or patient	2 (5%)

NRS = Numeric rating scale, VAS = Visual analogue scale, DN4 = Douleur Neuropathique 4, ** Additional information provided.

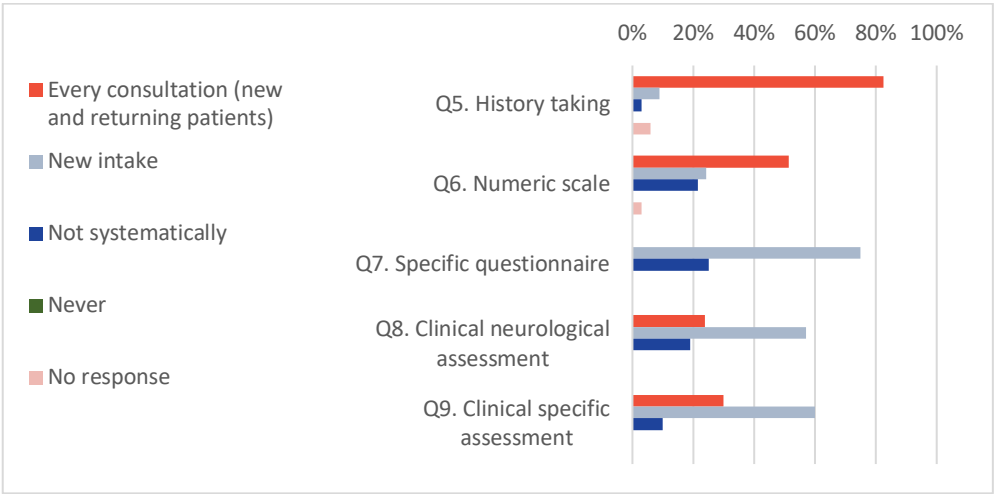

Figure 1. Current clinical assessment of painful symptoms and frequency of methods used.

Feasibility (Questions 13 - 15)

Twenty-three PTs (57.5%) agreed or strongly agreed that 11 minutes was an acceptable time for the combination of bedside tests for the assessment of pain. Nine (22.5%) PTs found 11 minutes unacceptable (i.e., disagree or strongly disagree) (Q13, Figure 2). Seven and two PTs suggested that 5 and 3 minutes, respectively, would be acceptable for bedside testing of painful symptoms. Regarding the confidence to perform the bedside tests in practice after watching both videos, 72,5% (n= 29) of PTs felt confident (50% agreed, 22.5% strongly agreed) (Q14, Figure 2). Three PTs argued that extra training would be necessary and felt that they lacked the knowledge to interpret the outcomes of the bedside tests. In total, 92.5% of the

participants (n= 37) agreed (strongly agreed and agreed) that the protocol would be safe (Q15, Figure 2).

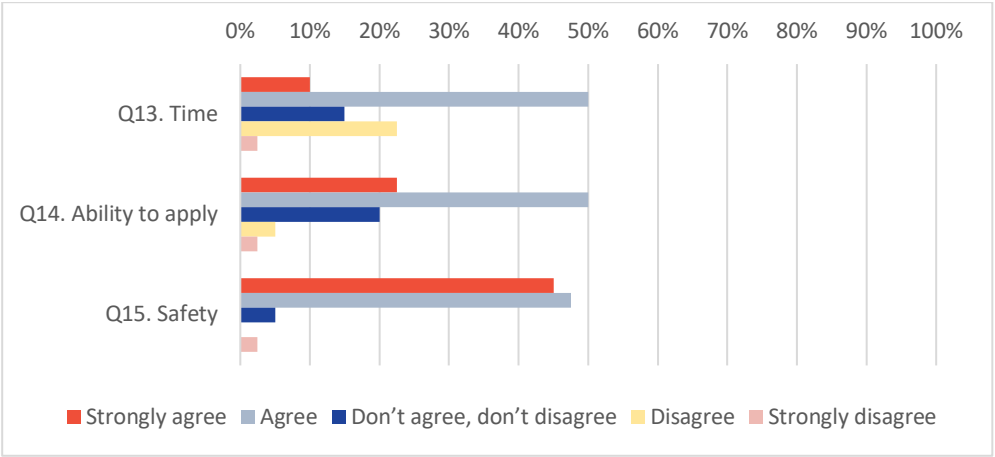

Figure 2. Feasibility of the bedside tests. **Q13** = Time (11') required for the combination of bedside tests is acceptable.; **Q14** = After watching the instructional video as well as the practical video, I feel able to apply these bedside tests in practice.; **Q15** = The bedside tests appear to be safe for my patient population.

Utility (Questions 16 - 25)

Overall, 72.5% (n= 29) of PTs stated that they were unable to perform one or more bedside tests at the time of the survey (Q16). Overall, the DN4 and CPTh received the highest utility among the participants, whereas PPT, TS, and CPM were scored the lowest (Q17, Figure 3). The main reasons for considering PPT, TS, and CPM to be the least useful were the lack of material (i.e., an algometer) and lack of time. Further evaluation of utility (Q18-24) is summarized in Figure 4. In general, most participants (strongly) agreed with statements regarding utility. Twenty-one percent of the respondents believed (strongly) the required material was difficult to obtain (Q23).

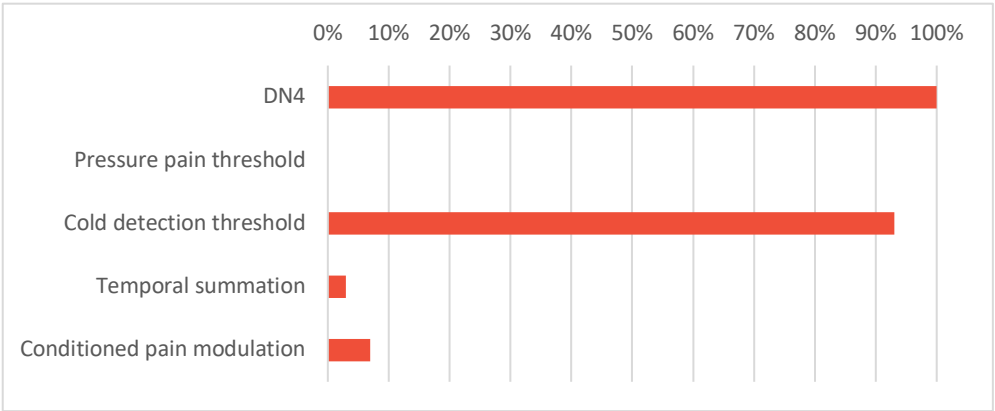

Figure 3. Utility of each bedside test, based on Q17: "*Which bedside tests would you be able to perform?*"

Question 25 assessed whether the combination of the proposed bedside tests could suffice for a complete assessment of painful symptoms in cancer survivors. Sixty-five percent of the participants (n= 26) agreed that the combination of these bedside tests contained all the elements for the assessment of painful symptoms. Participants who disagreed (35%, n= 14) mentioned that "*these bedside tests do not assess psychosocial factors of pain*" (ID19); that "*these tests do not consider subjective experiences of pain, such as assessed during history taking*" (ID26) and that "*it does not evaluate pain during movement*" (ID30). One participant disagreed that he/she felt that his/her knowledge of pain physiology and assessment of painful symptoms was too limited to answer this question correctly.

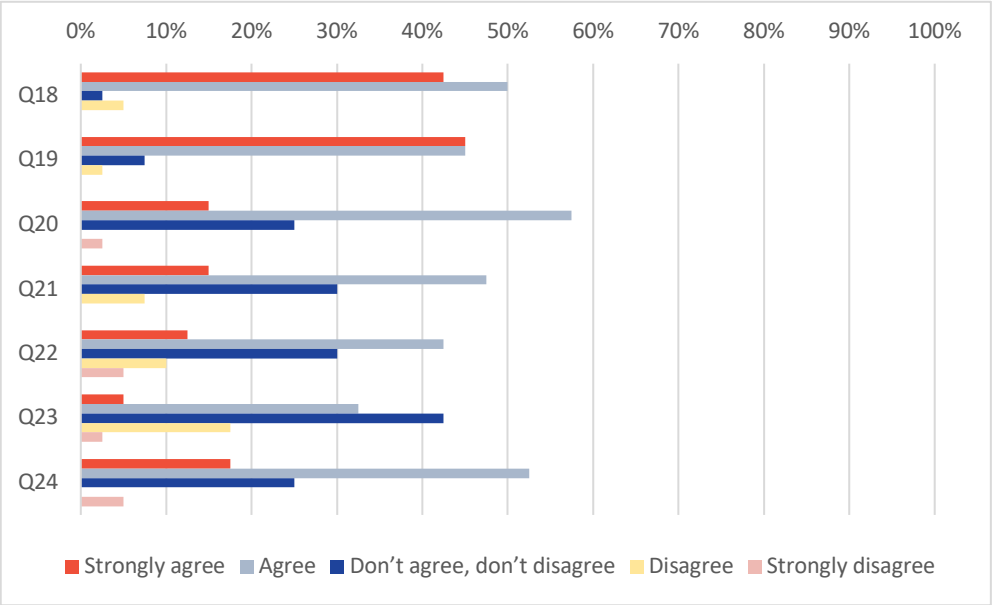

Figure 4. Utility of bedside tests. Q18 = The instructions given to the PT are clear.; Q19 = The instructions given to the patient are clear.; Q20 = The order of tests as presented make sense.; Q21 = The administration is easy.; Q22 = The results of these tests appear to be useful for patient records.; Q23 = The required material is easy to obtain.; Q24 = These tests are easy to perform.

Question 25 assessed whether the combination of the proposed bedside tests could suffice for a complete assessment of painful symptoms in cancer survivors. Sixty-five percent of the participants (n= 26) agreed that the combination of these bedside tests contained all the elements for the assessment of painful symptoms. Participants who disagreed (35%, n= 14) mentioned that "*these bedside tests do not assess psychosocial factors of pain*" (ID19); that "*these tests do not consider subjective experiences of pain, such as assessed during history taking*" (ID26) and that "*it does not evaluate pain during movement*" (ID30). One participant disagreed that he/she felt that his/her knowledge of pain physiology and assessment of painful symptoms was too limited to answer this question correctly.

Content validity (Questions 26 - 28)

Regarding *content validity*, the relevance and essentiality of the bedside tests were reported by calculating the I-CVI and CVR, respectively (Q26 and Q27, Table 3). The participants scored the DN4 questionnaire and PPT as relevant, whereas TS, using an algometer, was scored as requiring revision. CPTh using a cold pack and CPM should be considered for elimination based on the I-CVI. The S-CVI was not calculated as no item reached 1 on the I-CVI (Table 3). For essentiality, the critical value for the CVR was set at 0.29, based on the Lawshe table [41]. Given this, the DN4 and PPT were considered essential; other tests did not reach the cutoff and were therefore considered not essential (Table 3). In addition, participants rated the DN4, PPT, and CPTh as clear (Q28, Figure 5). TS and CPM were rated as "needs clarification" by 35% of the participants.

Table 3. Item Content Validity Index and Content Validity Ratio for each bedside test (Q26 and Q27)

	I-CVI *(Q26)*	**CVR** *(Q27)*
Douleur Neuropathique 4	0.88**	0.40†
Pressure pain threshold	0.83**	0.30†
Cold detection threshold	0.58	-0.15
Temporal summation	0.78*	-0.10
Conditioned pain modulation	0.68	-0.35

** Relevant items (> 0.79), * items that need revision (0.70 - 0.79), † essential items (≥ 0.29, based on Lawshe table)

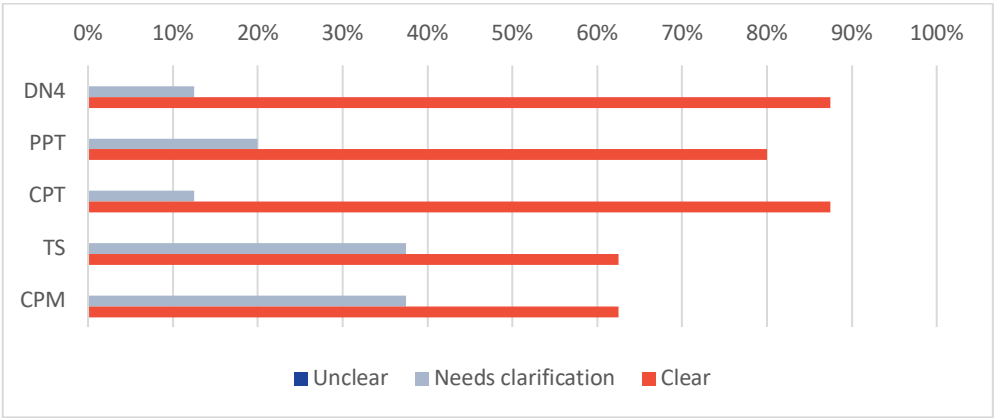

Figure 5. Clarity of bedside tests (Q28). DN4= Douleur Neuropathique 4 questionnaire; PPT= Pressure pain threshold; CPTh= Cold pain threshold; TS= Temporal summation; CPM= Conditioned pain modulation.

Face validity (Questions 29 - 30)

Face validity was assessed with questions 29 and 30 and was agreed upon by most PTs (Figure 6). One-third of the participants remained neutral, answering questions 29 and 30 (Figure 6).

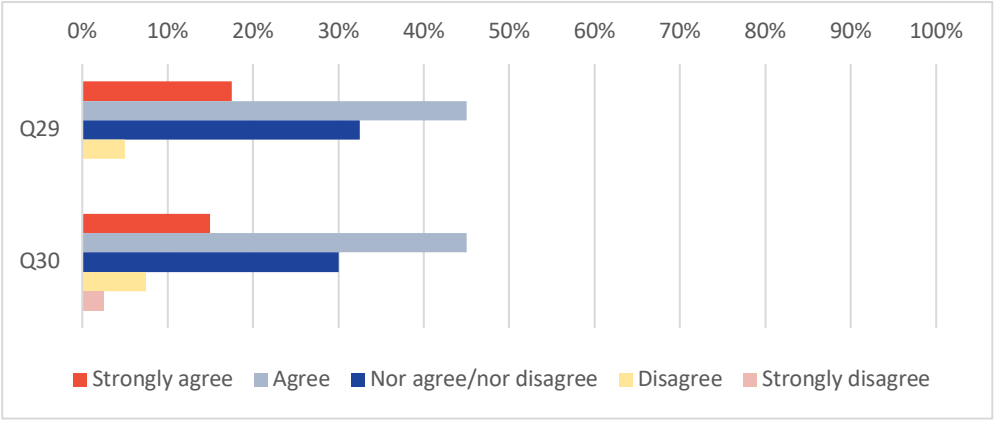

Figure 6. Summary of face validity. **Q29**= The combination of bedside tests measures what it is supposed to measure.; **Q30**= The combination of bedside tests seems to be an added value for guiding pain management in cancer patients.

Concluding remarks using open-ended questions (Questions 31 – 33)

Forty-five percent of PTs (n= 18) considered implementing the presented combination of bedside tests in their clinical practice (Q31). Of those who did not consider the tests for use in daily practice, 18 (81%) gave reasons for this answer. Reasons were themed into seven categories: (1) too time-consuming (39%, n= 7), (2) lack of material (44%, n= 8), (3) does not provide added value for pain management (22%, n= 4), (4) questionnaires are more accessible and relatable for therapists and patients (22%, n= 4), (5) no need for the cancer population (11%, n= 2), and (6) subjective assessment and history taking are sufficient (17%, n= 3).

Participants were also questioned on the advantages and disadvantages of the proposed combination of bedside tests using open-ended questions (Q32, 33). Thirty-eight participants (95%) mentioned disadvantages and were themed into five categories: (1) too time-consuming (55%, n=21), (2) lack of material (53%, n= 20), (3) discomfort for the patient (16%, n= 6), (4) focus on pain rather than function (11%,

n= 4), and (5) does not provide added value for pain management (13%, n= 5). Regarding the advantages (Q33), four themes summarized the arguments for the use of the combination of bedside tests: (1) objectification of painful symptoms (58%, n= 19), (2) follow-up of painful symptoms during rehabilitation (12%, n= 4), (3) classification of painful symptoms (i.e., neuropathic pain) (30%, n= 10), and (4) validation of patients' symptoms (15%, n= 5).

Discussion

This study used a survey to investigate the feasibility, utility, content, and face validity of the bedside QST in Dutch-speaking physical therapists who have experience in treating cancer survivors with persistent pain.

Overall, only 45% of PTs showed an interest in using the bedside tests in clinical practice. There are several reasons for this finding. Regarding *feasibility*, our study indicates that most respondents (60%) felt confident in performing the presented bedside tests with these instructions and found the tests safe for the breast cancer population. Regarding the time needed, only 60% of respondents found 11 minutes acceptable for the combination of four bedside tests and one questionnaire. Twenty-five percent of PTs found the time needed to perform the combination of all tests to be too long. Questions on *utility* indicate that the DN4 questionnaire and CPTH with the cold pack were considered most utile, whereas PPT, TS, and CPM were scored as least utile because they require specialized material (i.e., an algometer). In addition, most participants indicated that obtaining the required material seems difficult. Other aspects concerning *utility* were agreed upon by most participants (e.g., instructions to PT and patient are clear, order of tests makes sense, administration is easy, results of these tests are useful for patient records, and the tests are easy to perform).

As part of *content validity,* the DN4 questionnaire and PPT were rated as the most relevant and essential. Although there is currently no research on the content validity of DN4 and PPT, this finding is in line with the literature as the DN4

questionnaire has been endorsed for its use to screen for neuropathic pain[40], while the PPT has proven its value for the assessment of local and widespread hyperalgesia.[41] The bedside test for TS requires revision, and the tests for CPM and CPTH should be eliminated based on content validity. Concerning *face validity* of the bedside tests and DN4 questionnaire, only 63% of PTs (strongly) agreed that the tests measure what they are supposed to measure and 60% (strongly) agrees that the tests would be of added value for guiding pain management in cancer survivors. Even though the results seem promising, only 45% of the participants would implement the presented bedside QST with the DN4 questionnaire in their clinical practice. The main disadvantages were the time required to perform the tests, lack of material, and questionable added value.

The use of bedside QST protocols in clinical practice could potentially inform clinicians about the presence of somatosensory dysfunction. In doing so, clinicians could potentially gain information on the underlying pain mechanism (mechanistic pain descriptor) and tailor pain management strategies to improve outcomes of pain management in chronic pain populations.[13,14] This is in line with recent guidelines suggesting the use of QST in clinical practice for the evaluation of neuropathic and nociplastic pain in a chronic musculoskeletal pain population.[42–44] However, the guideline was limited to a set of clinical criteria (i.e. gain and loss in somatosensory functions) without clear and practical instructions for daily clinical practice on how to obtain/evaluate the proposed criteria.[42,43] Although such guidelines for the presence of any mechanistic pain descriptor do not (yet) exist for the cancer population, our results may add to their development. Based on our research, the DN4 questionnaire is a feasible and useful tool for use in clinical practice. In addition to a small brush and toothpick, no material was required to complete the DN4 questionnaire. In addition, neuropathic pain is considered to be present in 18.7-57.1% of breast cancer survivors; therefore, the need for its use is high, and recently proven valid in this population.[45–47] CPTH using a cold pack would be a feasible and utile test because of the simple required material; however, it lacked overall content

validity and was rated as irrelevant. However, the literature indicates that local cold allodynia was more prevalent in breast cancer survivors experiencing pain than pain-free breast cancer survivors.[48] As half of the participants indicated that they felt unconfident in their knowledge of pain physiology and assessment, and it is possible that relevance was not acknowledged by the respondents. In contrast, PPT using an algometer was proven valid but lacked utility, as it required the purchase of an algometer. The use of algometers is uncommon in clinical settings because of the high cost of purchasing them (120 – 1,500 USD). Hand-held dynamometers [49], erasers and thumbs [22], or other less expensive algometry alternatives [50] could possibly act as alternatives for the expensive algometer. However, this aspect needs to be explored further. Based on content validity, TS and CPM were not well accepted by the survey respondents (revision and elimination, respectively), although studies have found enhanced TS and decreased CPM to be associated with chronic pain in breast cancer survivors. [33,48] In addition, these tests also used an algometer, reducing utility. Given the relevance indicated in literature, acceptability of alternative protocols using either a von Frey monofilament[23], or a toothpick [22] and only 10 repetitions instead of 30 for TS is worth to investigate further. [51] Combined, these findings could form a new combination of tests with only the DN4 questionnaire, PPT and CPTH. Together, these tests would only take up 5.5 minutes, increasing the chances of PTs applying them in practice, as only 60% of respondents found 11 minutes acceptable for the combination of all four bedside tests and the DN4 questionnaire.

Although guidelines (partially) based on the QST are available in the literature [42,44], our results raise concerns about their clinical implementation. Participants indicated that the outcome of the bedside tests would not influence their pain management approach, which contradicts the guidelines for tailored pain management strategies. [13,14] Multiple reasons might explain this finding. First, as correctly indicated by most participants, these bedside tests do not measure psychosocial factors related to pain nor do they consider the subjective experience of pain. The bedside tests only

evaluated somatosensory function in breast cancer survivors experiencing persistent pain. To evaluate other factors associated with pain (e.g., mood, stress, and anxiety), patient-reported outcome measures (i.e., self-completed, standardized, and validated questionnaires) are essential for providing patient-centered and integrative care. [52,53] However, research has shown that implementing patient-reported outcome measures (e.g., questionnaires) is also challenging due to similar barriers found in the present study, including PTs' lack of knowledge, lack of time, availability of questionnaires, and lack of feasibility.[52,53] Ideally, a combination of bedside QST and patient-reported outcome measures are used, but implementation studies are needed to investigate both the separate and combined use in clinical practice. Second, some PTs mentioned that the use of such bedside tests places too much emphasis on (the reduction of) pain, instead of using function as an outcome. Using function as an outcome might be beneficial, as cancer survivors also experience fatigue and decreased physical activity. [54,55] PTs feel that improving fatigue and physical activity could potentially aid in the management of pain.[56,57] Third, as already mentioned, half of the participants felt unsure about their knowledge of pain physiology and assessment. Limitations in knowledge could explain why the participants were not convinced of the added value of these bedside tests in clinical practice. Multiple studies have already suggested that PTs' attitudes and beliefs influence their management of persistent pain. [52,58–61] Changes in the curriculum of future PTs can, however, improve the beliefs and attitudes of PTs and concurrently improve the management of persistent pain.[62,63] Fourth, although the aforementioned guidelines suggest a mechanism-based approach can improve pain management strategies in chronic pain populations[42], data thus far showed no relationship between the assessment of pain, treatment, and pain relief in ambulatory cancer care.[64] Some respondents, however, do see value in the quantification of painful symptoms (e.g., follow-up) and the use of such tests to validate patients' symptoms. Such a quantification could improve therapeutic relation as nearly 50% of the cancer survivors blamed their physician for not

intervening in their pain [65], and as 30% does not receive any aid in pain management.[66]

This study surveyed PTs, as they play an important role in the management of chronic pain. However, comprehensive pain assessment should be performed by other healthcare providers involved in cancer (after)care, such as pain physicians, oncologists, and nurse specialists. Future studies are warranted to explore whether similar barriers for implementation are encountered in other professions and lead to better insights into the role that different healthcare providers could play in pain assessment and management.[14] Also, specific countries and healthcare settings should be considered when translating the study results to other settings.

Strengths and limitations

To our knowledge, this is the very first study to investigate the feasibility, utility, content, and face validity of bedside QST by PTs in cancer survivors with persistent pain. This study uses an accessible methodology for PTs working in clinical practice using two short videos and an online survey based on previously used questionnaires regarding feasibility, utility, content, and face validity. Due to the study's novelty, limitations are present. First, the study design, a purpose-developed survey, relies on self-reported data from PTs, which is an inherent limitation of surveys. Watching videos with a limited time frame, in combination with a survey was chosen to include a larger sample of PTs. In addition, PTs were able to watch these videos at their own tempo and frequency. A practical intervention in combination with a think-a-loud procedure or interviews could have provided more in-depth information, however these study designs are more time-consuming for clinicians, which in turn can further complicate recruitment. Alternatively the videos could have been longer, providing more extensive background information on quantitative sensory testing. Second, participants did not require a minimal amount of experience or were selected based on their knowledge of pain physiology or QST paradigms. These factors could have influenced the recruitment and, in turn, the evaluation of the face and content

validity of our bedside protocols. Third, the response rate was not calculated, but was assumed to be low to very low as it took 10 months to recruit 40 PTs. Fourth, 47% of participants admit to having limited confidence in assessment and 45% had limited confidence in their pain neurophysiology knowledge, posing the question about their ability to judge content and face validity of the tests. Finally, some feasibility and utility questions related to the combination of bedside tests limit insights into the feasibility and utility of each individual bedside test.

Conclusion

Overall, only 45% of PTs showed an interest in using the bedside tests in clinical practice. The main practical reasons for not implementing the presented bedside QST tests were that they were too time-consuming and required specific materials. In addition, some participants questioned the added value of QST for their pain management approach. These findings indicate a gap between clinical practice and research, in which QST is incorporated in the current guidelines. Further research is required on the barriers to the implementation of tests assessing somatosensory (dys)function in clinical settings for cancer and non-cancer populations.

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Chapter 5

Development and internal validation of a preliminary clinical prediction model for the presence of nociceptive, neuropathic, or nociplastic pain in breast cancer survivors with persistent pain.

Development and internal validation of a preliminary clinical prediction model for the presence of nociceptive, neuropathic, or nociplastic pain in breast cancer survivors with persistent pain.

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Abstract

Context: The classification of a mechanistic pain descriptor is becoming increasingly popular in the cancer population. Despite the existence of clinical guidelines or criteria, diagnostic clinical prediction models are still lacking.

Objectives: To develop and internally validate three diagnostic clinical prediction models for nociceptive, neuropathic, and nociplastic pain in breast cancer survivors with persistent pain.

Methods: The outcome of the models was based on the Douleur Neuropathique 4 (DN4) questionnaire and the degree of temporal summation of pain at a remote location. Definite predictors were selected based on previous literature and knowledge of subject matter.

Results: All three final models included the following predictors: body mass index, age, type of breast surgery, type of axillary surgery, and use of radiation therapy. Additional predictors were added depending on the model. Differences in pain intensity during rest and activity, limited shoulder range of motion, and local pain were considered predictors of nociceptive pain. The neuropathic pain model included two separate DN4 items and the presence of a neuroanatomical distribution of pain. The central sensitization inventory, pressure pain threshold at a remote location, widespread pain, and preoperative pain were added to the nociplastic pain model. All developed models showed moderate discriminative ability, with optimism-corrected areas under the curve ranging from 0.592 to 0.681, and Brier scores ranging from 0.224 to 0.240.

Conclusion: All three clinical prediction models demonstrated promising results in identifying a mechanistic pain descriptor in breast cancer survivors with persistent pain. Future research should conduct thorough internal and external validation of the models.

Key words: Cancer-related pain, breast cancer, clinical prediction model

Introduction

Persistent pain is a common and major concern in breast cancer survivors after finishing treatment, affecting approximately 47% of them.[1] Such persistent pain can have a substantial impact on a person's quality of life, including physical function, sleep, emotional well-being, and fear of recurrence.[2–4]

Precision pain medicine and mechanism-based approaches are becoming increasingly popular for guiding pain management and improving its effectiveness. From a pain management perspective, both precision pain medicine or a mechanism-based approach postulate that treatment outcomes can be enhanced when the treatment is guided based on the presence or absence of a certain pain mechanism or mechanistic pain descriptor, enabling a more individualized treatment.[5,6] The International Association for the Study of Pain (IASP) introduced a classification system which describes three mechanistic pain descriptors including nociceptive, neuropathic, and nociplastic pain.[7] This classification system aims to provide a more comprehensive understanding and classification of pain, and serves as an important step towards improving pain assessment and possibly treatment.[5,6,8]

Currently, clinical guidelines and criteria exist for the identification of neuropathic [9] and nociplastic pain [10] but not nociceptive pain for chronic musculoskeletal pain. Both neuropathic and nociplastic classification guidelines combine different clinical criteria in a stepwise manner to determine the presence of a certain mechanistic pain descriptor in a graded manner (possible, probable, or definite) in cancer and non-cancer populations.[9,10] However, these guidelines remain unvalidated, and additional clinical data on the use of these guidelines in cancer and non-cancer populations are lacking. In addition to the lack of validation and clinical data in different populations, these guidelines have failed to determine the diagnostic probability for the presence of a mechanistic pain descriptor.

Diagnostic clinical prediction models use multiple variables or so called “predictors” to determine the probability for the presence of a particular outcome (i.e., condition

or injury). These clinical prediction models generally use clinically feasible predictors and aim to inform clinicians in further clinical decision-making.[11] Diagnostic clinical prediction models that can determine the type of mechanistic pain descriptor may play a crucial role in the management of persistent pain after breast cancer treatment. Therefore, our aim is to develop and internally validate three diagnostic clinical prediction models for the presence of respectively, nociceptive, neuropathic, and nociplastic pain in breast cancer survivors.

Methods

Source of data

Data were collected using a cross-sectional study design, in which participants were recruited between May 2020 and December 2022. This study was approved by the Ethical Committee of the University Hospitals Leuven (s62584, s60702) and the University Hospital of Antwerp (B322201940289), and was registered at clinicaltrials.gov (protocol number NCT03981809) prior to recruitment of participants. All participants provided written informed consent prior to enrollment. The study is reported following the recommendations of the Transparent Reporting of a multivariable prediction model for Individual Prognosis or Diagnosis (TRIPOD).[12]

Participants

Breast cancer survivors experiencing persistent pain were recruited from the oncology departments of the University Hospitals Leuven and University Hospital Antwerp. Breast cancer survivors with persistent pain were recruited using the following inclusion criteria: (1) ≥ 18 years of age, (2) treated for primary breast cancer at least three months ago, and (3) complete remission. Ongoing hormonal treatment and targeted immunotherapy were permitted. (4) Breast cancer survivors experiencing persistent pain needed to report mean pain intensity during activity ≥ 3/10 on the numeric rating scale (NRS) during the past week, with 0 indicating no pain and 10 indicating the most painful one can experience.[13,14] In addition, pain had to have a suspected causal relationship with breast cancer treatment (e.g., pain in

the axilla or shoulder, presence of widespread pain immediately after cancer treatment completion, or increased intensity of concurrent persistent widespread pain after cancer treatment). Breast cancer survivors with chemotherapy-induced peripheral neuropathy or aromatase inhibitor-associated musculoskeletal symptoms were not excluded. Breast cancer survivors were not eligible if they had (1) any active metastasis, (2) palliative status, (3) cancer recurrence, (4) bilateral cancer, (5) pregnancy or breastfeeding, (6) inability to speak and read Dutch, or (7) physical and mental inability to complete the assessment.

Data

All study participants had to fill in an online questionnaire and undergo a comprehensive assessment consisting of a physical examination, the Douleur Neuropathique en 4 questions (DN4) questionnaire, and quantitative sensory testing (QST) (Table 1). The comprehensive assessment was performed by the first author (VH) at the Department of Physical Medicine and Rehabilitation of the University Hospitals Leuven and the University Antwerp. Participants were seated in a quiet room with an approximate temperature between 21°C and 23°C.

Online questionnaires

Prior to the comprehensive assessment, the participants were asked to complete online questionnaires. Participants accessed the questionnaires via REDcap, an online platform for electronic data capturing.[15]

- Data on *breast cancer treatment* were obtained via online questioning and by consulting the electronic health records: type of breast surgery and axillary surgery, side of surgery, tumor size and lymph node stage, and type of (neo-)adjuvant treatment (radiotherapy, chemotherapy, or hormonal therapy).
- Next, questions on *participants' characteristics* were recorded, including age, sex, body mass index, social status, and hand dominance.

- For *pain characteristics,* the duration of pain (in months), pain intensity at present, maximum and minimum during the past week, and pain intensity during activity and rest during the past week were recorded using a visual analog scale (VAS). The presence of preoperative pain was recorded by evaluating the duration of pain and the time since the breast cancer diagnosis.
- Next, the participants were presented with multiple self-report questionnaires assessing psychosocial burden, disability, catastrophizing, and self-efficacy. All questionnaires were made available in their Dutch version.
    - The McGill Pain Questionnaire (MPQ) is a self-report questionnaire assessing **the sensory, affective, and evaluative characteristics of pain** using 20 groups of pain descriptors, with the first 17 groups using three pain adjectives and the last three groups using four adjectives. An overall score is calculated by summing the weighted scores or the ranks of the selected word chosen within the corresponding group (number of chosen words; range 0-20).[16,17]
    - **Depression, anxiety, and stress** over the past week were evaluated using the Depression, Anxiety, and Stress Scale (DASS-21). The DASS-21 contains 21 questions (seven for each subscale), with scores ranging from 0 (did not apply to me at all) to 3 (applied to me very much, or most of the time). Higher scores indicate a greater severity of symptoms in that subscale. [18,19] The DASS-21 has an overall good-to-excellent internal consistency (Cronbach's alpha = 0.82-0.97).[18,20]
    - The Pain Disability Index (PDI) is a brief questionnaire used to assess **disability severity**. It consists of seven items that measure the level of pain interference with various aspects of daily living on a scale from 0 to 10, with 0 indicating no disability and 10 indicating complete disability. The seven items in the PDI are summed to produce a total score, which ranges from 0 to 70, with higher scores indicating greater levels of disability.[21] The PDI

showed a high degree of internal consistency (Cronbach's alpha = 0.87) and a good relative reliability (intraclass correlation coefficient = 0.80).[21]

- **Pain catastrophizing** was evaluated using the Pain Catastrophizing Scale (PCS). This self-report questionnaire consists of 13 questions that evaluate the thoughts and feelings of previous painful experiences on a scale from 0 (not at all) to 4 (all the time). The total score ranges from 0 to 52 (with higher scores indicating a greater level of catastrophizing). In addition to the total sum of scores, three dimensions are present within the PCS: (1) rumination, defined as irrationals thoughts regarding pain (score range from 0 to 16); (2) magnification, defined as the increased threat value of pain (score range from 0 to 12); (3) helplessness, defined as the inability to handle perceptions of suffering (score range from 0 to 24).[22,23] In general, the PCS has a good internal consistency (Cronbach's alpha = 0.92) and test-retest reliability (Spearman ρ = 0.88).[24]
- The **confidence** people with persistent pain have in performing activities despite their pain was evaluated using the pain self-efficacy questionnaire (PSEQ). This 10-item self-report questionnaire uses a 7-point numerical scale ranging from 0 to 6. On this scale, 0 signifies "not at all confident" and 6 signifies "completely confident." The PSEQ covers a range of functions such as work, social activities, household chores, and pain management without medication. The total score was obtained by adding up the scores for each of the 10 items, resulting in a score ranging from 0 to 60. Higher total scores indicate stronger self-efficacy beliefs.[25] The PSEQ has a good internal consistency (Cronbach's alpha = 0.79-0.92) and good test-retest reliability (intraclass correlation coefficient 0.86).[25]
- Symptoms that may be related to the neurophysiological state, termed **central sensitization**, were evaluated using the Central Sensitization Inventory (CSI). The CSI, a self-report questionnaire, contains 25 questions,

each scaled from 0 (not at all) to 4 (all the time). The total score ranges from 0 to 100, with a score of 40 or higher score indicating the suspected presence of central sensitization.[26,27] The CSI has a high degree of internal consistency (Cronbach's alpha = 0.88) and test-retest reliability (Pearson's *r* = 0.82).[28]

Clinical assessment

- First, participants' *pain symptoms* were assessed using a body chart. This evaluation included the assessment of the most painful location and all painful symptoms for the presence of widespread pain. If the participant indicated that the pain was in the area of the chest, trunk, axilla, shoulder, or arm, it was considered local. Widespread pain was considered when other regions were marked as painful. In addition, the presence of a neuroanatomical distribution of pain or sensory dysfunction was evaluated based on the location of pain symptoms.
- Second, the *range of motion* and *strength* of the upper limbs were assessed. Range of motion of the shoulder was assessed by instructing the participants to actively move both arms above their head. Limited range of motion was indicated if apparent deficits in range of motion were visually present during flexion of the shoulder. Strength was assessed using manual muscle testing. The participants were instructed to hold their arm horizontally in the scapular plane and to resist the downward manual force of the assessor. Strength was evaluated using the Oxford scale.[29]
- Third, the area indicated as most painful was inspected for apparent *tissue changes* (e.g., redness and swelling). Axillary *web syndrome* was assessed by inspection during shoulder flexion and palpation of the cords. Additionally, the presence of *lymphedema* was evaluated using a single upper arm circumference measurement and by calculating the percentage difference between the two arms.

- Fourth, the presence of *disproportionate pain* was assessed using clinical judgment to determine whether the pain was proportionate to the breast cancer treatment and timeframe after treatment.
- For a concise overview of the clinical assessments, please refer to Table 1.

Douleur Neuropathique en 4 questions (DN4)

After the physical examination, the DN4 questionnaire**,** a tool developed for the screening of neuropathic pain, was administered. It consists of seven items related to signs and symptoms, and three items related to clinical examination. In breast cancer survivors, the DN4 is able to stratify possible, and definite postsurgical neuropathic pain using the cutoff value of 4 out of 10.[30,31]

Quantitative sensory testing (QST)

A QST assessment, consisting mainly of static and dynamic protocols that would be clinically feasible, was performed. The following parameters were assessed: mechanical detection threshold (MDT), mechanical pain threshold (MPT), pressure pain thresholds (PPT), temporal summation (TS), and conditioned pain modulation (CPM). An average wash-out period of approximately two minutes was foreseen between each test.[32] The order of testing was chosen to minimize the overlap between tests, maximize the wash-out period, and improve the practicality and time needed to perform the general comprehensive assessment.

Mechanical detection and pain thresholds were evaluated using von Frey monofilaments (Optihair2-Set, Marstock Nervtest, Germany) at the opposite tibialis anterior and the most painful location. A standardized set of 12 von Frey monofilaments (Optihair2, Marstock Nervtest, Germany) exerting forces between 0.25 and 512 mN was used to assess mechanical detection and pain thresholds (MDT, MPT). Starting with an 8 mN monofilament, the monofilaments were applied at a rate of 2 seconds on and 2 seconds off, in ascending and descending order, respectively. The participants kept their eyes closed and verbally indicated when a force was detected for the assessment of MDT (e.g., the lowest mechanical force

felt). Similarly, for the assessment of MPT (e.g., the lowest mechanical force perceived as painful), participants verbally indicated when a force was experienced as unpleasant. To reduce guessing, two successive forces had to be detected (MDT) or felt unpleasant (MPT) by the participants. The geometric means of the descending (last detected or painful stimulus) and ascending (first detected or painful stimulus) sequences were calculated (in mN). [33,34]

PPT was evaluated using a digital algometer (Wagner FDX, Greenwich CT, USA). Participants were instructed to say 'Stop' when the amount of pressure at which the perception of unpleasantness was first perceived. PPT was determined by two series of ascending pressure at a rate of approximately 0.1 kgf/s until appraised as unpleasant.[35] The arithmetic mean of the two PPT trials was used.

All mechanical thresholds were assessed at the upper part of the opposite tibialis anterior and the most painful location.[35] Detection thresholds performed at the most painful location can be used to evaluate the presence of primary hyperalgesia and allodynia (increased sensation in reaction to stimuli) or the presence of hypoalgesia and hypoesthesia (decreased sensation in reaction to stimuli).

TS and CPM were performed to evaluate aberrations in the central somatosensory processing, characterized by secondary or widespread hyperalgesia. Secondary hyperalgesia indicates a hyperexcitable central neural activity, characteristic for the neurophysiological state of central sensitization which is generally considered the underlying mechanism behind nociplastic pain.[36–38]

TS of pain was assessed using a weighted von Frey monofilament (Optihair2-Set, Marstock, Germany, 256 mN) at the upper part of the tibialis anterior muscle opposite to the side of the breast cancer treatment. Participants were asked to rate their perceived pain from 0-10 on the numeric rating scale (NRS) after the first stimulus. After the first stimulus, a train of thirty repetitions followed at a frequency of 1 Hz. Directly after the last stimulus was applied, the participants were again asked to rate their perceived pain from to 0-10 on the NRS. If the difference between the

last and first scores was > 2 on the NRS, exaggerated temporal summation of pain was assumed. We used the minimal clinically important difference of more than 2 points on the NRS to define presence of exaggerated temporal summation of pain, as recommend by the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT group).[39]

CPM was evaluated using a parallel protocol with a blood pressure cuff (Boso Profitest, Jungingen, Germany) as a conditioning stimulus and PPT at the upper part of the contralateral tibialis anterior as a test stimulus. First, a single, 8,5-cm-wide chamber blood pressure cuff was applied to the non-affected arm, 2 cm superior to the cubital fossa, and inflated manually by the assessor via hand squeeze until the participant rated the intensity of pain experienced as a 5/10 on a 0-10 NRS. Arm ischaemia was not intended to happen.[40] After 45 and 90 seconds of conditioning, PPT was performed respectively with ascending pressure at a rate of approximately 0.1 kgf/s until the participant verbally indicated that the pressure was unpleasant.[33] Cuff occlusion has been proven to provide a sufficient CPM effect and shows acceptable reliability in healthy individuals.[41] Furthermore, PPT is frequently utilized and has excellent intra-session reliability for CPM.[42,43] The absolute CPM effect was calculated by subtracting both PPT at 45 and 90 seconds of conditioning from the PPT without conditioning. The absolute CPM effect using differences in the PPT was not dichotomized between responders and non-responders.

Outcome

The outcome of our three binary diagnostic clinical prediction models is the presence of nociceptive (yes/no), neuropathic (yes/no), or nociplastic pain (yes/no). In the most ideal situation, the presence of the outcome should be determined using the most reliable, widely used method, or 'reference standard'.[11] Currently, no such 'reference standard' diagnostic tool exists for the presence of these mechanistic pain descriptors. To identify the presence of each mechanistic pain descriptor, we adopted a consensus-based approach based on the existing literature in non-cancer

populations [9,10] and cancer populations [30,44], combined with the clinical and scientific expertise of our research team for pain and cancer survivorship.[45–47] As a result, the total DN4 score, a tool developed for the screening of neuropathic pain, was combined with the presence or absence of exaggerated TS at the upper part of the tibialis anterior muscle opposite to the affected side. By combining these variables, the following criteria were established for each mechanistic pain descriptor.

- *Neuropathic pain* was considered when the participants scored ≥ 4 on the DN4 questionnaire at the most painful location and did not exhibit an exaggerated temporal summation of pain at a remote location.
- *Nociceptive pain* was considered when participants scored < 4 on the DN4 questionnaire at the most painful location and did not exhibit an exaggerated temporal summation of pain at a remote location.
- *Nociplastic pain* was considered when participants exhibited an exaggerated temporal summation of pain at a remote location. For nociplastic pain, the score of the DN4 questionnaire was not considered as patients with presumed nociplastic pain are also known to exhibit neuropathic-like signs and symptoms and exhibit high scores on neuropathic pain questionnaires.[50,51]

Table 1. Detailed overview of the comprehensive assessment with the initial measurements of all candidate predictors.

	Candidate predictor	Predictor assessment	Predictor outcome	Location
Candidate predictors obtained from **online questionnaires & electronic health record**	**Age**	Self-reported questionnaire	Age in years	n/a
	Body Mass Index	Self-reported questionnaire	kg/cm^2	n/a
	Tumor location	Electronic health record	Left/Right	n/a
	Type of breast cancer surgery	Electronic health record	Lumpectomy vs. Mastectomy	n/a
	Type of axillary surgery	Electronic health record	SLNB vs. ALND	n/a
	Use of chemotherapy	Electronic health record	Yes/No	n/a
	Use of radiotherapy	Electronic health record	Yes/No	n/a
	Use of endocrine therapy	Electronic health record	Yes/No	n/a
	Use of targeted therapy	Electronic health record	Yes/No	n/a
	Time since diagnosis (months)	Electronic health record	Time in months	n/a
	Pain intensity, now	Self-reported questionnaire	Visual Analogue Score (0-100)	General
	Pain intensity, past week - minimum pain - maximum pain - average pain during activity - average pain during rest	Self-reported questionnaire	Visual Analogue Score (0-100)	General
	Pain duration (in months)	Self-reported questionnaire	Time since start pain in months	General
	Central Sensitization Inventory	Self-reported questionnaire 25 questions	Likert type scale, total score 0-100	General
	McGill Pain Questionnaire	Self-reported questionnaire 20 groups pain descriptors	Number of chosen words, total score 0-20	General
	Depression Anxiety Distress Scale 21	Self-reported questionnaire 21 questions	Likert type scale (0-3), total score 0-36	General
	Pain Disability Index	Self-reported questionnaire 7 questions	Scale 0-10, total score 0-70	General

Table 1. Continued

	Pain Catastrophizing Scale	Self-reported questionnaire 13 questions	Likert type scale (0-4), total score 0-52	General
Candidate predictors obtained during **clinical assessment**	**Most painful location**	Body chart	Location of most pain	General
	Presence of widespread pain	Body chart	Presence of regional / widespread of pain: Yes / No	General
	Myofascial tissue - Visible tissue damage - Axillary Web Syndrome	Visual inspection and palpatory assessment	Likert-type scale (0-5), completely agree - completely disagree, for each subdomain	Most painful location
	Lymphedema	Single circumference measurement upper limb	Difference in circumference between affected and unaffected upper limb, expressed in %	Affected and unaffected upper arm, 30 cm proximal of the lateral epicondyle
	Range of motion	Visual inspection	Limited range of motion: Yes / No	Affected and unaffected upper limb
	Strength, Flexion	Manual muscle testing	Oxford scale 0-5	Affected upper limb
	Neuroanatomical distribution of pain or sensory dysfunction	Clinical assessment	Presence of a neuroanatomical distribution of pain: Yes / No	Most painful location / general
	Disproportionate pain	Clinical assessment	Presence of disproportionate pain: Yes / No	Most painful location
DN4	**Douleur Neuropathique 4 Questionnaire**	Questionnaire and clinical assessment (brush, pinprick sensation)	Total score 0-10	Most painful location
Candidate predictors obtained during **quantitative sensory testing**	**Pressure pain threshold**	Digital pressure algometer	Method of limits: arithmetic mean of 2 trials (0-12 kgf)	Most painful location & Contralateral tibialis anterior
	Mechanical detection threshold	von Frey monofilaments	Geometric mean first and last detected stimulus (0-512 mN)	
	Mechanical pain threshold	von Frey monofilaments	Geometric mean first and last painful stimulus (0-512 mN)	
	Temporal summation	256 mN von Frey monofilament	Difference in pain intensity immediately after 30 stimulations and after the first stimulation (NRS)	

Table 1. Continued

Conditioned pain modulation	Blood pressure cuff and algometer	Difference in PPT between a conditioned test stimulus and test stimulus without conditioning (kg/cm^2)	Non-affected upper arm (conditioning) & tibialis anterior (test stimulus)

NRS= Numeric rating scale, SLNB= Sentinel lymph node biopsy, ALND= Axillary lymph node dissection

Predictors

For the selection of clinical diagnostic predictors, we used available literature and subject matter knowledge to select clinically meaningful predictors. First, we compiled a list of candidate predictors relevant to all the three mechanistic pain descriptors. These predictors are related to patient and cancer treatment characteristics and were selected based on previous research: age, body mass index (BMI), type of breast cancer surgery (breast conserving surgery vs. mastectomy), type of axillary surgery (sentinel lymph node biopsy vs. axillary lymph node dissection) and, the use of radiotherapy.[50–52]

Second, for each mechanistic pain descriptor, additional predictors were selected based on previous literature [53] and expert consensus within our research team.[45–47] Predictors that were not selected for the model were considered unclear, impractical, or not supported by sufficient evidence. Furthermore, we attempted to include as few predictors as possible in each model to maximize the feasibility and minimize model overfitting.

Nociceptive pain:

1. Difference in pain intensity during rest and activity (VAS)
2. General limited range of motion of the shoulder: yes - no
3. Widespread character of pain: yes - no

Increased pain during activity was considered a feature of nociceptive pain by consensus of experts in the field of pain, suggesting a more mechanically predictable pain.[53] Restricted range of motion of the upper limb is a commonly reported side effect of breast cancer treatment and is often associated with nociceptive pain.[45,53–

[55] Localized pain, in contrast to widespread or regional pain, was considered to be a feature of nociceptive pain, resembling local nociceptive processes.[53] Localized pain was defined as the pain in the area of the chest, trunk, axilla, shoulder, or arm.

Neuropathic pain:

1. Single DN4 item 1 (burning pain): yes - no
2. Single DN4 item 8 (touch hypoesthesia): yes - no
3. Neuroanatomical distribution of pain: yes - no

The predictive variables for neuropathic pain were selected to resemble the updated grading system for neuropathic pain published by Finnerup and colleagues.[9] Therefore, two items of the DN4 were selected as predictors: one related to the sensory descriptor and one related to bedside sensory examination. Following breast cancer surgery, the breast and the area innervated by the intercostobrachial nerve (axilla, upper side of the chest, lateral breast, and medial upper arm) comprise the neuroanatomical area, in which typical neuropathic pain characteristics can be expected when the respective nerve is affected

Nociplastic pain:

1. Central sensitization inventory: scores ranging from 0-100
2. Pressure pain threshold at a remote location: 0-12 kgf
3. Widespread character of pain: yes - no
4. Presence of preoperative pain: yes - no

The use of the CSI and PPT at a remote location was proposed in the clinical criteria and grading system by the IASP Terminology Task Force for nociplastic pain in the non-cancer population[10], and these criteria were subsequently adapted to cancer survivors.[44] A widespread distribution of pain is characteristic of nociplastic pain, related to the generalized (hyper)excitability of the somatosensory nervous system.[53] Multiple studies in cancer and non-cancer populations have indicated that the presence of prior (and thus here preoperative) pain is a strong predictor for the development of central sensitization, and in the present study thus possibly nociplastic pain after breast cancer surgery.[52,56,57]

Sample size

Sample size was calculated following the recommendations for sample size calculation required for developing a clinical prediction model, by Riley et al.[58]. We used a c statistics of 0.74 and, 20.3% for the prevalence of persistent pain in BCS, as reported by Meretoja et al..[50] An initial sample size of 249 was calculated based on a priori defined, preliminarily amount of 10 predictive variables. Sample size calculations were performed using the *pmsampsize* package in R.[59]

Missing data

Missing data in any predictor variables was handled by multiple imputation for which we generated 50 imputed datasets.[60] Performance metrics were pooled across the imputations using Rubin's rules.[61] Predictors with more than 20% missingness were excluded.[60]

Statistical analysis

All analyses were conducted using R version 4.2.2.[62] Continuous variables are reported as mean and standard deviation (SD) or median and interquartile range (IQR); categorical variables are reported as frequencies and proportions.

Before conducting a logistic regression analysis and minimizing multicollinearity, we performed a correlation analysis among the predictors of each mechanistic pain descriptor. If two predictors demonstrated a correlation coefficient exceeding 0.7, the predictor that was considered less feasible or relevant was excluded from logistic regression analysis to avoid multicollinearity. After correlation analysis, we performed a logistic regression analysis to examine the relationship between the predictors and the binary outcome, with the presence or absence of a certain mechanistic pain descriptor. The logistic regression model was fitted using the *brglm* package in R, which allows the fitting of binomial regression models with beta-binomial priors. To assess the performance of the clinical prediction models, we calculated two performance measures: area under the curve (AUC) and Brier score. Using Harrell's enhanced bootstrap method with the *boot* package, we performed

bootstrapping with 1000 iterations to estimate the optimism in the model's performance. This method involves drawing bootstrap samples, fitting the model to each sample, and calculating performance measures for each sample. The apparent and optimism-corrected area under the curve (AUC) and Brier scores were reported. The optimism-corrected AUC or Brier score is defined as the apparent performance measure minus the bootstrap-corrected performance measure estimated using Harrell's enhanced bootstrap method. The AUC or c statistic in binary predictive models represents the discriminative ability of the model and corresponds to the probability that a random subject with the clinical outcome has a higher predicted probability than a random subject without the clinical outcome.[63] The Brier score represents an overall performance measure and measures the mean squared difference between predicted probabilities and actual outcomes, with lower values indicating better calibration and accuracy of the models. A non-informative model with 50% incidence of the outcome can range from 0 for a perfect model to 0.25. The maximum Brier score for a model is lower when the incidence of the outcome is lower.[63,64]

Results

Participants

A total of 92 breast cancer survivors were eligible and included in the development of the three preliminary prediction models. The main exclusion criteria were insufficient pain (n = 29) and a lack of interest in participating (n =26). Figure 1 depicts the flow of study participants. Eight participants were excluded because they had over 20% missing data.

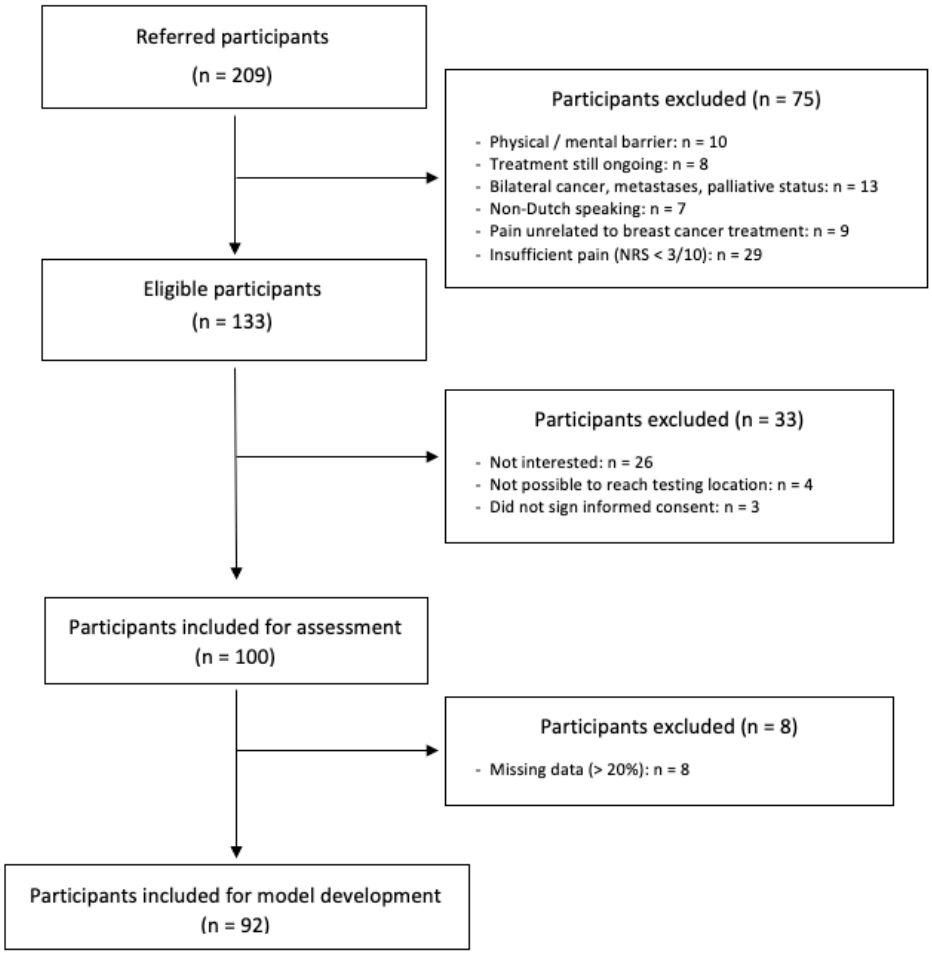

Figure 1. Flowchart of the study population.

Patient and tumor characteristics are shown in Table 2. Breast cancer survivors had a mean (SD) age of 54.85 (9.92) and a mean average pain intensity during rest the last past week of 39.02 (22.76). Of the 92 breast cancer survivors, 27.1% (n=25) showed a predominant nociceptive pain mechanism, 31.5% (n=29) showed a predominant neuropathic pain mechanism, and 41.3% (n=38) showed a predominant nociplastic pain mechanism (Table 3).

Table 2. Patient and tumor characteristics. Mean ± SD, median (IQR) and range are presented unless specified otherwise (n = 92).

Patient characteristics		Mean ± SD	Median (IQR)	Range
Patient-related characteristics	**Age** (years)	54.85 ± 9.92	54 (13)	34 - 84
	Body mass index (kg/m^2)	26.18 ± 4.28	26.31 (5.88)	17.31 - 41.09
	Social status	n (%)		
	Unemployed	15 (16.3%)		
	Partially employed	22 (23.9%)		
	Fully employed	31 (34.7%)		
	Retired	24 (26.1%)		
	Dominant side, right, n (%)	89 (96.7%)		
Pain-related characteristics	**Pain intensity, now** (VAS 0-100)	47.20 ± 22.50	50.00 (38.00)	7 - 88
	Average pain intensity during activity, past week (VAS 0-100)	49.63 ± 21.39	48.50 (36.00)	8 - 92
	Average pain intensity during rest, past week (VAS 0-100)	39.02 ± 22.76	33.00 (34.50)	0 - 87
	Average pain intensity minimum, past week (VAS 0-100)	26.2 ± 18.5	23.5 (26.8)	0 - 65
	Average pain intensity maximum, past week (VAS 0-100)	71.7 ± 16.8	73.0 (21.3)	17 - 100
	Location of the most painful site	n (%)		
	Chest or lateral trunk	40 (43.5%)		
	Arm, shoulder, or axilla	28 (30.4%)		
	Chest, lateral trunk, arm, shoulder, and axilla	17 (18.5%)		
	Chemotherapy-induced neuropathy	14 (15.2%)		
	Widespread pain	9 (9.8%)		
	Predominant mechanistic pain descriptor	n (%)		
	Nociceptive pain	25 (27.1%)		
	Neuropathic pain	29 (31.5%)		
	Nociplastic pain	38 (41.3%)		
Breast cancer-related characteristics	**Time since cancer diagnosis** (months)	51.1 ± 48.5	37.5 (43.3)	
	Time since end of cancer treatment (months)	51.1 ± 64.9	30.0 (54.0)	
	Tumor location, right, n (%)	47 (51.1%)		
	Tumor size (histopathological staging)	n (%)		
	pTx, pTis, pT0	12 (13.0%)		
	pT1	31 (33.7%)		
	pT2	26 (28.3%)		
	pT3	12 (13.0%)		
	unknown (Tx-T3)	11 (12.0%)		
	Lymph node stage (histopathological staging)	n (%)		
	pN0	39 (42.2%)		
	pN1	29 (31.5%)		
	pN2	9 (9.8%)		
	pN3	4 (4.3%)		
	unknown	11 (12.0%)		

Table 2. Continued

Breast cancer-related characteristics	**Type of surgery**	n (%)
	Mastectomy & SLNB	24 (26.0%)
	Mastectomy & ALND	33 (35.9%)
	Mastectomy only	1 (1.1%)
	Breast conserving surgery & SLNB	18 (19.6%)
	Breast conserving surgery & ALND	12 (13.0%)
	Breast conserving surgery only	2 (2.2%)
	Axillary lymph node dissection only	2 (2.2%)
	Radiotherapy, yes, n (%)	67 (72.8%)
	Chemotherapy	n (%)
	Paclitaxel (Taxol) or Docetaxel (Taxotere)	57 (62.0%)
	Other	3 (3.2%)
	No chemotherapy	32 (34.8%)
	Endocrine therapy	n (%)
	Tamoxifen	29 (31.5%)
	Aromatase inhibitors	36 (39.1%)
	No hormonal therapy	29 (31.5%)
	Target therapy	n (%)
	Trastuzumab only	11 (12.0%)
	Trastuzumab & Pertuzumab	5 (5.4%)
	No target therapy	76 (82.6%)

VAS= Visual analogue score, SLNB= Sentinel lymph node biopsy, ALND= Axillary lymph node dissection

Model development and performance

Three diagnostic clinical prediction models were developed for each mechanism of pain. All the predictors included in the final model are presented in Table 3.

Table 3. Overview of the variables that defined the outcome of the models and predictors presented for each clinical prediction model and for all participants. Mean ± SD, median (IQR) are presented unless mentioned otherwise.

Outcome variable / Predictor	**All participants (n=92)**	**Nociceptive pain (n=25)**	**Neuropathic pain (n=29)**	**Nociplastic pain (n=38)**
DN4 total score /10	4.09 ± 2.29 4.00 (4.00)	1.40 ± 1.02 1.00 (1.00)	5.55 ± 1.30 5.00 (3.00)	4.74 ± 1.97 5.00 (2.00)
DN4 ≥ 4/10	58 (63.0%)	0 (0%)	29 (100%)	29 (76.3%)
Temporal summation score	2.45 ± 2.25 2.00 (3.00)	0.88 ± 0.95 1.00 (2.00)	0.86 ± 0.97 1.00 (2.00)	4.68 ± 1.54 4.00 (3.00)
Age	54.85 ± 9.86 54.00 (13.00)	51.44 ± 8.95 50 (14.00)	55.86 ± 11.62 53.00 (17.00)	56.32 ± 8.38 56.50 (11.00)
Body mass index	26.18 ± 4.25 26.31 (5.88)	26.59 ± 3.64 26.47 (5.59)	24.91 ± 4.22 24.91 (6.30)	26.88 ± 4.43 27.01 (6.29)
Type of breast surgery: Mastectomy, n (%)	55 (59.78%)	14 (56.0%)	14 (48.3%)	27 (71.1%)
Type of axillar surgery: ALND, n (%)	51 (55.43%)	13 (52.0%)	14 (48.3%)	24 (63.2%)

Table 3. Continued

Presence of radiation therapy, n (%)	67 (72.8%)	15 (60.0%)	21 (72.4%)	31 (81.6%)
Nociceptive pain				
Difference in VAS during activity and rest	10.61 ± 20.20 7.50 (25.50)	7.88 ± 24.65 2.00 (32.00)		
Limited shoulder range of motion, n (%)	58 (63.0%)	19 (36.0%)		
Absence of widespread pain, n (%)	49 (53.3%)	16 (64.0%)		
Neuropathic pain				
DN4 item 1 (burning), n (%)	31 (33.7%)		16 (55.2%)	
DN4 item 8 (hypoesthesia), n (%)	55 (59.8%)		23 (79.3%)	
Neuroanatomical location symptoms, n (%)	44 (47.8%)		17 (58.6%)	
Nociplastic pain				
Presence of widespread pain, n (%)	43 (46.7%)			24 (63.2%)
Presence of preoperative pain, n (%)	20 (21.7%)			7 (18.4%)
PPT at remote location	3.75 ± 1.84 3.44 (2.55)			3.15 ± 1.69 2.74 (2.01)
Central sensitization inventory score	45.15 ± 14.99 46.50 (19.00)			47.61 ± 16.13 48.00 (20.25)

ALND= Axillary lymph node dissection, DN4= Douleur Neuropathique 4 questionnaire, VAS= Visual analogue scale, PPT= Pressure pain threshold

The apparent and optimism-corrected performance measures are listed in Table 4. Multicollinearity between the definite predictive variables for each model was avoided by assessing the mutual correlations; however, no strong correlations (>0.7) were found.

Eight predictors were selected for the *nociceptive pain* clinical prediction model: age, BMI, age, type of axillary and breast surgery, use of radiotherapy, difference in pain intensity during rest and activity in the past week, limited shoulder ROM due to pain, and absence of widespread pain. The nociceptive pain model exhibited an optimism-corrected AUC and Brier score of 0.592 (95% CI 0.583 to 0.794) and 0.22 (95% CI 0.136 to 0.229), respectively (Table 4).

The clinical prediction model for *neuropathic pain* contained nine predictors: age, BMI, type of axillary and breast surgery, use of radiotherapy, DN4 item 1 (presence

of burning sensation), DN4 item 8 (presence of hypoesthesia to touch), and the presence of a neuroanatomical distribution of pain. The neuropathic pain model showed an optimism-corrected AUC and Brier score of 0.652 (95% CI 0.651 to 0.827) and 0.226 (95% CI 0.142 to 0.231), respectively (Table 4).

The *nociplastic pain* model also contained eight predictors: age, BMI, type of axillary and breast surgery, use of radiotherapy, presence of widespread pain, presence of preoperative pain, symptoms related to central sensitization, and PPT performed at a remote location. The nociplastic pain model showed optimism-corrected AUC and Brier scores of 0.681 (95% CI 0.660 to 0.840) and 0.240 (95% CI 0.154 to 0.242), respectively (Table 4).

Table 4. Apparent and optimism-corrected performance measures for each clinical prediction model

	Apparent performance measures		**Optimism-corrected performance measures**	
	AUC (95% CI)	*Brier score (95% CI)*	*AUC (95% CI)*	*Brier score (95% CI)*
Nociceptive	0.695 (0.632 - 0.737)	0.186 (0.173 - 0.210)	0.592 (0.583 - 0.794)	0.224 (0.136 - 0.229)
Neuropathic	0.738 (0.676 - 0.776)	0.188 (0.175 - 0.210)	0.652 (0.651 - 0.827)	0.226 (0.142 - 0.231)
Nociplastic	0.758 (0.702 - 0.789)	0.199 (0.185 - 0.223)	0.681 (0.660 - 0.840)	0.240 (0.154 - 0.242)

AUC= Are under the curve, CI= Confidence interval

Discussion

This study is the first to develop a preliminary diagnostic clinical prediction model for the presence of a predominant mechanistic pain descriptor in breast cancer survivors with persistent pain after cancer treatment. All the developed models exhibited moderate discriminative ability, with optimism-corrected AUCs ranging from 0.592 to 0.681. The AUC values indicate that the models have moderate success in evaluating the presence of a certain mechanistic pain descriptor. Furthermore, the optimism-corrected Brier scores range from 0.224 to 0.240. Brier scores suggest that the models are relatively consistent and provide accurate probabilistic predictions. Overall, these results indicate that the developed models demonstrate a reasonable level of discriminative ability and accuracy.

Based on the total score of the DN4 and TS of pain at a remote location, 27.1% of breast cancer survivors showed a predominant nociceptive pain mechanism, 31.5% showed a predominant neuropathic pain mechanism, and 41.3% showed a predominant nociplastic pain mechanism. The number of participants classified as having neuropathic pain is similar to that in previous studies reporting neuropathic pain prevalence rates ranging from 32.6% to 58.2%.[65] Furthermore, the number of participants classified as having nociplastic pain in our study can be considered high. However, the presence of nociplastic pain in breast cancer survivors has not been thoroughly investigated as most studies only differentiated between neuropathic and non-neuropathic (nociceptive) pain [66], and as nociplastic pain has only been introduced by the IASP recently.[7] Nonetheless, the limited amount of studies that attempted to distinguish pain types different from neuropathic and nociceptive pain usually reported on the presence of central sensitization, considered the underlying mechanism of nociplastic pain.[36–38] A cross-sectional study by De Groef et al. reported that 38% of breast cancer survivors showed signs of central sensitization when evaluated by the CSI.[45] In addition, Leysen et al. observed a "CS pain component" in 44% of breast cancer survivors, using the same CSI.[26] As studies on nociplastic pain in cancer survivors are scarce, we relied on studies from the musculoskeletal field to guide the selection of predictors.[10,53] We therefore included the CSI as a predictor for nociplastic pain as patients suffering from primary chronic pain such as fibromyalgia showcase heightened psychosocial burden.[67] Previous research however demonstrated that the CSI is more closely related to psychosocial factors than to aberrations in central pain mechanisms such as present in nociplastic pain.[68,69] Alternatively, other questionnaires assessing psychosocial burden, such as the PCS or DASS-21, could have been included but were not considered as the CSI evaluates multiple psychosocial factors in one instrument and has proven to be feasible in clinical practice.[70] In our study, PPT at a distant location was used a measure of general nociceptive sensitivity instead of relying on solely the CSI for nociplastic pain.[44] Our nociplastic pain model included: a measurement of

nociceptive sensitivity through PPT, assessment of psychosocial burden using the CSI and two pain-related questions: presence of widespread pain and preoperative pain.

Although this study lacked a 'reference standard' to determine the presence of our outcomes, such as a specific predominant mechanistic pain descriptor, we used methods that could be considered as a 'reference standard.' To determine our outcomes, we used the DN4 questionnaire with a cutoff score of 4/10, combined with the presence or absence of exaggerated TS of pain at a remote location. The DN4 is recommended by neuropathic pain guidelines [9], is considered a valid and reliable questionnaire for the screening of neuropathic pain in breast cancer survivors [30], and our study demonstrated similar prevalence rates compared to other studies.[65] Although recommendations of its use are lacking, the TS of pain has been used extensively in research to evaluate the presence of aberrant central somatosensory processing in cancer and non-cancer populations.[71,72] The presence of remote exaggerated TS of pain indicates secondary or widespread hyperalgesia, characteristic of the neurophysiological state of central sensitization, which is generally considered the underlying mechanism of nociplastic pain. In order to assign nociplastic pain to participants, the DN4 was considered less important, as patients with nociplastic pain are known to demonstrate neuropathic-like symptoms.[48,49] In our sample, 29 breast cancer survivors demonstrated a combination of high scores on the DN4 (≥4/10) and the presence of exaggerated TS of pain, corresponding to 76.3% of the participants assigned with the nociplastic pain. Therefore, nociplastic pain is often presented as a continuum of pain manifestations with varying degrees of presentation.[73] It is possible that these breast cancer survivors suffered from nociplastic pain concurrently with neuropathic pain, or that they only demonstrated nociplastic pain with neuropathic-like symptoms. The selected variables to define our outcome were not able to distinguish between these two groups; however, alternatives besides a "mixed pain mechanism" model are not available. In addition, the development of such a "mixed pain mechanism" clinical prediction model might hinder clinical implementation, as more predictors need to be assessed. In addition,

the addition of a fourth model might be redundant, as our three models make it possible to evaluate the presence or absence of all three mechanistic pain descriptors in a single patient.

Strengths and limitations

The major strength of this study is its "methods over metrics" perspective using a rigorous and methodological approach to model development, consistent with prior recommendations. [59,60,63,74] Another strength is that the selection of predictive variables was based on previous literature and knowledge of the subject matter within the research team, providing a set of clinical variables aimed at being feasible. This method of selecting predictive variables is more appropriate than performing univariate analyses and basing predictor selection solely on a p-value.[59,60,63,74] Such a univariate analysis could produce an unfeasible set of predictors, which in turn would render the prediction model useless. Finally, except for the eight participants who were excluded due to an overall high percentage of missing data (> 20%), there were no missing data in the selected predictors.

This study has several limitations that need to be addressed, the first of which is the small sample size. An initial sample size of 249 was calculated a priori using the recommendations of Riley et al. and data from Meretoja et al.; however, we were only able to include 92 breast cancer survivors with persistent pain.[50,58] This insufficient sample size limited the internal validity of our clinical prediction models and, consequently, limited further clinical suggestions for the use of the three models. Covid-19 restrictions and the subsequent hesitancy to re-enter hospitals have hampered recruitment. In addition, pain in cancer survivors is still under-recognized by physicians, and patients often apply a do not ask, do not tell principle during their consultations.[75] Therefore, it is possible that cancer survivors with persistent pain were not properly referred. Furthermore, this study was unable to externally validate the clinical prediction models on an independent validation dataset.

Implications for clinical practice and future research

This study is one of the first to develop a preliminary diagnostic clinical prediction model for the presence of a predominant mechanistic pain descriptor in breast cancer survivors with persistent pain. As these prediction models do not require highly specialized equipment, we assume that they are feasible for clinical use. However, as we were unable to include a sufficient number of breast cancer survivors with persistent pain, our models have not yet been deemed valid for clinical implementation. Therefore, we are unable to provide a clinical tool or spreadsheet to implement these models in clinical practice.

Future research should focus on the acquisition of data on pain in breast cancer survivors, and sequentially improve the internal validity of these models. Additionally, the model should be updated if other predictors are considered relevant for inclusion in the prediction models. Ideally, external validation of these models should follow using an independent, external validation dataset resembling real-life situations. Finally, after the prediction models are externally validated, a knowledge translation strategy that aims to maximize their adoption and appropriate use should be implemented, after which the clinical feasibility of the models can be determined. However, pending external validation, these preliminary models can already undergo pilot testing with healthcare providers.

Conclusions

All three clinical prediction models for neuropathic, nociceptive, and nociplastic pain demonstrated average discriminative ability and showed promise in classifying pain symptoms into mechanistic pain descriptors in breast cancer survivors with persistent pain. However, additional data and external validation are required to provide fully validated and useful prediction models.

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General discussion

By 2024 approximately 10.000 Belgian women will be diagnosed with breast cancer.[1] Fortunately, owing to advances in detection accuracy and treatment modalities, the overall five-year survival rate of breast cancer patients has improved to 92.4%.[1] Nevertheless, breast cancer treatment often results in side effects such as chronic pain.[2] Such pain is known to negatively affect the quality of life of breast cancer survivors.[3–5] Different types and mechanistic descriptors (nociceptive, neuropathic, and nociplastic) of pain exist; however, the prevalence of these mechanistic descriptors of pain in (breast) cancer survivors remains unknown. Furthermore, mechanism-based approaches to pain have been suggested to improve pain management.[6,7] Evaluation of pain and sensory dysfunction using modalities such as quantitative sensory testing (QST) has been proposed within this mechanism-based approach.[8] Unfortunately these modalities remain mostly inapplicable in clinical practice, hindering mechanism-based approaches to pain in daily practice. In addition to clinical alternatives for QST, the development and use of diagnostic clinical prediction models for the evaluation of mechanistic pain descriptors can aid in treatment stratification and future decision-making in clinical practice.

Therefore, this project aimed to answer the following research questions:

1. What is the prevalence of pain and what are the characteristics of pain experienced by survivors of solid cancers?
2. What are the differences in somatosensory function in terms of loss and gain in function between breast cancer survivors with and without persistent pain using reference data from healthy controls and patients with fibromyalgia?
3. What is the concurrent validity of the clinically applicable protocols for dynamic quantitative sensory testing in breast cancer survivors with persistent pain when compared to a reference test?
4. How feasible, useful, and valid is bedside quantitative sensory testing to assess somatosensory function in cancer survivors with persistent pain?

5. How can mechanistic pain descriptors such as nociceptive, neuropathic, and nociplastic pain be evaluated in clinical practice in breast cancer survivors with persistent pain using clinical prediction models, and what is the internal validity of these models for the evaluation of mechanistic pain descriptors in such patients?

1. Main findings

Before the start of this project, data on the prevalence of pain, especially pain characteristics in solid cancer survivors, were scarce. The last systematic review, conducted in 2016, included studies published until 2014. This systematic review concluded that 39.3% of cancer survivors who completed curative treatment experienced pain.[9] Even though informative, other pain characteristics besides the prevalence and severity were not presented. Therefore, in Chapter 1, we aimed to provide an update on the overall prevalence of pain in solid cancer survivors and, whenever available, provide the prevalence rates of the different mechanistic pain descriptors (nociceptive, neuropathic, and nociplastic), as well as different pain characteristics (i.e., location, severity, and duration) and assessment methods of the patients' pain complaints.

1.1 Chapter 1. What is the prevalence and characteristics of pain experienced by solid cancer survivors?

We systematically reviewed the existing literature from 2014 to the present and performed a meta-analysis on the prevalence and characteristics of pain in solid cancer survivors. Thirty-eight articles with a low risk of bias were included in the meta-analysis, resulting in a pooled pain prevalence of 47% (95%CI 39–55%), with a heterogeneity of 98.99%. Studies examining the prevalence of pain in breast cancer survivors (BCS) were the most prevalent (n=30, 80.9%; 11,996 participants). Consequently, 84.2% of the studies only included female participants. The results of this systematic review should be interpreted with caution because of the substantial unexplained heterogeneity. Meta-regression analysis using cancer type, treatment location, pain measurement, and follow-up time as covariates did not explain the high heterogeneity. Furthermore, owing to the lack of data, we were unable to provide prevalence data regarding the presence of different mechanistic pain descriptors or other pain characteristics in solid cancer survivors.

Even though scientific research into pathophysiology of persistent pain after breast cancer treatment has improved our understanding of persistent pain after breast cancer treatment, the mechanisms underlying this debilitating side effect remain elusive. It is unclear why some BCS experience persistent pain while others do not. Several studies proposed that BCS with persistent pain exhibit aberrations in peripheral and central somatosensory functioning.[10–16] Peripheral and central somatosensory functioning play an instrumental role in the perception of pain and changes within these pathways are possibly associated with the presence of persistent pain in BCS. In Chapter 2, we compared the somatosensory profiles of BCS with healthy controls serving as a negative control group and patients with fibromyalgia serving as a positive control group (i.e., showing signs of aberrant central somatosensory functioning).

1.2 Chapter 2. What are the differences in somatosensory function in terms of loss and gain in function between breast cancer survivors with and without persistent pain using reference data from healthy controls and patients with fibromyalgia?

Using a cross-sectional study design, we aimed to compare QST data and describe the somatosensory profiles of BCS with and without persistent pain by comparing them with each other and with reference data from healthy controls and patients with fibromyalgia. Patients suffering from fibromyalgia are considered a positive control group while healthy individuals are considered a negative control group. Differences and similarities were found in the somatosensory profiles of BCS with and without persistent pain compared with the healthy control group and patients with fibromyalgia. BCS with persistent pain experienced hyperesthesia (or gain in sensory function, hyperalgesia) for pressure at the trunk compared with healthy controls and pain-free BCS. Both pain-free BCS and BCS with persistent pain demonstrated hypoesthesia (or loss of sensory function) in response to thermal stimuli at the trunk. Furthermore, they demonstrated hypoesthesia for mechanical detection at the trunk compared to healthy controls and patients with fibromyalgia. Regarding the dynamic QST paradigms, BCS with persistent pain exhibited higher

temporal summation (TS) of pain scores than BCS without pain but not compared to patients with fibromyalgia or healthy controls. Conditioned pain modulation (CPM) did not differ between the groups, suggesting that inhibition of nociceptive signals by the central somatosensory nervous system was not affected in BCS with or without pain. Furthermore, we investigated psychosocial burden and found that BCS with persistent pain showed an increased psychosocial burden compared to pain-free BCS, and similar to patients with fibromyalgia. Taken together, these findings suggest that BCS with persistent pain experience aberrations in the peripheral somatosensory nervous system, such as hypoesthesia for thermal and mechanical stimuli, along with hyperesthesia (hyperalgesia) in pressure pain threshold (PPT) at the trunk. With regard to the central somatosensory nervous system, BCS with persistent pain demonstrate increased facilitation of nociceptive signals, while demonstrating normal inhibition of nociceptive signals as healthy controls or pain-free BCS.

The evaluation of somatosensory function in clinical practice is a longstanding challenge, particularly for the evaluation of central nociceptive processing using dynamic QST paradigms. Previous studies have suggested that dynamic QST paradigms can provide important information for stratification and decision-making in clinical practice.[6,7] *However, a major barrier to the implementation of dynamic QST paradigms in clinical practice is that it is time-consuming, expensive, and requires special training. Attempts have been made to develop bedside QST protocols that are suitable for clinical use. However, these approaches have not been validated in comparison with QST protocols, which are considered reference laboratory-based protocols. In Chapter 3, we investigated the concurrent validity of dynamic bedside QST protocols compared to a reference protocol.*

1.3 Chapter 3. What is the concurrent validity of the clinically applicable protocols for dynamic quantitative sensory testing in breast cancer survivors with persistent pain when compared to a reference test?

In this cross-sectional study, the concurrent validity of two clinically applicable protocols (also known as bedside tests) for CPM and TS was investigated by comparing both protocols with a reference protocol for each dynamic QST paradigm. For the bedside *CPM protocol*, we utilized a blood pressure cuff (BPC) and cold pressor test (CPTe) as conditioning stimuli at the unaffected upper limb, respectively. PPT was used as a test stimulus at the upper part of the tibialis anterior muscle using a parallel protocol. To evaluate *TS of pain* using bedside tools, we used a von Frey monofilament 256 mN) and an algometer 1 kg/cm^2) to exert 30 stimuli at a frequency of 1 Hz at the affected site trunk) and the opposite tibialis anterior muscle. The TSA-2 by Medoc Ramat Yishai, Israel) was used for the *CPM reference protocol*, which consisted of a parallel heat stimulation on the volar side of both forearms. Prior to the parallel stimulation, the intensity of the heat stimulus was individualized. The *TS reference protocol* consisted of 30 repetitive heat stimuli at the trunk and unaffected tibialis anterior muscle using the TSA-2 and same individualized heat temperature that was determined in the CPM reference protocol. Our study found that both bedside CPM protocols were strongly correlated with each other r=0.787-0.939, p<0.005), but not correlated with the reference protocol. The bedside TS protocols were moderately correlated r=0.455, p=0.012) with each other at the lower limb, but not at the trunk, using absolute change scores. No significant correlation was found between the bedside and reference TS protocols. These findings suggest that dynamic bedside QST protocols are well correlated with each other, and are thus interchangeable for use in clinical practice. The participants preferred the use of a BPC and algometer for the evaluation of CPM and TS, respectively.

Bedside QST protocols have been developed to improve their implementation in both clinical research and practice, reducing the time to perform, and providing cheaper and less complex alternatives to laboratory-based testing

protocols. For clinical practice, bedside QST protocols are only useful when the end user finds them feasible and of added value in clinical practice. Therefore, in Chapter 4, we questioned physical therapists regarding the use of bedside QST in their practice.

1.4 Chapter 4. How do physical therapists perceive the feasibility, utility, and validity, including face and content validity, of utilizing bedside quantitative sensory testing to assess somatosensory function in cancer survivors with persistent pain?

A cross-sectional study of 40 Dutch-speaking physical therapists (PTs) was conducted using an online survey. Twenty physical therapists from Belgium and 20 physical therapists from the Netherlands were included. Several bedside QST alternatives were presented in two videos: one video introduced the theoretical background information, and the other contained clear instructions with a practical demonstration. The QST paradigms that were shown to the participants were as follows: cold pain threshold (CPTh) using a cold pack, PPT with an algometer, TS using a von Frey monofilament (256 mN), CPM using a blood pressure cuff as the conditioning stimulus and PPT as the test stimulus. In addition, the Douleur Neuropathique en 4 questions (DN4) was also presented. Physical therapists were asked to judge the feasibility, utility, face, and content validity of the bedside alternatives. Most physical therapists considered the bedside tests to be feasible, whereas 40% believed that the time (11 minutes) to perform the tests was too long. The DN4 and CPTh test were rated as the most utile, as they required the least amount of material compared to PPT, TS, and CPM. For content validity, the DN4 and PPT were rated as the most relevant. Approximately 60% of the physical therapists (strongly) agreed with the face validity of the bedside tests. In general, only 45% of physical therapists showed an interest in using bedside tests in clinical practice. Barriers to implementation include lack of time and material.

Breast cancer survivors can experience persistent pain. However, different mechanistic pain descriptors *can present as persistent pain. Therefore, clinical guidelines for the evaluation of persistent pain (nociplastic and neuropathic pain) have been developed and adapted for cancer survivors.*[17–19] *Although these clinical guidelines aim to improve the clinical evaluation of pain and consequently pain management, they remain unvalidated. In addition, these guidelines fail to determine the diagnostic probability for the presence of a* mechanistic pain descriptor*. Providing clinicians with a diagnostic probability for the presence of a particular condition, such as a certain* mechanistic pain descriptor*, can further guide clinical decision-making using a mechanism-based approach.*

1.5 Chapter 5. How can mechanistic pain descriptor such as nociceptive, neuropathic, and nociplastic pain be evaluated in clinical practice in breast cancer survivors with persistent pain using clinical prediction models, and what is the internal validity of these models for the evaluation of mechanistic pain descriptors in such patients?

In this cross-sectional study, our primary objective was to establish a diagnostic clinical prediction model for each mechanistic pain descriptor described by the International Association for the Study of Pain (IASP), namely nociceptive, neuropathic, and nociplastic pain. Our study cohort consisted of 92 BCS with persistent pain after breast cancer treatment. The outcome of our diagnostic clinical prediction models was the probability for presence of nociceptive, neuropathic, and nociplastic pain respectively. The outcome of each model was defined by the score on the DN4 questionnaire and the presence or absence of TS of pain at a remote location. In total, more than 40 candidate predictors were selected based on previous studies. For each mechanistic pain descriptor, definite predictors were selected based on recent literature, expert opinion, and consensus within the research team. The predictors body mass index, age, type of breast surgery, type of axillary surgery, and use of radiation therapy were included in all three models. Additional predictors were added depending on the desired mechanistic pain descriptor. Difference in pain intensity during rest and activity, general limited

shoulder range of motion, and local pain were considered predictors of the nociceptive pain model. The neuropathic pain model included two separate DN4 items (presence of burning sensation and hypoesthesia to touch) and the presence of a neuroanatomical distribution of pain or sensory dysfunction. The Central Sensitization Inventory (CSI), PPT at a remote location, presence of widespread pain, and presence of preoperative pain were added to the nociplastic pain model. The performance of each clinical prediction model was evaluated using the optimism-corrected area under the curve (AUC) and Brier score. All the developed models exhibited moderate discriminative ability, with optimism-corrected AUCs ranging from 0.592 to 0.681, indicating that the models have moderate success in evaluating the presence of a certain mechanistic pain descriptor. Furthermore, the optimism-corrected Brier scores ranged from 0.224 to 0.240, suggesting that the models are relatively consistent and provide accurate probabilistic predictions. Overall, these results indicate that the developed clinical prediction models for the presence of a certain mechanistic pain descriptor demonstrated a reasonable level of discriminative ability and accuracy. However, further internal, and external validation is required to provide fully validated clinical prediction models.

2. Interpretation and critical reflection

Our systematic review in **Chapter 1** reported an overall pain prevalence rate of 47%. However, owing to the limited number of studies (nociceptive, neuropathic, and nociplastic) in cancer populations, we were unable to draw conclusions regarding the prevalence of a certain mechanistic pain descriptor. A more recent systematic review from 2023 by the same research group, van den Beuken-van Everdingen et al., was also unable to provide more information than an update of the overall pain prevalence (35.8%) and prevalence of moderate to severe pain (22.8%).[20] Nevertheless, they provided a positive evolution for the overall prevalence of pain in cancer survivors, as they noticed a decrease in pain prevalence rates when comparing both systematic reviews.[9,20] This positive evolution might have been brought forth by improved cancer treatment modalities, such as targeted therapy, and improved attention and knowledge of pain after cancer treatment by healthcare providers. In addition, it is presumed that the treatment of cancer-related pain has improved with the implementation of a more multidirectional interdisciplinary approach.[21] Nevertheless, a prevalence rate of 35.8% still provides a reason to invest in future research on the prevention and treatment of cancer-related pain in the general cancer population. Regarding pain prevalence rates in BCS, a systematic review by Wang et al., published in 2020 with 146 included studies, reported a similar pain prevalence in comparison to our findings.[2] The author found that pain after breast cancer surgery was 46% when it was self-reported, considered any location, and any severity. Notably, the prevalence rates reported by the original studies ranged from 2% to 78%, probably owing to the definition and evaluation of pain after breast cancer. Moreover, they found a significant subgroup effect for patient-reported versus clinician-assessed pain, indicating that the clinical assessment of pain systematically underestimates pain prevalence. Although the authors reported the prevalence of persistent neuropathic pain after surgery, they were unable to provide data on the prevalence of nociceptive or nociplastic pain mechanisms. Although these mechanistic descriptors of pain have been around since

2016, studies on their presence in cancer and non-cancer populations are lacking.[22] The most likely explanation for the scarcity of prevalence data is the complicated nature of pain, mechanistic pain descriptors in particular, and its assessment. Although guidelines for the presence of neuropathic and nociplastic pain exist, the clinical criteria mentioned in these guidelines are often unclear and cumbersome to evaluate in clinical research. Furthermore, symptoms can be shared across different pain mechanisms[23], and momentarily, there are no guidelines for the presence of nociceptive pain in cancer and non-cancer populations. Taken together, these factors complicate the routine screening of pain (mechanisms) in research and clinical practice, and further impede the generation of mechanistic pain descriptor prevalence rates.

In **Chapter 2**, we confirmed that BCS with persistent pain demonstrated clear aberrations in the peripheral somatosensory nervous system, with hypoesthesia (or sensory loss) for thermal and mechanical stimuli, along with hyperesthesia (sensory gain, hyperalgesia) for pressure, in the area treated for breast cancer. This finding is supported by previous research that assessed somatosensory functioning in BCS.[10–12,14,24] Hypoesthesia can coexist with hyperesthesia; however, the pathophysiological mechanisms remain elusive, but small and large fiber function might be related.[12] Hyperesthesia such as mechanical allodynia in the area treated for breast cancer is associated with peripheral and central sensitization, and neuropathic pain.[25] Regarding central sensitization, our study found that CPM was similar across all groups, indicating no difference in the inhibitory function of the central somatosensory nervous system between healthy controls, BCS with or without pain, and patients with fibromyalgia. This finding is not supported by previous studies.[26] It is possible that our parallel heat protocol for evaluating CPM could not produce a sensitive CPM effect. Besides the fact that CPM is known to be highly variable, our protocol showed limited reliability in previous studies.[27,28] The addition of a second CPM protocol using different test and conditioning stimuli may improve the reliability and CPM effect. BCS with persistent pain, however, demonstrated a higher

TS of pain at a remote location than pain-free BCS, and these scores were similar to those of patients with fibromyalgia. These findings indicate that BCS with pain demonstrate increased facilitation of nociceptive processing within the central somatosensory nervous system, similar to patients with fibromyalgia, which is consistent with findings from previous studies.[26] In this study patients with fibromyalgia represented a positive control group, characterized by enhanced sensitivity and aberrations in central processing of nociceptive signals. A previous study using a similar design showed that patients with fibromyalgia exerted general hyperesthesia (hyperalgesia) for pressure, heat, cold, and noxious mechanical stimuli.[29] However, in our study, patients with fibromyalgia experienced hyperesthesia (hyperalgesia) only for pressure and noxious mechanical stimuli, but not for thermal stimuli. Other studies either confirm or refute these findings and, therefore, suggest that these disparities may be indicative of the heterogeneity within patients with fibromyalgia and the possible existence of various subgroups.[30,31] Lastly, BCS with persistent pain demonstrated a higher psychosocial burden than pain-free BCS and similar to fibromyalgia. It is possible that increased psychosocial burden was present before commencing cancer treatment in a percentage of cancer survivors, as was reported in previous studies, or that psychosocial burden is caused by persistent pain.[32,33]

With the validity study in **Chapter 3,** we compared two bedside CPM protocols to a reference CPM protocol, and similarly for TS in a breast cancer population with persistent pain. The bedside CPM protocols in this study were proven to be effective in previous studies[34,35]; however, they have not been routinely used in (breast) cancer survivors.[26,36] Both bedside CPM protocols (BPC and CPTe) seem interchangeable because of their strong correlation and demonstrated a higher percentage of responders (pro- and antinociceptive) than the reference protocol. The limited correlation between the bedside CPM protocols and the reference protocol might be explained by the different methodologies: type of conditioning stimulus (heat, pressure, or cold), type of test stimulus (heat or pressure), location

of test and conditioning stimulus (forearms, lower limb), timing and applied surface of conditioning stimulus (9 cm^2, whole hand, an 8,5-cm-wide occlusion cuff), and calculation of the CPM effect (pain ratings vs. PPT). Previous studies have indicated that pressure is the most reliable type of stimulus and is sensitive enough to measure the CPM effect rather than using changes in pain ratings (which we utilized in the reference CPM protocol).[37,38] Regarding the conditioning stimulus (cold, pressure, or heat), further research is needed to elucidate which stimulus is the most sensitive and reliable for producing a CPM effect in cancer survivors with persistent pain. In this study, we evaluated TS using either an algometer providing 1 kg/cm^2 pressure or a von Frey monofilament of 256 mN. Unfortunately, these stimuli produced excessive pain in 13 BCS at the area treated for breast cancer, and were therefore deemed useless for the assessment of TS at this location. In contrast, the same stimuli were not strong enough to produce a meaningful noxious signal at the opposite tibialis anterior muscle. This resulted in zero pain ratings after the first stimulus, hindering the calculation of relative changes. To overcome this issue, TS should be individualized at the test location, ensuring that the stimulus is perceived as noxious but not too noxious to prematurely end the procedure due to excessive pain. Previous studies recommend a stimulus that generates a 3 or 4/10 on the numeric rating scale (NRS).[35] In this study, we individualized the reference TS protocol, but not at the location of the test, but at the forearms prior to performing the CPM protocol. BCS demonstrated hypoesthesia for thermal stimuli at the area treated for breast cancer; therefore, performing TS at this location failed to produce TS of pain using heat stimuli. At the opposite tibialis anterior muscle, we were also unable to produce TS of pain, possibly due of the different sensory distribution in the leg compared to the forearms. Considering these findings, and previous literature, it might be more informative and feasible for the participants to perform an individualized TS protocol at a remote location, possibly on the opposite side of injury to evaluate the facilitatory pathways of nociception.[39]

In **Chapter 4**, we investigated how physical therapists judge assessment tools by presenting them with several bedside QST protocols using two videos and an online survey. In this study, only 45% of PTs showed an interest in using bedside QST in clinical practice. Physical therapists indicated lack of time and material as barriers to implementation. Considering the required material, we attempted to minimize the amount and complexity of the required material to increase its feasibility. The materials required to perform the bedside QST protocols were an algometer, a cold pack, a von Frey monofilament, and a blood pressure cuff. Reflecting back, we could have replaced the von Frey monofilament with an algometer to assess TS. As mentioned in Chapter 3, an algometer can be used for TS, CPM, and PPT, making it a versatile instrument for evaluating both local and widespread somatosensory (hyper)sensitivity. If an algometer is considered too expensive (€295.00 - 395.00) or unavailable, alternatives such as a hand-held dynamometer[40] or even the back of a closed syringe[41] could be worthwhile alternatives. Cheaper alternatives might increase implementation; however, as they lack normative data, their interpretation can be hindered. We acknowledge that consultation time is restricted in physical therapy and other healthcare settings. In the practical video, we performed all bedside protocols in 11 minutes; however, in practice, not all tests should be performed, and a selection should be based on clinical reasoning, just as in any examination. We did not specifically mention this possibility in our study, which could have biased our results. Seven out of 40 PTs indicated that 5 minutes (instead of 11) would be a feasible time, which is sufficient time to perform TS and CPM, or TS and PPT at least. Furthermore, PTs rated their confidence in and knowledge of pain neurophysiology as being limited. Limited confidence and knowledge of pain neurophysiology may have influenced our results, particularly in terms of face validity. However, it is not known whether this lack of knowledge actually improved or worsened study outcomes. Previous studies reported that education in pain for PTs is still limited and inadequately addressed in undergraduate curricula.[42] Moreover, the content of pain education for undergraduate physical therapy

students appears considerably variated between countries.[42] Undergraduate, and in addition, postgraduate pain curricula should integrate specific knowledge and skills to improve pain management.[42] A postgraduate pain program such as offered by the European Pain Federation (EFIC) is a well-developed and comprehensive curriculum providing postgraduate healthcare providers with the knowledge and skills necessary to effectively manage and treat pain in their clinical practice.[43] Curriculum designers are encouraged to adapt current curricula to incorporate the biopsychosocial framework and the IASP Curriculum Outline on Pain.[44] We did not assess participants' knowledge of pain neurophysiology via a questionnaire, such as the Neurophysiology of Pain Questionnaire (NPQ).[45] The NPQ could have provided more clarity in light of these results (i.e., knowledgeable PTs were more or less inclined to implement bedside QST protocols based on their judgement of feasibility, utility, face, and content validity). Besides a lack of time, material, and knowledge, attitude toward assessing and treating chronic pain might also play a crucial role. Clinical behavior of PTs is influenced by individual attitudes and personal habits.[46] Altogether, these factors impede the implementation of protocols aimed at providing a clearer picture of the aporia called pain.

To the best of my knowledge no study on the use or implementation of bedside QST exists, more specifically dynamic QST protocols. Most studies that investigate bedside alternatives for laboratory-based QST have advocated for their practicality and application in clinical settings.. However, these studies have failed the critical assessment of the feasibility of implementing these bedside QST in real clinical contexts, with the involvement of healthcare professionals. Therefore, we conducted the feasibility study to address this gap. Despite limitations such as a small sample size, low response rate and potential selection bias, the results indicate that physical therapists are reluctant to implement dynamic QST protocols such as CPM or TS in their clinical practice. We have already addressed the questionable added value towards treatments, lack of time and lack of equipment. Additionally, physical therapists may encounter challenges related to their attitude and knowledge in

effectively leveraging these tools to their advantage for their practice and patients. Furthermore, it is worth noting that the adoption of dynamic QST in clinical practice might be premature, given the existing uncertainties surrounding their stability, validity, reliability, underlying mechanisms, and the interpretation of their outcomes on an individual basis.

In this study, we only focused on PTs, as they are often considered frontline clinicians in pain management.[47] However, pain management is not exclusively restricted to PTs, as other healthcare providers such as general physicians and pain physicians are often involved, especially in multidisciplinary pain management settings. Owing to time limitations and resources, we were unable to invest in the recruitment of nurses, pain physicians, and general physicians. The inclusion of these healthcare providers could have provided knowledge on which type of healthcare provider is already informed about such protocols, which healthcare providers are most eager to improve implementation, and which are capable of providing such assessments in the future. The use of QST paradigms in clinical practice has been proposed by clinical guidelines and other studies, promoting a mechanism-based perspective on pain with the ultimate goal of improving treatment outcomes.[7,8,17,18] Although mechanism-based approaches have improved numerous medical conditions, such as diabetes and peptic ulcers, no data exists for the treatment of pain based on the present mechanistic pain descriptors (nociceptive, neuropathic, and nociplastic). In addition, this approach faces several challenges, the first of which is that the exact pathophysiological mechanisms underlying each of them remain unclear. Therefore, the actual ascription of an operant mechanistic pain descriptor in a patient remains challenging. In addition, patients can present with a mixture of mechanistic pain descriptors, which increases the complexity of this approach. Furthermore, nociceptive pain mechanisms have not yet received clinical guidelines and bedside QST protocols require a standardized manner and the clinical setting may hinder such standardized assessments. To improve standardization, instructions, reference test locations, and normative data should be provided. Unfortunately, normative

data of bedside QST protocols are not readily available, which in turn decreases the interpretation of results. We will not delve further into the other challenges, as Smart and colleagues provide a thorough summary and emphasize that tools that seek to categorize complex clinical phenomena such as pain should do so without simplifying them to the extent to which they no longer account for those phenomena.[48] Future research should aim to introduce these paradigms to a broader spectrum of physical therapists and other healthcare providers. To enhance the quality of investigations, an enhanced study design, such as in-person training sessions, could yield improved insights. Moreover, it might be valuable to consider conducting a Delphi study in order to delve deeper into the perspectives and insights of physical therapists. However, it is important that potential QST users are informed on the current limitations inherent to dynamic QST protocols.

In **Chapter 5**, we aimed to develop and internally validate three diagnostic clinical prediction models for the presence of nociceptive, neuropathic, and nociplastic pain mechanisms in BCS experiencing persistent pain. Therefore, we performed a comprehensive psychophysical assessment using questionnaires assessing psychosocial burden, a physical assessment, and a comprehensive QST protocol recording over 40 candidate predictors. The first step in developing a clinical prediction model is to define the outcomes. In an ideal world, the presence of the outcome would be determined using the most reliable, commonly used method, or "reference standard".[49] At present, there is no established diagnostic tool considered as the definitive reference standard for identifying the presence of these mechanistic pain descriptors. Consequently, we employed a consensus-based strategy integrating knowledge from the available literature in both non-cancer and cancer populations along with the clinical and scientific expertise of our research team. Even though, this process sounds straightforward, it remained challenging to select outcome variables that can be considered as ‘reference standard’. To assess the presence of a certain mechanistic pain descriptor, we utilized the Douleur Neuropathique 4 questionnaire score combined with remote temporal summation

of pain. The use of both variables allowed us to identify the presence of nociceptive, neuropathic, and nociplastic pain. Neuropathic pain was determined by a score of ≥ 4 on the DN4 questionnaire at the most painful location, along with the absence of an exaggerated temporal summation of pain at a remote location. Nociceptive pain was identified by a score of < 4 on the DN4 questionnaire at the most painful location coupled with the absence of an exaggerated temporal summation of pain at a remote location. Nociplastic pain was identified by the presence of an exaggerated temporal summation of the pain at a remote location. In the case of nociplastic pain, the score on the DN4 questionnaire was not considered, as patients with presumed nociplastic pain often exhibit signs and symptoms resembling neuropathic pain, leading to higher DN4 scores.[50] A limitation to this method is that BCS can exert exaggerated temporal summation of pain and high scores on the DN4 indicating the presence of both nociplastic and neuropathic pain. However, using the aforementioned classification, it was categorized solely as nociplastic pain. One pain mechanism does not exclude another, and there is a possibility of concurrent presence. Therefore, the inclusion of a mixed pain mechanism category would enhance the classification of pain among BCS. However, the term 'mixed pain' may be considered redundant because it can encompass two or three different mechanistic pain descriptors without specifically identifying which ones are present. This lack of specificity makes it challenging to determine the exact underlying mechanistic pain descriptor in a particular case. Categorizing complex clinical phenomena such as pain remains a challenging task. Furthermore, these mechanistic pain descriptor are not considered diagnoses; rather, they are mechanistic descriptors, whereas chronic cancer-related pain is considered a diagnostic concept. For the selection of definite predictors, we used the findings of our previous chapters of this doctoral project, existing literature, and consensus within our research team. Typically, there are two approaches for selecting predictors: data-driven and subject-matter knowledge-driven. Data-driven variable selection approaches are based on the evaluation of p-values for testing covariate coefficients (βi) against zero, or

incorporating an automated approach for the selection of predictors (e.g., penalized regression methods). Using data-driven variable selection, relevant predictors may be omitted in error, while irrelevant factors may be maintained.[51,52] Using subject-matter knowledge refers to including risk factors that have substantial evidence of predictive significance and are simple to gather in ordinary clinical practice. Since PTs have indicated that the time to evaluate painful symptoms is limited, we opted for the latter methodology to select a feasible set of predictors. This subject-matter knowledge-driven methodology, which is also recommended in the field, allowed us to select relevant predictors that could be easily assessed within the constraints of a typical consultation. Therefore, all clinical prediction models shared the same five basic patient- and treatment-related predictors (age, body mass index, presence of radiotherapy, and axillary and breast surgery), all of which have been associated with persistent (neuropathic or nociplastic) pain in numerous studies.[53,54] Additional predictors were added for each clinical prediction model; however, their selection provided some challenges, as these predictors needed to be specific to the mechanistic pain descriptor, as well as ease of evaluation and interpretation. Consequently, we based our selection on the guidelines for nociplastic[17] and neuropathic pain[55], a recently published Delphi study[23], and consensus within the research team. The clinical prediction models for neuropathic and nociplastic pain resemble their clinical guidelines*;* however, dynamic QST protocols were deemed unfeasible due to the required time and material, and difficulties in the interpretation of test results.[17,55] Altogether, 15 predictors would need to be assessed by the healthcare provider to obtain a predictive outcome for each mechanistic pain descriptor. The number of predictors for each model was deliberately kept small to improve feasibility in clinical practice and due to the limited inclusion of BCS with persistent pain. Although 249 BCS with persistent pain were required for development and internal validation, we were only able to recruit 92 BCS with persistent pain. Consequently, our preliminary clinical prediction models are limited in terms of generalizability, pose an increased risk of overfitting, and may

demonstrate unreliable model performance estimates. As clinical prediction models are used to guide clinical decision-making, it is generally not recommended to provide clinical recommendations based on preliminary models, which also lack external validation. The required sample size was calculated using the recent recommendations by Riley et al.[56] We therefore used the data reported in the study of Meretoja et al., who developed and externally validated a prognostic clinical prediction model for persistent pain in BCS.[57] A priori, we indicated the use of 10 predictive variables for each model. Using the reported c statistics of 0.74 and 20.3% for the prevalence of persistent pain in BCS, we concluded a sample size of 249 using the *pmsampsize* package in *R*. Two critical reflections were obtained using this methodology. First, we did not calculate the sample size for each of the three clinical prediction models. Meretoja et al. only reported the prevalence of persistent pain; they did not mention the prevalence of mechanistic pain descriptors. Studies on these mechanistic pain descriptors in BCS are essential for developing well-powered clinical prediction models. Second, the reported c statistic of 0.74 in this study should be interpreted with caution, as the applied methodology in developing the prognostic model may not be robust. The authors dichotomized several continuous variables (such as body mass index, depression, and anxiety), which decreases statistical power and interpretation.[58] We assume that the ideal sample size is larger than 249; however, as the prevalence of these mechanistic pain descriptors in BCS remains unknown, it is preliminary to suggest a different sample size.

3. Methodological strengths and limitations

This doctoral project has notable strengths that are worth mentioning. In this project, a comprehensive biopsychosocial assessment of BCS with persistent pain was performed using self-report questionnaires and psychophysical testing such as QST, resulting in a thorough assessment of the participants' pain experience. QST comprised of both static and dynamic protocols and was performed in a standardized manner. Furthermore, QST was evaluated in an optimized order to maximize wash-out periods and minimize the time needed to perform the full protocol. Second, QST was performed at two locations, the most painful site and a remote location, to evaluate nociceptive processing in both the peripheral and central somatosensory nervous system. Moreover, because gold standards for dynamic QST paradigms are lacking, multiple dynamic QST protocols have been utilized, allowing for a comprehensive exploration of aberrant changes in the central somatosensory nervous system. Third, a single assessor performed all the QST assessments, thereby eliminating the need to evaluate the effects of inter-rater variability. This single assessor had five years of clinical expertise and was trained in the use of QST. In addition, as chronic post-cancer treatment pain is not well-defined in terms of clinical criteria, all participants were screened for eligibility by the same assessor. The assessor judged whether the pain that was present in a breast cancer survivor was related to cancer treatment or was concurrently present, independent of cancer treatment. All the participants were similarly judged by only one assessor. Fourth, numerous studies have advocated bedside QST alternatives that are easy to implement in the clinical practice. However, these studies failed to evaluate the feasibility of using these tools in actual clinical settings. This doctoral project aimed to narrow the gap that still exists between research and clinical practice. Although this project does not provide all answers to questions regarding the use of QST in clinical practice, it serves as a promising starting point for further exploration. Finally, to enhance the clinical relevance and implementation of our findings, we approached this project from a clinical perspective. Therefore, we opted to rely on

subject-matter knowledge and consensus among scientific and clinical experts to determine the selection of predictions for clinical prediction models, rather than relying on univariate regressions to select predictors based on heuristic and dichotomous p-values. This approach is recommended for the development of novel clinical prediction models and allowed us to develop models that were better aligned with clinical practice, which may improve their implementation.[49,59,60]

This doctoral project had several limitations that should be acknowledged. The first limitation is the small sample size of our primary aim (Chapter 5). Our primary aim required a sample size of 249 BCS with persistent pain; however, we were able to include only 92 (37%) of the 209 referred participants. The limited sample size may be attributed to our recruitment strategy being limited to two centers as well as covid-19 restrictions and hospital hesitancy after the covid-19 lockdown. Additional reasons for not reaching the required sample size might be the under-recognition of pain in cancer survivors. Physicians do not routinely screen for pain, and many cancer survivors remain reluctant to discuss their symptoms with their physicians. Often, these survivors will use a “don’t ask, don’t tell” principle or do not want to distract the physician.[61] Another possible reason for the lack of participants is the lack of moderate to severe pain and/or disability in these patients. A recently published study on the effectiveness of pain neuroscience education in BCS reported pain ratings at four months after breast cancer surgery.[62] These BCS were recruited within the same center (University Hospitals Leuven) and reported a mean pain rating on a visual analogue scale (VAS) of 23.7, together with a pain-related disability lower than 10 on the Pain Disability Index (PDI). Based on our data, the pain intensity of the included participants ranged from 0 to 100 depending on the type of pain rating (maximum, minimum, during activity, during rest, or now), confirming high variability in the experience of pain. In addition, we recruited patients from two university hospitals; however, one hospital was added as a second center two years after the start of the project, which resulted in a less efficient recruitment flow. Consequently, only nine BCS with pain were referred from the second center.

Second, our sample only included women with breast cancer. The original aim of this doctoral thesis was to develop a diagnostic clinical prediction model that included all solid cancer survivors, including lung, gastrointestinal, head and neck, and prostate cancers. However, we were unable to find a sufficient number of participants from other cancer types besides breast cancer. Even though studies suggest that other solid cancer survivors experience pain, we were not able to include them in our study.[20,63] A limitation of these pain prevalence studies however is the fact that pain is not universally defined and evaluate. Some studies have defined pain as > 1/10 on the NRS, while others have defined it as > 4/10, consequently skewing pain prevalence rates. Moreover, the underrecognition of pain after cancer treatment and concurrent hesitancy to discuss this with physicians might be present. Consequently, this project focused solely on BCS.

Third, as breast cancer is predominantly found in women (1% of men), we cannot generalize our findings and prediction models to men. Additionally, our sample primarily comprised Caucasian women with an average age of 55 years, which may limit the generalizability of our findings to other populations and to younger women.

Fourth, our diagnostic clinical prediction models lacked both internal and external validations. Owing to sample size limitations, our study was not able to provide a thorough internal validation of the clinical prediction models. A sufficient sample size is required to perform internal validation of such models. Furthermore, clinical prediction model studies typically involve external validation of the prediction model using a different independent dataset to assess its performance in real-life situations. Due to these factors, we described our models as preliminary and not yet fit for use in a clinical setting. It must be acknowledged that future research is necessary to update and validate our preliminary models, both internally and externally by providing more data

Finally, it is important to acknowledge that our study deviated from the recommended comprehensive QST protocol proposed by the German Research

Network on Neuropathic Pain (DFNS).[64] This deviation was due to the prior utilization of a similar protocol by other researchers within our research group.[28,62] Implementing the full DFNS protocol at two different locations would have posed practical challenges for both assessors and participants involved in our study (e.g., time to perform the protocol and required material). Consequently, we were unable to compare our findings with reference data from the DFNS, which provides multicenter, age- and sex-matched standards. The lack of comparison with studies employing the DFNS protocol limits our ability to contextualize our results within the existing body of research using the same protocol.[64,65] Additionally, our temporal summation protocols were limited to the production of a noxious stimulus at the tibialis anterior, as we either utilized a von Frey monofilament with 256 mN pressure or an algometer with 1 kg/cm^2 pressure. Von Frey monofilaments were not intended to stimulate nociceptors with its spherical head, alternatively pinprick stimulators may produce noxious stimuli more consistently. The pressure exerted by the algometer was often considered non-painful by the participants, resulting in the absence of a wind-up. Additionally, only one train was used, whereas the DFNS protocol used multiple trains to evaluate the presence or absence of an exaggerated temporal summation.[64] To assess mechanical pain thresholds, we also used von Frey monofilaments rather than the recommended pinprick stimulators. This resulted in skewed results, as it took a high amount of pressure to exert a noxious stimulus with the von Frey monofilament compared to the DFNS-recommended pinprick stimulators, limiting the comparison with other studies. These limitations should be considered, and future research should address them accordingly by increasing the sample size, broadening the inclusion of cancer types, adopting standardized pain assessment tools, and conducting multi-site studies.

4. Clinical implications

This section provides recommendations for clinical practice based on the results of this doctoral project and my clinical experience and perspective.

Based on the findings from the systematic review in **Chapter 1**, we recommend that healthcare providers be aware of the high prevalence rate of pain in (breast) cancer survivors. Different mechanistic pain descriptors can be present in cancer survivors. However, it is currently unclear which mechanistic pain descriptors are manifested in cancer survivors. Given the considerably high prevalence of persistent pain after breast cancer, routine screening for pain in all phases (acute, subacute, and chronic) can be valuable for improving pain management and, consequently, cancer survivorship. To facilitate routine screening for pain, we recommend improving the communication between physicians and patients regarding pain management. This includes proactive discussions about pain, assessing patient satisfaction with proposed treatments, and regularly measuring cancer-related or treatment-related pain during consultations.[61] Additionally, empowering patients to discuss pain and pain interventions during outpatient visits and involving them in shared decision-making can enhance patient empowerment, improve knowledge on pain and consequently pain management.[61]

In **Chapter 2**, we investigated the somatosensory profiles of BCS. BCS with persistent pain demonstrate hyperesthesia (hyperalgesia) to pressure in the area linked to the cancer treatment. Clinically, these women have difficulty lying on their affected side or cannot withstand the pressure of their bra, which decreases their quality of life. As PTs, we should be mindful of this discomfort to provide proper advice related to their sleeping position or the most comfortable bra. In addition, performing forms of manual therapy in the treated area may be very painful for some cancer survivors, as even the slightest pressure can cause discomfort. In such cases, hands-off modalities may be more appropriate, in terms of comfort and aggravation. Additionally, it is unclear whether manual interventions can produce a clinically significant reduction in pain in areas exerting hyperesthesia (hyperalgesia) for

pressure. Furthermore, BCS worry about their pain.[5] Indeed, we found that these cancer survivors demonstrated a higher psychosocial burden and presumably higher facilitation of nociceptive signals, as evaluated by TS. BCS with persistent pain may benefit from a comprehensive multidisciplinary pain management approach consisting of physical therapy, psychotherapy, and pharmacological interventions. From a personal perspective, the integration of pain (neuroscience) education and cognitive-behavioral therapy seems to decrease worrisome feelings and threats, and improve the acknowledgement and understanding of pain after cancer treatment. Although these modalities might not improve pain intensity, they might provide a different perspective on pain and decrease pain-related disability in cancer survivors with persistent pain. This perspective is also supported by evidence in cancer and non-cancer populations.[66,67] Physical therapists should be mindful not only of looking for a mechanistic pain descriptor, but also of looking at the person in front of them and the many challenges that they face.

The findings from **Chapter 3** suggest that both bedside CPM protocols are interchangeable, based on their strong correlation. Clinicians should, therefore, be able to choose the protocol that they are able to perform with the least effort. In terms of feasibility, the use of a BPC as a conditioning stimulus appears to be a more feasible option than cooling tap water to approximately 12 °C in clinical settings. A recent study by Mertens et al. confirmed our recommendations by concluding that the BPC seems more useful in clinical settings, while the CPT would be more appropriate in research settings.[68] For a clinician, it would be worthwhile to assess CPM and TS with a limited amount of material required. A bedside TS protocol using an algometer at a remote location might be worth considering as such an algometer could also be used for both CPM and PPT. However, methodological limitations of TS using an algometer should be considered, as a clinician would require additional, albeit limited, training to standardize the impulse frequency and precision of the given pressure. Furthermore, normative data for bedside QST protocols are unavailable; therefore, interpretation in a clinical setting can be challenging. On the

other hand, it might be worthwhile to consider these protocols for intra-individual assessment in longer pain management programs to provide more objective measurements in time, in addition to PROs.

With the feasibility study described in **Chapter 4**, PTs demonstrated that they have limited time and material for performing comprehensive assessments in clinical practice. Our results indicate that only 45% of PTs implemented the set of bedside tests presented to them. In addition, only a minority of PTs reported using PROs and pain-specific clinical assessment tools in addition to a standard physical examination. Other studies have confirmed that even the use of PROs in clinical practice is limited, although PROs require a minimal amount of material and can be completed outside of the appointment time.[69] If PTs experience barriers in implementing PROs, it may be even harder to implement bedside QST paradigms or even diagnostic clinical prediction models. Research has shown, however, that educational programs can improve the implementation of PROs, and potentially it can do the same for bedside QST implementation.[70] In addition, PTs felt that the use of bedside QST protocols is of added value for the management of pain in cancer survivors, indicating that they might consider it if material was accessible and time to perform the protocols shorter.

Static QST, such as the evaluation of sensory thresholds, can be integrated into the neurological assessment, allowing for a controlled and standardized approach to quantify sensory loss or gain within the affected region. In that sense, the use of static QST might be more applicable for patients suffering from suspected neuropathic pain. It seems to be more suitable for diagnostic area purposes such as distinguishing between neuropathic pain patients and healthy controls.71 In terms of treatment decisions, it's essential to recognize that current results from static QST do not offer treatment guidance, either on a group or an individual level.

Whether dynamic QST outcomes offer treatment guidance is still debatable, especially on an individual level. Dynamic QST does hold the potential to add value

in the clinical assessment by evaluating impairments in central nociceptive processing, which PROs may not fully capture.72,73 Its applicability may be particularly relevant for patients experiencing persistent and/or widespread pain, making it a valuable complement to PROs. At the individual level, interpreting CPM outcomes poses challenges due to its high variability, making it less straightforward to assess. Consequently, CPM may find more utility when employed at a group level. In this context, it could prove valuable in pre-surgical settings for identifying individuals at risk of developing chronic pain,74,75 potentially enhancing perioperative pain management strategies. However, the question remains open as to whether CPM data, applied at a group level, can truly add value to the task of tailoring perioperative pain management strategies for individual patients.75 In contrast, TS might be a more suitable option for clinical practice when focusing on individual patients. It appears to offer greater stability and less variability in measurement compared to CPM, and the interpretation of TS results tends to be more readily comprehensible. Alternatively, exercise-induced hypoalgesia might also be worthwhile paradigm to consider in the oncological population. Exercise is considered paramount in the rehabilitation after cancer, in the prevention of cancer, and is recommended for sufferers of chronic pain. However, exercise-induced hypoalgesia, just like CPM is highly variable in chronic pain and may be impaired in some people, with pain intensity remaining unchanged or even increasing in response to exercise.76

These dynamic QST protocols inform us on how the nociceptive apparatus receives and processes nociceptive signals but they do not necessarily inform us of a certain mechanistic pain descriptor in an individual. It remains essential to emphasize the importance of conducting a comprehensive subjective assessment before incorporating dynamic QST protocols into clinical practice. With that said, even when clinicians decide to employ these assessment tools, it remains crucial to integrate their results into the broader context of the subjective assessment, including PROs.

For instance, consider a breast cancer survivor experiencing chronic shoulder pain after breast cancer treatment. It's entirely plausible for their CPM results to fall within the normal range while their TS results deviate into the abnormal. It is also possible that both CPM and TS remain normal, or both show an impairment. These findings introduces interesting questions towards clinical practice: How should one interpret these findings, and what implications do they hold for treatment strategies? Understanding the implications of these findings and determining an appropriate course of action remains very challenging for a clinician. Physical therapists faced with such results may wonder how to tailor their treatment plan or whether they should refer the patient to another healthcare professional. It's crucial to acknowledge that, at this juncture, given our current understanding of dynamic QST protocols like CPM and TS, their results serve as supplementary information rather than definitive determinants. In a patient suffering from chronic pain we need to consider the entire clinical picture and not just CPM/TSP results. Ultimately, our focus should remain on treating patients, with due consideration for their unique circumstances, rather than fixating solely on QST results or mechanistic pain descriptors.

Potentially there is more merit of adopting dynamic QST protocols and pain-specific diagnostic clinical prediction models in specialized pain clinics, where clinicians work in multidisciplinary teams and pain management is more standardized. In the future, it is possible that health insurers will demand more objective measures of pain in people who are on a long trajectory of pain management. Our study also showed that participating physical therapists had limited knowledge and confidence in pain neurophysiology. As mentioned, we suggest that undergraduate pain curricula are adapted properly, providing sufficient pain neurophysiology and assessment tools for clinical settings. Physical therapists and other healthcare providers should actively participate in postgraduate educational pain programs. Such active participation might require a change in attitude or incentives from health insurers or governmental organizations, such as educational credits.

In **Chapter 5**, we developed three diagnostic clinical prediction models for the presence of nociceptive, neuropathic, and nociplastic pain in BCS with persistent pain. Our intention was to develop a clinically feasible tool; however, the lack of internal and external validity of the models prevented us from making concrete clinical recommendations. An example of such a clinically feasible tool would be the web-based application provided by Meretoja et al. for the prediction of persistent pain in BCS, using a prognostic clinical prediction model.[57] To produce a similar clinical prediction model for the presence of nociceptive, neuropathic, and nociplastic pain, we would require a larger sample size in the development cohort and in the external validation dataset. Using unvalidated models in practice could potentially cause more harm than good, as these models support medical decision-making.[51,73] Therefore, we followed the general recommendations that these models are first validated using sufficient sample sizes before implementing them in practice.[51,60,73] If these clinical prediction models are validated in the future, then these clinical prediction models would be able to estimate the probability of a certain mechanistic pain descriptor being present in a breast cancer survivor. Additionally, because one mechanistic pain descriptor does not exclude another, the presence of multiple mechanistic pain descriptors within one breast cancer survivor is possible and can be assessed. While the clinical prediction models presented in this study lack validation, healthcare providers may still consider using a set of predictors or a selection of predictors as feasible alternatives to the existing guidelines for nociplastic and neuropathic pain. These predictors can potentially provide valuable insights and assist clinicians in making informed decisions regarding pain management.

As pain remains a sensory and emotional event, clinicians should consider first treating patients and second mechanisms. Research has highlighted the presence of a certain silence or reluctance to discuss pain after cancer treatment, suggesting the existence of a form of "omèrta" surrounding this topic. It is crucial for patients and healthcare providers to engage in open communication before initiating any type of

pain assessment. The patients' narrative and subjective experience should remain at the forefront, ensuring that their unique pain concerns are heard.

An alternative perspective to a mechanism-based approach is the Musculoskeletal Clinical Translation Framework (MCTF) introduced by Mitchel T and colleagues.[71] This framework is based on the biopsychosocial approach that incorporates the assessment of a mechanistic pain descriptor in addition to the assessment of psychosocial factors such as yellow and blue flags.[72] This approach provides both clinician and patient guidance in pain management using a shared decision-making process, and could be an interesting comprehensive assessment tool. This framework does not require materials, except for PROs, and can be easily adopted by healthcare providers.

5. Future research

The findings of this doctoral project offer suggestions for future research and are divided into different chapters in the doctoral thesis.

A systematic search and review of evidence regarding the prevalence of a disease remains important.[74] Prevalence studies provide valuable information to researchers, guideline developers, and policymakers, enabling them to understand the disease burden. This knowledge aids in identifying priorities for healthcare, prevention strategies, and policy decisions.[74] Our systematic review in **Chapter 1** lacks information on the prevalence of different mechanistic pain descriptors in cancer survivors. Investigating the prevalence of such mechanistic pain descriptors will require newly developed gold-standard methods or validated practical guidelines using different clinical criteria. Currently, research lacks gold-standard methods and validated guidelines, making research on the prevalence of mechanistic pain descriptors challenging. It is crucial for future research to continue unraveling the underlying mechanistic pain descriptor (nociceptive, neuropathic, or nociplastic pain) and its contributors through basic scientific investigations; simultaneously, clinicians should continue to provide the most effective pain management we have currently, using a biopsychosocial framework. Essentially, we should let perfect not be the enemy of the good. Finally, longitudinal studies are needed to investigate the prevalence of mechanistic pain descriptors in different cancer populations at different stages of the cancer survivorship continuum.

Somatosensory profiling has gained popularity over the last few years, particularly in the fields of neuropathy and neuropathic pain, and provides new insights into potential treatment strategies based on QST outcomes. In **Chapter 2**, we evaluated somatosensory functioning using several QST parameters. Studies investigating somatosensory profiles in different patient populations with and without (neuropathic) pain most often implement the comprehensive QST protocol, as described by the DFNS. We hope that future research will continue to implement this comprehensive protocol, as it provides normative data for different ages and

body locations, and its universal use in research will further improve comparability with other studies. Unfortunately, the DFNS does not provide a recommendation for a CPM paradigm in their protocol. Therefore, we recommend that studies researching somatosensory profiles utilize the DFNS protocol with the cold pressor test and a second CPM paradigm using different stimuli as recommended.[34] It is important to not only assess somatosensory functioning using mere QST but also incorporate patient-reported outcomes (PROs) measures to evaluate psychosocial burden in cancer populations. Furthermore, longitudinal study designs are warranted to investigate the evolution of somatosensory profiles and psychosocial factors over a period of time, such as preoperatively to approximately one year after finishing cancer treatment.

The evaluation of pain using dynamic QST paradigms is advancing; however, further improvements are warranted. The use of dynamic QST paradigms, such as CPM and TS, to assess the central pathways of nociceptive processing is also being extensively promoted.[36] Nonetheless, these dynamic QST paradigms lack validity. With our study in **Chapter 3**, we aimed to improve knowledge on dynamic QST concurrent validity by comparing it to a reference protocol, although there is currently no gold standard for evaluating central nociceptive pathways. Furthermore, there is a lack of uniformity in the literature on the use of dynamic QST paradigms. Different methodologies have been previously described. For instance, CPM can be applied in a sequential or parallel manner using cold, heat, or pressure as a conditioning stimulus for either 30 second or up to 3 minutes at different locations.[68] 77 Similarly, TS differs in its applied frequency, type, and number of stimuli, location, and use of one or more trains. Depending on how these protocols are applied, statistical analyses can differ based on either relative or absolute calculations.[34,78] Even though CPM recommendations have been made previously, it seems that almost ten years later, these recommendations have not been well adopted in research.[34] A uniform methodology and statistical analysis would improve the collection of normative data

in different populations, increase research exchanges, and improve comparisons between studies that utilize dynamic QST protocols.

Using the feasibility study described in **Chapter 4**, we aimed to narrow the gap between research and clinical practice by involving physical therapists in the judgment of several bedside QST protocols. Although this was one of the first studies to investigate the validity, utility, and feasibility of bedside QST protocols for physical therapists, the study was limited in its methodology, as it included a limited number of physical therapists (n=40) in Belgium and the Netherlands. Therefore, future research should include more physical therapists and other healthcare providers from multiple countries and settings. Furthermore, providing physical therapists with their own set of QST tools might help their judgment in terms of validity, utility, and feasibility. Additionally, the physical therapists expressed limited knowledge and confidence in pain neurophysiology and assessment methods. For future research, the addition of an educational session focusing on pain neurophysiology and assessment methods might improve insight into the use of such protocols in clinical settings. Finally, we performed an online survey, but a Delphi study, a think-aloud protocol or even focus groups could potentially provide even more valuable information regarding the future implementation of these protocols.

In **Chapter 5**, we developed three preliminary clinical diagnostic prediction models for the presence of a mechanistic pain descriptor in a breast cancer survivor experiencing pain. Future research should prioritize the collection of data on pain in BCS to enhance the internal validity of these models through multi-site studies. Our study provides a methodologically strong basis for future research, as we were able to provide, albeit limited, performance measures on which new models can be developed. Furthermore, it is important to update the models by considering new and relevant predictors as science progresses. Subsequent external validation using independent datasets that reflect real-life situations is crucial. Once validated externally, a knowledge translation strategy should be employed to promote the adoption and appropriate utilization of these models in clinical practice. Pilot testing

with healthcare providers should be conducted while awaiting external validation. The use clinical vignettes might facilitate such pilot testing. Identifying the barriers and facilitators to the implementation of such models is required to improve their implementation in clinical practice.

In this doctoral thesis, we present three clinical prediction models as diagnostic tools. In addition to evaluating persistent pain after breast cancer treatment, it may be worthwhile to consider the prevention of cancer-related pain by using prognostic clinical prediction models. Future research should investigate whether pain after breast cancer treatment can be prevented in patients with breast cancer who are at risk of developing persistent pain. Meretoja et al. published a preoperative prognostic prediction model for persistent pain after breast cancer surgery; however, only preoperative pain in the operative area was used as a predictor.[57] It might be worthwhile to consider other factors to indicate at-risk patients, such as the presence of widespread pain, impaired central processing of nociceptive signals, and an increased psychosocial burden. These clinical markers of pain can be supplemented by objective biomarkers such as inflammatory markers, neuroimaging, and epigenetic markers.[79,80] Future longitudinal clinical trials should investigate whether these factors are associated with persistent pain after breast cancer treatment and whether interventions can prevent the occurrence of persistent pain.

6. Conclusion

Chronic pain remains a significant burden among solid cancer survivors; however, its underlying mechanisms remain elusive. Our study revealed that breast cancer survivors with chronic pain demonstrated hyperesthesia (hyperalgesia) to pressure, and hypoesthesia to thermal and mechanical stimuli in the treated area. Additionally, they demonstrated increased facilitation of nociceptive signals and heightened psychosocial burden, suggesting the presence of central aberrations within the somatosensory nervous system.

Dynamic quantitative sensory testing paradigms such as conditioned pain modulation and temporal summation are commonly employed to evaluate central aberrations within the somatosensory nervous system. These dynamic paradigms are often evaluated using expensive laboratory equipment that requires time and additional training. Bedside alternatives have been suggested, but are mostly unvalidated in comparison with laboratory-based protocols. Bedside conditioned pain modulation protocols demonstrated a good correlation with themselves but lacked correlation with their laboratory-based equivalents. Bedside temporal summation protocols failed to provide such correlations. Nevertheless, physical therapists expressed reluctance to implement bedside QST protocols, deeming them infeasible in clinical practice.

Based on these findings, we developed three diagnostic clinical prediction models to estimate the probability of nociceptive, neuropathic, and nociplastic pain in breast cancer survivors. Unfortunately, we are not able to recommend these models (yet) for use in clinical practice, as they have yet to receive further internal and external validation.

In conclusion, this doctoral thesis provides insights into persistent pain and somatosensory function in survivors of breast cancer. Although dynamic QST paradigms hold promise for evaluating central somatosensory function, their implementation in clinical practice remains challenging. Future research is needed

to refine and validate the diagnostic clinical prediction models from this doctoral project. Taken together, these findings narrow the gap between research and clinical practice and contribute to the understanding, evaluation, and treatment of persistent pain in breast cancer survivors.

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Scientific curriculum vitae

About the author

Vincent Haenen was born in Edegem, Belgium on the first of November 1990. He graduated high school in 2008. Vincent received the Master's degree in Rehabilitation Sciences and Kinesiology for Musculoskeletal Conditions (MSc) with a distinction at the University of Antwerp in 2014. After a successful internship abroad in 2013, he moved to Basel (Switzerland). There, he pursued a career as an employed physical therapist. During his time abroad, he maintained close contact with Belgium, especially in the context of continued education. After four years, he decided that it was time to return to Belgium. At home, he started his own practice and also worked as a freelance physical therapist. After one year, Vincent had the opportunity to combine his work in clinical practice with research activities as a research assistant. Six months later, in 2020, he officially started working as a full-time PhD researcher. The project consisted of a collaboration between the University of Antwerp (Research Group MOVANT) and KU Leuven (Research Group GRID) and was under the supervision of Prof. An De Groef, Prof. Mira Meeus, Prof. Nele Devoogdt and Prof. Dr. Bart Morlion. The focus of this doctoral project is the clinical assessment of pain in cancer survivors.

Vincent is a member of the CarEdOn research group (National Research Group on Care in Edema and Oncology) and Pain in Motion Research Group (International Research Group on Pain). In addition to his work as a PhD researcher, Vincent was involved in teaching activities within the Master's program of Rehabilitation Sciences and Kinesiology at the University of Antwerp. Additionally, Vincent mentored Bachelor and Master's students during their thesis research at the University of Antwerp, the KU Leuven, and the Berekuyl Academy (The Netherlands).

Publications in international journals with peer review

1. **Haenen, V.**, Evenepoel, M., De Baerdemaecker, T., Meeus, M., Devoogdt, N., Morlion, B., Dams, L., Van Dijck, S., van der Gucht, E., De Vrieze, T., Vyvere, T.V., De Groef, A. (2023). Pain prevalence and characteristics in survivors of solid cancers: a systematic review and meta-analysis. *Supportive care in cancer*, *31* (1). doi: 10.1007/s00520-022-07491-8
2. **Haenen, V.**, Dams, L., Meeus, M., De Groef, A. (2022). Altered somatosensory functioning and mechanism-based classification in breast cancer patients with persistent pain. *Anatomical record-advances in integrative anatomy and evolutionary biology*. doi: 10.1002/ar.25121
3. Vervullens, S., **Haenen, V.**, Meert, L., Meeus, M., Smeets, R.J E M., Baert, I., Mertens, M.G C A M. (2022). Personal influencing factors for pressure pain threshold in healthy people: A systematic review and meta-analysis. *Neuroscience and biobehavioral reviews*, *139*. doi: 10.1016/j.neubiorev.2022.104727
4. Evenepoel, M., **Haenen, V.**, De Baerdemaecker, T., Meeus, M., Devoogdt, N., Dams, L., Van Dijck, S., Van der Gucht, E., De Groef, A. with De Groef, A. (corresp. author) (2022). Pain Prevalence During Cancer Treatment: A Systematic Review and Meta-Analysis. *Journal of pain and symptom management*, *63* (3), E317-E335. doi: 10.1016/j.jpainsymman.2021.09.011
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12. Dams, L., Van der Gucht, E., Smeets, A., Devoogdt, N., De Vrieze, T., Bernar, K., Morlion, B., Fieuws, S., Godderis, L., **Haenen, V.**, De Groef, A. (2022). Effect of pain neuroscience education after breast cancer surgery on pain-, physical-, and emotional functioning: a double-blinded randomized controlled trial (EduCan trial). *Pain*. doi: 10.1097/j.pain.0000000000002838
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16. De Groef, A., Demeyer, H., de Kinkelder, C., Dukers-van Althuis, S., Asnong, A., Dams, L., Van der Gucht, E., De Vrieze, T., **Haenen, V.**, Evenepoel, M., Geraerts, I., Roelants, M., van Uffelen, J., Troosters, T., Devoogdt, N. (2022). Physical Activity Levels of Breast Cancer Patients Before Diagnosis Compared to a Reference Population: A Cross-Sectional Comparative Study. *Clin Breast Cancer*, *22* (5), e708-e717. doi: 10.1016/j.clbc.2021.12.006
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18. Van der Gucht, E., Dams, L., Bernar, K., De Vrieze, T., **Haenen, V.**, De Groef, A., Godderis, L., Morlion, B., Meeus, M., Devoogdt, N. (2022). The Dutch language version of the Pain Disability Index (PDI-DLV): psychometric properties in breast cancer patients. *Physiotherapy theory and practice*. doi: 10.1080/09593985.2022.2059036
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22. De Vrieze, T., Gebruers, N., Nevelsteen, I., Tjalma, W.A A., Thomis, S., De Groef, A., Dams, L., **Haenen, V.**, Devoogdt, N. (2020). Breast cancer-related lymphedema and its treatment: how big is the financial impact? *Supportive care in cancer*, *29* (7), 3801-3813. doi: 10.1007/s00520-020-05890-3

Oral presentations at international congresses

1. **Haenen, V.**, De Groef, A., Meeus, M., Devoogdt, N., Morlion, B., Dams, L. Comparison of two clinically applicable conditioned pain modulation and temporal summation protocols in breast cancer survivors with persistent pain.
   Presented at the Pain Science in Motion, Maastricht, 2022.
2. **Haenen. V**., Quantitative sensory testing, what's in a name?
   Invited speaker at the Belgian Pain Society - Young Researchers day, Ghent, 2023.

Poster presentations at international and national congresses

1. **Haenen, V.**, Meeus, M., Lups, D., Ubaghs, S., Devoogdt, N., Morlion, B., Dams, L., De Groote, A., Vandevyvere, T., De Groef, A. The feasibility, utility, and validity of bedside quantitative sensory testing in cancer survivors with persistent pain: a survey among dutch-speaking physical therapists.
   Presented at the European Pain Federation EFIC, Budapest, 2023.
2. **Haenen, V.**, Dams, L., Meeus, M., Devoogdt, N., Morlion, B., De Groote, A., Vandevyvere, T., De Groef, A. Continuum of somatosensory profiles in breast cancer survivors with and without pain, compared to healthy controls and patients with fibromyalgia.
   Presented at the Belgian Pain Society - Young Researchers day, Ghent, 2023.
3. **Haenen, V.**, Evenepoel, M., Meeus, M., Morlion, B., Devoogdt, N., Van der Gucht, E., Dams, L., De Vrieze, T., Vandevyvere, T., De Baerdemaecker, T., Van Dijck, S., De Groef, A. Pain prevalence and characteristics during and after cancer treatment: a systematic review and meta-analysis.
   Presented at the European Pain Federation EFIC, Dublin, 2022.
4. **Haenen, V.**, Dams, L., De Groef, A., Devoogdt, N., Morlion, B., Meeus, M. Somatosensory profiling: think before you act.
   Presented at the Pain Science in Motion, Maastricht, 2022.
5. **Haenen, V.**, Meeus, M., Devoogdt, N., Morlion, B., Dams, L., De Groote, A., Vandevyvere, T., De Groef, A. Concurrent validity of conditioned pain modulation and temporal summation paradigms in breast cancer survivors with persistent pain.
   Presented at the University of Antwerp Cancer Research Day, Antwerp, 2022.
6. De Groef, A., Hallemans, A., Gebruers, N., Meirte, J., Saeys, W., Truijen, S., **Haenen, V.**, Johnson, C., Meert, L., Peeters, L., Fransen, E., Meeus, M., Durnez, L. The impact of COVID-19 lockdown on the general health status of people with chronic health conditions in Belgium: a cross-sectional survey study.
   Presented at the European Pain Federation EFIC, Dublin, 2022.

7. De Groef, A., Evenepoel, M., Meeus, M., Van Dijck, S., Dams, L., **Haenen, V.**, Devoogdt, N., Wiles, L., Catley, M., Vogelzang, A., Oliver, I., Hibbert, P., Morlion, B., Moseley, GL., Heathcote, LC. Feasibility and pilot testing of the eHealth Pain Education after CANcer (PECAN)-program for breast cancer survivors with persistent pain: a mixed-method study.
   Presented at the European Pain Federation EFIC, Dublin, 2022.
   Dam, L., Van Der Gucht, E., **Haenen, V.**, Lauwers, M., De Pauw, S., Steurs, T., Devoogdt, N., Smeets, A., Bernar, K., De Vrieze, T., De Groef, A., Meeus, M. Who is at higher risk of long-term pain and disability following breast cancer?
   Presented at the European Pain Federation EFIC, Dublin, 2022.
8. Dams, L., **Haenen, V.**, Van der Gucht, E., Devoogdt, N., Smeets, A., Bernar, K., De Vrieze, T., De Groef, A., Meeus, M. Absolute and relative reliability of a comprehensive quantitative sensory testing protocol in women treated for breast cancer.
   Presented at the IASP Virtual Series on Pain & Expo. Online, 2021.
9. Van der Gucht, E., Dams, L., Bernar, K., De Vrieze, T., **Haenen, V.**, De Groef, A., Godderis, L., Morlion, B., Meeus, M., Devoogdt, N. The Dutch Language Version of the Pain Disability Index (PDI-DLV): Psychometric Properties in Breast Cancer Patients.
   Presented at the IASP Virtual Series on Pain & Expo. Online, 2021.
10. Dams, L., **Haenen, V.**, Van der Gucht, E., Devoogdt, N., Smeets, A., Bernar, K., De Vrieze, T., De Groef, A., Meeus, M. Absolute and relative reliability of a comprehensive quantitative sensory testing protocol in women treated for breast cancer.
    Presented at the 2nd ICPTO. Online, 2021.
11. Dams, L., De Groef, A., Van der Gucht, E., **Haenen, V.**, Bernar, K., Penen, F., De Baerdemaecker, T., Devoogdt, N., Meeus, M. Quantitative sensory testing in women treated for breast cancer: a systematic review and meta-analysis.
    Presented at the IASP Virtual Series on Pain & Expo. Online, 2021.

12. De Groef, A., Meeus, M., Dams, L., Van der Gucht, E., Penen, F., **Haenen, V.**, Devoogdt, N. Is breast- cancer related lymphedema a painful condition? Sensory profile of women with self-reported lymphedema: a case-control study.
    Presented at the IASP Virtual Series on Pain & Expo. Online, 2021.

Master thesis supervision

1. Sensory profiling of breast cancer survivors with and without persistent pain by Devanshi Nalinbhai Vasa and Rachana Rettagunta Suresh. KU Leuven, 2021-2023. Co-supervisor for two years.
2. The feasibility, usability, and validity of a newly developed assessment tool for persistent pain in cancer survivors by Dorien Lups and Simone Ubaghs, The Berekuyl Academy & Vrije Universiteit Brussel, 2020-2022. Co-supervisor for two years.
3. Face and content validity, feasibility, and utility of a novel pain assessment tool for pain in cancer patients by Laura Pattyn and Aurélie Van de Walle, University of Antwerp, 2020-2022. Co-supervisor for two years.
4. Comparison of test protocols for pain modulation pathways in women with pain after breast cancer treatment by Sofie De Vleeschauwer and Noor Vansteenvoort. KU Leuven, 2019-2021. Co-supervisor for two years.
5. Validation of a screening tool for conditioned pain modulation in breast cancer survivors by Ilona Heremans and Delphine Van Parijs. KU Leuven, 2019-2020. Co-supervisor for one year.

Courses and workshops

1. Kiné et cancer du sein: comorbidities du bras - UCLouvain. Louvain-la-Neuve (Belgium), October 2020.
2. Kiné et cancer du sein: comorbidities du bras - UCLouvain. Louvain-la-Neuve (Belgium), December 2021.
3. Pain Science in Motion post-conference workshop: Tips and tricks on how to make Pain Science Education for cancer patients ‘stick’ along the cancer care continuum. Maastricht (The Netherlands), May 2022
4. Pijn na borstkanker: meten is weten webinar – KU Leuven, Online (Belgium), October 2023