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## **Chronic pain in breast cancer survivors: nociceptive, neuropathic or central sensitization pain?**

### **Chronic pain in breast cancer survivors**

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**Keywords:** *chronic pain, breast cancer (survivors), neuropathic, central sensitization, nociceptive, quality of life*

### **ABSTRACT**

**Introduction:** The differentiation between acute and chronic pain can be insufficient for an appropriate pain management. The aim of this study was to evaluate the prevalence of the predominant pain type (nociceptive, neuropathic or central sensitization pain) in breast cancer survivors (BCS) with chronic pain. The secondary aims were to examine 1) differences in health-related quality of life (HRQoL) between the different pain groups; 2) the associations between patient-, disease- and treatment-related factors and the different pain types.

**Methods:** To determine the prevalence of the predominant type of pain, a recently proposed classification system was used. BCS were asked to complete the Visual Analog Scale for pain (VAS), Douleur Neuropathique 4 Questionnaire (DN4), Margolis Pain Diagram, Central Sensitization Inventory (CSI) and Short form 36 (SF-36).

**Results:** 91 BCS participated, whereof 25.3% presented neuropathic pain, 18.7% nociceptive pain and 15.4% central sensitization (CS) pain. Mixed pain was found in 40.6%. A significant intergroup difference in HRQoL was found for SF-36 “general health” ( $p=0.04$ ). The odds for the presence of CS rather than nociceptive pain, are 26 times higher in patients exposed to hormone therapy in comparison to the non-exposed (OR:25.95, 95%CI 1.33–504.37,  $p=0.03$ ).

**Conclusion:** Neuropathic pain is most frequent in BCS. Strong associations were found between CS and hormone therapy.

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## INTRODUCTION

According to the International Agency for Research on Cancer (IARC), breast cancer is the most common malignancy in women worldwide, with 1.67 million newly diagnosed cases in 2012 [1]. Fortunately, advances in treatment strategies and early diagnosis due to the improved screening and detection techniques have increased the five-year survival rates [1, 2]. Although surveillance for cancer recurrence is the number one priority during follow-up visits, one should be aware that an important portion of survivors are affected with complications, such as pain, with prevalence numbers ranging from 11 to 50% [3-7]. Approximately 30% of breast cancer survivors (BCS) would experience above-average pain up to ten years after treatment ending [8].

Bokhari et al. stated that the additional suffering from persistent pain can be physically and psychologically overwhelming for women who were already confronted with the diagnosis of breast cancer and who attempted to cope with the various treatment regimens [7]. Accordingly, a reduction in health-related quality of life (HRQoL) was found in BCS with pain [9].

The mechanisms underlying the pathogenesis of pain in cancer survivors remain an enigma, despite the increased amount of research [3, 10-12]. This phenomenon could be elucidated by the fact that previous studies mainly focused on pain in patients with advanced cancer and not on pain during the

extended period of cancer survivorship [13]. However, several patient-, treatment- and, cancer-related risk factors have been demonstrated to be significantly related to the development of chronic pain in BCS such as lymphedema, axillary lymph node dissection (ALND), chemotherapy, radiotherapy, hormone therapy, the use of pain medication, etc. [10, 14]. New or worsening pain must be carefully evaluated since this could also indicate recurrence or the development of secondary malignancies [3].

Nevertheless, differentiating acute from chronic pain can be insufficient to provide an appropriate patient-tailored treatment with a specific pain management. Therefore, different types of chronic pain will be distinguished in this study, based on a recently developed classification system [15]. Within this classification system, chronic pain will be subdivided in nociceptive, neuropathic, central sensitization (CS) pain and mixed pain [15, 16]. Nociceptive pain has been defined as “pain that arises from actual or threatened damage to non-neural tissue and is due to the activation of nociceptors” [17]. Furthermore, it is characterized by a pain sensation that is in proportion to the amount of tissue damage [16]. The International Association for the Study of Pain (IASP) defined neuropathic pain as “pain initiated or caused by a primary lesion or dysfunction in the nervous system” [17]. Since this definition lacked both diagnostic specificity and anatomic precision, it was revised more recently by the IASP Special Interest Group on Neuropathic Pain as “pain arising as a direct consequence of a lesion or disease affecting the somatosensory system” [18-23]. Furthermore, a subdivision must be made between peripheral or central neuropathic pain, based on the location of the initial lesion in order to enable an evidence-based treatment [17]. CS is described as “an increased responsiveness of nociceptive neurons in the central nervous system (CNS) to their normal or subthreshold afferent input” [17]. As a result of the hyperexcitability of the CNS neurons, no or minimal tissue damage could be sufficient to trigger pain perception. This might form a possible explanation for the discrepancy between the experienced pain and the extent of the injury. It has been suggested in previous studies that, independent of the type of surgery, both peripheral and CS mechanisms are present in BCS [24, 25]. Due to the nature of the disease and the multimodal treatment, breast cancer patients are often exposed to a mixture of nociceptive, neuropathic and/or CS pain, also called mixed

pain [15]. Still, prevalence data of the three main types of pain within the BCS population are currently lacking.

It is expected that the majority of the BCS with pain will present themselves with a neuropathic component, as it is the most commonly described complication in literature [7, 26, 27]. Bokhari et al. found that 20% up to 50% of BCS experienced neuropathic pain after breast cancer treatment[7]. The presence of neuropathic pain can be related to the disease or to the acute or chronic effects of the cancer treatment. As described by Fallon et al., chemotherapy-induced neuropathic pain is thus found in 90% of patients undergoing neurotoxic chemotherapy [28]. Similarly, pain after breast cancer surgery appears to be predominantly of a neuropathic nature [29]. A clear example is the post-mastectomy pain syndrome (PMPS), in which neuropathic pain in the ipsilateral breast, chest or arm can be detected after breast surgery. PMPS is often seen after axillary lymph node dissection (ALND) [30].

The aim of this cross-sectional study was to evaluate the prevalence of the predominant type of pain in the BCS population. The secondary aims of this study were to examine 1) the difference in HRQoL between the different pain groups; and 2) to investigate the relations between the presence of different pain components (nociceptive, neuropathic and CS pain) and patient-, cancer- and treatment-related factors.

## **METHODS**

### **Trial design**

To examine the prevalence of the predominant pain type in BCS with chronic pain, a cross-sectional observational study was conducted. The Medical Ethics Committee of the University Hospital Brussels approved the research protocol B.U.N. 143201524229. Written and signed consent were obtained from all participants.

## Participants

### *Inclusion criteria:*

In order to be eligible, patients had to fulfill the definition of cancer survivorship introduced by the National Cancer Institute's Office of Cancer Survivorship, in which a cancer survivor is "a patient with a history of cancer that is beyond the acute diagnosis and treatment phase"[31]. Patients had to be in complete remission and should have finished their primary treatment with a curative intent at least 3 months prior to study participation. Adjuvant hormonal therapy and targeted therapy formed the exception to the rule, and were tolerated. Furthermore, the participants had to be up to 1 year post – diagnosis and needed to suffer from pain or a sensitive disorder (like numbness, tingling, etc.) anywhere in the body, which caused either a severity of minimally 30 mm on a 100 mm visual analogue scale (VAS) for pain or produced an important limitation of their activities of daily living (ADL), which is defined as a score lower than the reference value of 63.2 on the "Physical Functioning" subscale of the Short Form 36 (SF-36) [32].

In order to give informed consent and to complete the assessment tools, patients had to be able to speak and read Dutch.

### *Exclusion criteria:*

Patients suffering from other chronic diseases, severe psychological or psychiatric diseases, cognitive impairments, dementia, new neoplasms or metastases were excluded. Furthermore, survivors with pain/sensitive disorders and ADL limitations that did not attain the above-mentioned reference value [32] or provided incomplete questionnaires (i.e. one or more answers missing), were omitted from the study.

### *Recruitment and setting*

For this cross-sectional study, convenience sampling was implemented. BCS suffering from chronic pain that presented themselves at the Oncologic Center in the University Hospital Brussels between September 2014 and April 2017, were screened for eligibility and were subsequently requested to participate in this study. Each BCS of the Oncologic Center was contacted by telephone and if they were considered eligible, a questionnaire was provided at their appointment in the University Hospital Brussels. In addition, support and rehabilitation groups for BCS were contacted. After consent of participation, they were provided with a number of questionnaires. Acquaintances of the researchers were also contacted and questionnaires were presented personally or sent by mail. All questionnaires were accompanied with a stamped pre-addressed envelope for its return.

### **Outcomes**

The primary outcome, the prevalence of the predominant pain type in BCS, was obtained by running through the clinical algorithm (Figure 1). Therefore, the medical chart of the patient was reviewed and the results of the following five questionnaires were taken into account:

#### *Visual Analogue Scale for pain (VAS)*

The VAS is a subjective and frequently used method for the assessment of pain intensity. The scale consists of a straight line of 100 mm, of which the ends are defined as the extreme limits of pain perception (“no pain” to “maximum pain”). Patients were asked to place a perpendicular (vertical) line on the horizontal line at the point that represents their overall average pain intensity during the past week. A score of 0 to 4 mm is considered as no pain, 5 to 44 mm as mild pain, 45 to 74 mm as moderate pain and 75 to 100 mm as severe pain [33]. The VAS scale generates reliable and valid data for the quantitative assessment of pain severity [34, 35].



#### *Douleur Neuropathique 4 Questionnaire (DN4)*

The DN4-questionnaire was developed by the French Neuropathic Pain Group with the aim to discriminate neuropathic pain from nociceptive pain. The DN4-questionnaire consists of 10 items grouped in 4 sections. The first 7 items are related to the quality of pain (burning, painful cold, electric shocks) and its association to abnormal sensations (tingling, pins and needles, numbness, itching). The 3 remaining items are associated with the neurological examination in the painful area (touch hypoesthesia, pinprick hypoesthesia, tactile allodynia). A score of 1 is allocated to each positive item and a score of 0 to each negative item. The total score is calculated as the sum of all 10 items. In the current study, a total score of  $\geq 4/10$  is seen as cut-off point for the diagnosis of neuropathic pain, which is in concordance with literature[36-38].

Van Seventer et al. conducted a study concerning the validation of the Dutch version of the DN4-questionnaire. They concluded that a cut-off point of 5/10 for the full questionnaire resulted in a sensitivity of 75% and a specificity of 79%, while a cut-off point of 4/7 for the partial questionnaire resulted in a sensitivity of 74% and a specificity of 79% [39].

#### *Margolis Pain Diagram*

The Margolis pain diagram consists of a dorsal and a ventral drawing of the body[40]. Participants were asked to point out the places where they experienced pain during the last 4 weeks for at least 24 hours.

### *Central Sensitization Inventory (CSI)*

CSI aims to assess symptoms thought to be associated with CS pain. The total score of the CSI ranges from 0 to 100. A score of 40 or higher on the CSI indicates the presence of CS pain [41]. Mayer et al. demonstrated the psychometric strength, clinical utility, and initial construct validity of the data generated with the CSI in chronic pain patients with CS-related symptoms [42]. Likewise, the Dutch CSI has been shown to have good clinimetric properties in patients with chronic pain [43], as well as in post cancer pain patients (unpublished data – paper in progress)[44].

### *Short form 36 (SF-36)*

The SF-36 is widely used for the measurement of the experienced HRQOL. The instrument encompasses 8 different subtopics: Physical Functioning (10 items), Social functioning (2 items), Role limitations by physical problems (4 items), Role limitations by emotional problems (3 items), Emotional well-being (5 items), Vitality (4 items), Pain (2 items) and General health (5 items).

To calculate the total score, a part of the rough scores is re-encoded. Subsequently, the item scores are summed up to scale scores and transformed into a 100-point scale, with higher scores on each subscale corresponding to better health conditions[45]. A validation study of the SF-36 was performed by McHorney et al.[46]. They demonstrated that the physical functioning scale and role of physical limitations scale were the best subscales to distinguish the severity of the medical state[46]. The mental health scale and role limitations-emotional scale were the best subscales to discriminate the severity of possible ongoing psychological/psychiatric conditions[46]. The other subscales evaluated both physical and mental components of health [46]. In this study, only the scales “physical functioning”,

“mental health”, “general health” and “vitality” were used as these were thought to represent the most useful information in relation to CS. According to the developers of this questionnaire, the overall score of the SF-36 cannot be used to generate an accurate image of the HRQoL [47].

Secondary and explanatory outcomes (age, type of cancer, previous cancer treatment, current medical status and the presence of arthralgia) were inventoried at baseline for all participants using a questionnaire (appendix 1). One explanatory outcome, the presence of arthralgia, was assessed using the Margolis pain diagram [40]. Arthralgia is typically presented as symmetrical joint pain, which can be seen in hands, feet, knees, etc. [48]. In case of doubt, the participant was contacted for further information.

### **Classification system**

A recently developed classification system was applied to diagnose nociceptive, neuropathic and CS pain [15]. This involves two steps: 1) diagnosis or exclusion of neuropathic pain; 2) differentiation between predominant nociceptive versus CS pain. The clinical algorithm [15] is presented in Figure 1.

### *Diagnosis of neuropathic pain*

Treede et al. and Haanpää et al. provided an overview of the diagnostic criteria and clinical diagnosis of neuropathic pain [15, 18, 49] (table 1). Taking all criteria into account, the items “history of neurological lesion or disease” and “logical neuroanatomical pain and sensory dysfunction pattern” could be seen as those that form the cornerstone for the differentiation between neuropathic and non-neuropathic pain. Furthermore, the authors highlight the importance of the sensory testing conducive to diagnose possible sensory dysfunction [18]. The testing involves the stimulation of sensory fibers in order to assess the relationship between the stimulus and perceived sensation. Within the context of neuropathic pain, several sensations are possible: hyperesthesia, hypoesthesia, hyperalgesia,

hypoalgesia, allodynia, paraesthesia, dysesthesia, etc. Not only the type of sensation but also the location of the sensation is of a crucial matter since neuropathic pain is characterized by a neuro-anatomically logical distribution whereas non-neuropathic CS pain is rather widespread in areas that are not segmentally related to the primary source of nociception.

For the purpose of this study, the practitioner investigated the patient using basic sensory testing during the physical examination, if the scoring from the DN4-questionnaire was suggestive for the diagnosis of neuropathic pain ( $\geq 4/10$ ). Pain was classified as neuropathic if the criteria in figure 1 were met.

#### *Nociceptive versus CS pain*

In order to differentiate nociceptive pain from CS pain, the classification algorithm presented in figure 1 and described in detail elsewhere [15] was used. In this algorithm, the presence of the following three major classification criteria was screened: disproportionate pain experience, diffuse pain distribution and hypersensitivity of senses unrelated to the musculoskeletal system [15].

First, the patient was screened for the presence of *disproportionate pain*, which is defined as “pain in which the severity and the related disability are disproportionate to the nature and extent of the injury”. For the purpose of this study the amount of tissue damage (inventoried by clinical assessment and medical charts) was compared with the self-reported pain (registered by the VAS) and the associated limitations reported by the SF-36. In CS pain, patients experience a pain intensity and related disability that is disproportional to the nature or extent of the injury. In patients with nociceptive pain, on the other hand, the pain intensity and related disability are comparable to the nature and the extent of the tissue damage.

Second, the pain distribution was assessed by using the Margolis Pain Diagram. *Diffuse pain distribution* was considered when at least one of the following criteria was present:

- bilateral pain;
- pain varying in anatomical location during palpation;

- hemilateral pain;
- widespread pain;
- allodynia or hyperalgesia outside the segmental area of primary nociception examined by palpation and sensory testing.

If the patient experienced disproportional pain with a diffuse distribution, both criteria were met and the classification of CS pain could be established. If only the disproportionate pain condition was fulfilled, further screening of the last criteria was required.

The third criterion examines the *hypersensitivity* to senses unrelated to the musculoskeletal system, such as light, smell, cold, noise, medication etc. To diagnose the hypersensitivity, the CSI was used in which a score of 40 or higher was suggestive for CS pain.

### **Statistical analysis**

Statistical analyses were performed using IBM SPSS Statistics 24.0. The descriptive data were expressed as means ( $\pm$  standard deviation (SD)). Frequencies, reported as percentages, were provided for the nominal variables and the prevalence of the predominant type of pain in the BCS population. To investigate the difference in HRQoL between the different pain groups, following analyses were performed: a Kolomogorov-Smirnov test was carried out to check for normality of the subscales of the SF-36 questionnaire "Physical functioning", "General health", "Emotional well-being" and "Vitality". Since it is described in literature that parametric tests can be applied for non-normally distributed data if sample sizes are large enough without causing major problems, one-way ANOVA tests were performed for the above-mentioned subscales [50, 51]. For the significant F-test, an additional exploration of the differences among the means was performed by the Gabriel's Post Hoc procedure. The Gabriel procedure was chosen since the samples of the different pain groups were slightly different[52]. To investigate the associations between patient- (age, pain medication use), disease- (histological grade) and treatment-related factors (breast surgery, axillary surgery, chemotherapy, radiotherapy, hormone therapy) and the presence of different pain components (nociceptive, neuropathic and CS pain), one-way ANOVA tests were performed for the continuous

variables and Kruskal-Wallis tests for the nominal variables. Gabriel's Post Hoc procedures were executed for the significant one-way ANOVA test results, and Mann-Whitney U-test for the significant Kruskal-Wallis test results. Subsequently, odds ratios (OR) were computed for the significant outcomes of the Gabriel's Post Hoc Procedure and the Mann-Whitney U-test in order to provide insight in the association between the different pain types and the patient-, treatment and cancer-related factors.

## RESULTS

### Sample size

A total of 129 potentially eligible patients were reached, whereof 111 questionnaires were filled in and returned. After screening of the returned questionnaires, 20 patients were excluded for the following reasons: recurrence of the breast cancer (n=1), metastasis (n=1), pain/sensitive disorders and the ADL limitations were too small (n=11), other chronic diseases (n=1), being less than 1 year post-diagnosis (n=2) and limited data in the questionnaires (n=4), resulting in a total of 91 patients.

In **Figure 2** the flowchart of this process is presented.

### Patient characteristics

As presented in Table 2 participants had a mean age of 59.3 ( $\pm 11.9$ ) years and were 4.1 ( $\pm 4.1$ ) years post-breast cancer diagnosis. Patients had an average scoring of 47.5 ( $\pm 20.3$ ) mm for the VAS, 38.2 ( $\pm 13.4$ ) for the CSI and 3.0 ( $\pm 1.9$ ) for the DN4 questionnaire. Mean scores of the SF-36 (Table 2) were 54.5 ( $\pm 26.1$ ) for "Physical Functioning", 51.7 ( $\pm 18.1$ ) for "General Health", 68.9 ( $\pm 19.4$ ) for "Emotional Well-being" and 55.1 ( $\pm 19.2$ ) for "Vitality".

Every participant in this study went through a surgical procedure, 45 (n= 49.5 %) were subjected to a breast conserving therapy, the remainder 43 (47.3%) to a mastectomy. A sentinel lymph node biopsy (SLNB) was performed in 52 patients (57.1%), a supplementary axillary lymph node dissection

(ALND) was performed in 38 patients (41.8%). Almost every participant had radiotherapy as part of their cancer treatment (n=82, 90.1%). Numerous patients (n=72, 79.1%) were treated with hormonal therapy and 48 patients (52.7%) received chemotherapy. Pain medication use was reported by 20.9% (n=19). Furthermore, 33.0% (n=30) were found to have arthralgia.

### **Type of pain**

**Figure 3** demonstrates the distribution of the different types of pain. Among the 91 patients, 23 (25.3%) were classified as having a dominance of neuropathic pain and 17 (18.7%) predominant nociceptive. Fourteen (15.4%) patients experienced predominant CS pain. For the remaining 37 patients, a combination of pain types was found. Mixed neuropathic-CS pain was found in 15 patients (16.5%). Combined neuropathic-nociceptive pain was observed in 11 (12.1%), while 7 (7.7%) suffered from a mixed neuropathic, nociceptive and CS pain. Finally, only four (4.4 %) had both nociceptive pain and CS.

In summary, a CS pain component was observed in 40 (44%), a nociceptive pain component in 39 (42.9 %) and a neuropathic pain component in 56 (61.5%).

### **Differences in HRQoL between different pain groups**

The One-way ANOVA revealed a significant difference for the "General Health" subscale ( $p = 0.04$ ) between the seven pain groups. The Gabriel's Post-Hoc analysis for the "General Health" subscale revealed no significant results. No significant intergroup differences could be observed for the "Physical Functioning" subscale ( $p = 0.07$ ), the "Vitality" subscale ( $p = 0.31$ ) and for the "Emotional Well-being" subscale ( $p = 0.12$ ).

## Association between patient-, cancer- and treatment-related variables and type of pain

One-way ANOVA testing showed no significant difference between groups for the variable “age” ( $p = 0.13$ ) (Table 2).

The Kruskal-Wallis test demonstrated a significant intergroup difference for “hormone therapy” ( $p = 0.02$ ). Mann-Whitney testing revealed a significant difference between the nociceptive and CS pain group ( $p = 0.003$ ). Further analysis led to the following finding: the odds for the presence of CS rather than nociceptive pain, were 26 times higher in patients exposed to hormone therapy in comparison to those not exposed to hormone therapy (overall OR: 25.95 95% CI 1.33 – 504.37,  $p = 0.03$ ). For the remainder variables, “histological grade” ( $p = 0.84$ ), “breast surgery” ( $p = 0.88$ ), “axillary surgery” ( $p = 0.71$ ), “chemotherapy” ( $p = 0.27$ ), “radiotherapy” ( $p = 0.51$ ) and “pain medication” ( $p = 0.10$ ) non-significant results were obtained.

## DISCUSSION

The purpose of this cross-sectional study was to examine the prevalence of the predominant type of pain in a sample of BCS. Based on our sample of 91 BCS, the hypothesis can be accepted: neuropathic pain (25.3%) was the most prevalent pain component, followed by nociceptive pain (18.7%) and CS pain (15.4%).

Fuzier et al. demonstrated that 61% of the pain patients reported a neuropathic pain component three months after tumorectomy and SLNB [53]. This finding is in agreement with the results of this study although the examined population is not entirely concordant with ours.

As mentioned in the introduction, neuropathic pain can be caused by the cancer itself or by the invasive character of the cancer treatment, like chemotherapy, radiotherapy or surgery [28, 29].

Chemotherapy-induced painful peripheral neuropathies may result from the use of several neurotoxic agents [54]. Plexopathies, osteonecrosis, fractures, pelvic pain, connective tissue fibrosis and secondary malignancies may develop long after completion of radiotherapy and result in significant



chronic pain conditions [12, 55-58]. Furthermore, a broad spectrum of types of surgery can be held responsible for the development of chronic pain such as mastectomy, amputation, thoracotomy etc. [59]. Surgical treatment can cause neuropathic pain due to unintentional resection of a nerve or due to adhesions, inflammation or fibrous tissue, in the direct area of the nerve [53, 60, 61].

Nevertheless, in this study, no significant differences were found for the occurrence of neuropathic pain and the presence or absence of treatment-related factors (such as radiotherapy, chemotherapy, type of surgery,...). A possible explanation for these findings could be that, taking into account the amount of time required for tissue to heal, treatment-related tissue damage cannot be held responsible for the pain experienced years after treatment and implies modifications of the peripheral and/or central nervous system, which have been demonstrated in this study.

An important portion of the patients (44%, n=40) was diagnosed with CS pain. Interestingly, 30 out of 40 CS patients represented themselves with arthralgia due to the intake of aromatase inhibitors or selective estrogen-receptor modulators. Furthermore, a significant difference was found in the occurrence of CS, with patients exposed to hormonal therapy, being more likely to develop CS.

Looking at prevalence numbers in literature, approximately 75% of the breast cancer survivors are diagnosed with a hormone-receptor-positive breast cancer [62]. Therefore, aromatase inhibitors are incorporated as part of the standard adjuvant therapy in predominantly postmenopausal women [63].

Despite the fact that they improve the disease-free survival by 10-40%, up to 50% of the breast cancer survivors report joint pain as a side effect [64-69].

The underlying mechanism for the pathogenesis of the arthralgia remains a perplexity. A recent study on animals suggests that aromatase inhibitors might selectively target the transient receptor potential ankyrin 1 (TRPA1) channel [70]. The stimulation of TRPA1 through the aromatase inhibitors is associated with the release of pro-inflammatory neuropeptides from sensory nerve endings, which mediate neurogenic inflammatory responses in the innervated peripheral tissue [70]. Furthermore, the aromatase inhibitors generate a typical TRPA1-dependent behavior, characterized by acute nociception and delayed mechanical allodynia. The findings of this study correspond to the representation of peripheral rather than central sensitization. Whether we can talk about peripheral or

central sensitization in case of aromatase inhibitor-induced arthralgia, remains an enigma and requires further investigation.

The used classification system is mainly based on patient-reporting outcome measures (PRO), which remain considered by some to be less valid or objective than clinical measures. An interdisciplinary workgroup, called Assessing the Symptoms of Cancer using Patient-Reported Outcomes (ASCPRO) published a comprehensive discussion in 2010 targeting this issues [71]. A symptom was defined as “the subjective evidence of disease or physical disturbance observed by a patient”, affirming the fact that symptoms can only be properly inventoried through patient report [71]. The main concern about PRO's is the patient's error in reporting subjective symptoms. Although some state that patient-based errors are no more prevalent or problematic than errors associated with “objective” measures, a so-called response shift may occur in cancer survivors, which is characterized by changes of the internal standard of reference and reconceptualization of their health status, possibly resulting in underscoring their pain intensity [72-74]. This response shift might explain the remarkable finding that the older and already longer cured patients in our study, had practically no pain and were consequently found ineligible. Furthermore, the use of this PRO may be subject to recall bias since the data collection mainly relied on past experiences and therefore may be threatened by the limitations of the individual's memory.

Our study does present some limitations.

First, there is the cross-sectional design of this study, which rules out investigation of any temporal aspects. Therefore, causal conclusions could not be drawn about whether symptoms were ongoing or late effects of the cancer treatment. Furthermore, the self-evaluation of the pain is possibly dependent on the moment they completed the survey, not taking into account specific circumstances (e.g. life events) that can alter the experienced pain.

Second, there is the potential for selection bias, since the recruitment mainly relied on the patients' willingness to participate in this study. Furthermore, the use of convenience sampling might lead to the under- or overrepresentation of particular groups within the sample. This might not only undermine the generalization of the study results for all BCS, but possibly also threaten the accuracy

of the presented prevalence estimates. In the future, adequately powered studies are required to establish a more accurate and reliable picture of the prevalence estimates.

Third, this study is the first in reporting the prevalence of predominant nociceptive, neuropathic and central sensitization pain in BCS, using a pain mechanisms-based classification. But, further research is mandatory to investigate the construct and criterion validity of the proposed classification system before their use in clinical practice can be recommended.

Last, is the possible risk for recall bias. However, the risk is considered as minimal since the survey only contains a few questions regarding the past and is mainly focused on the current state of the participant.

Since medical science reduces the mortality rate for cancer patients, specialized care beyond the treatment phase is needed. Healthcare providers must take deliberate steps to incorporate the assessment of pain in clinical practice in order to improve the HRQoL and promote optimal functioning beyond the primary treatment and well into survivorship. The classification of pain may be useful in order to provide a patient-tailored treatment plan that meets up the individual needs of the cancer survivor since chronic pain is a malicious force that not only taxes physical resources of the patient but is also characterized by behavioral and emotional responses.

## **CONCLUSION**

Neuropathic pain is the most prevalent in cancer survivors with about 60% of the patients demonstrating this type of pain, isolated or in combination with another type of pain. Strong associations were found between CS and the use of hormone therapy.

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Table 1: Main criteria for the differentiation between neuropathic and non-neuropathic CS pain [15, 18, 49]

<b>Neuropathic Pain</b>	<b>Non-neuropathic CS Pain</b>
Presence of a lesion or disease of the nervous system	Absence of a lesion or disease of the nervous system
Confirmation of an abnormality or post-traumatic/postsurgical damage of the nervous system	No confirmation of an abnormality or post-traumatic/postsurgical damage of the nervous system
Medical cause for the nervous system damage	No medical cause for the nervous system damage
Logical neuroanatomical pain pattern	Illogical neuroanatomical pain pattern
Burning, shooting or pricking pain sensation	Vague and dull pain sensation
Location of sensory dysfunction is neuroanatomically coherent	Increased sensitivity in non-segmental related areas



Table 2: Patient characteristics, One-Way ANOVA test results, Kruskal-Wallis test results

	All (n = 91)	Nociceptive Pain (n = 17)	Neuropathic pain (n = 23)	CS (n = 14)	Neuropathic pain + CS (n = 15)	Nociceptive pain + CS (n = 4)	Nociceptive pain + neuropathic pain (n = 11)	Nociceptive pain + neuropathic pain + CS (n = 7)	p-value
VAS-score (mean $\pm$ SD)	47.5 $\pm$ 20.3	43.7 $\pm$ 20.3	42.1 $\pm$ 21.8	57 $\pm$ 20.2	48.9 $\pm$ 19.2	50.3 $\pm$ 3.3	40.5 $\pm$ 17.8	60.9 $\pm$ 13.6	
DN-4 score (mean $\pm$ SD)	3 $\pm$ 1.9	2.3 $\pm$ 1.6	3.7 $\pm$ 1.8	1.4 $\pm$ 1.5	2.5 $\pm$ 1.4	4.3 $\pm$ 3.9	3.6 $\pm$ 1.4	4.1 $\pm$ 1.7	
CSI score (mean $\pm$ SD)	38.2 $\pm$ 13.4	33.2 $\pm$ 13.7	34.7 $\pm$ 14	36.1 $\pm$ 10.9	44.3 $\pm$ 12.6	44.5 $\pm$ 22	38.2 $\pm$ 7.3	49.9 $\pm$ 10.1	
Arthralgia									
No		15 (88.2%)	23 (100%)	3 (21.4%)	5 (33.3%)	1 (25%)	10 (90.9%)	4 (57.1%)	
Yes		2 (11.8%)	0 (0%)	11 (78.6%)	10 (66.7%)	3 (75%)	1 (9.1%)	3 (42.9%)	
Age (years) (mean $\pm$ SD)	59.3 $\pm$ 11.9	62.4 $\pm$ 7.4	58.6 $\pm$ 13.8	57.5 $\pm$ 9	65.8 $\pm$ 12.5	56.3 $\pm$ 4.7	54.1 $\pm$ 13.5	54 $\pm$ 14.3	0.13
Histological grade									0.73
1		3 (17.6%)	3 (13.0%)	3 (21.4%)	1 (6.7%)	1 (25%)	1 (9.1%)	0 (0%)	
2		2 (11.8%)	7 (30.4%)	6 (42.9%)	8 (53.3%)	1 (25%)	4 (36.4%)	5 (71.4%)	
3		3 (17.6%)	2 (8.7%)	2 (14.3%)	3 (20%)	0 (0%)	2 (18.2%)	1 (14.3%)	
Missing		9 (52.9%)	11 (47.8%)	3 (21.4%)	3 (20%)	2 (50%)	4 (36.4%)	1 (14.3%)	
Breast surgery									0.86
Breast conserving therapy		9 (52.9%)	10 (43.5%)	7 (50%)	9 (60%)	2 (50%)	6 (54.5%)	2 (28.6%)	
Mastectomy		8 (47.1%)	11 (47.8%)	7 (50%)	5 (33.3%)	2 (50%)	5 (45.5%)	5 (71.4%)	
Missing		/	2 (8.7%)	/	1 (6.7%)	/	/	/	
Axillary surgery									0.68
SLNB		7 (41.2%)	13 (56.5%)	9 (64.3%)	10 (66.7%)	3 (75%)	7 (63.6%)	3 (42.9%)	
ALND		10 (58.8%)	9 (39.1%)	5 (35.7%)	5 (33.3%)	1 (25%)	4 (36.4%)	4 (57.1%)	
Missing		/	1 (4.3%)	/	/	/	/	/	
Chemotherapy									0.27
No		8 (47.1%)	11 (47.8%)	8 (57.1%)	10 (66.7%)	2 (50%)	3 (27.3%)	1 (14.3%)	
Yes		9 (52.9%)	12 (52.2%)	6 (42.9%)	5 (33.3%)	2 (50%)	8 (72.7%)	6 (85.7%)	
Radiotherapy									0.51
No		1 (5.9%)	3 (13%)	1 (7.1%)	2 (13.3%)	0 (0%)	0 (0%)	2 (28.6%)	
Yes		16 (94.1%)	20 (87%)	13 (92.9%)	13 (86.7%)	4 (100%)	11 (100%)	5 (71.4%)	
Hormone therapy									0.019**
No		8 (47.1%)	6 (26.1%)	0 (0%)	1 (6.7%)	1 (25%)	3 (27.3%)	0 (0%)	
Yes		9 (52.9%) <sup>§</sup>	17 (73.9%)	14 (100%) <sup>§</sup>	14 (93.3%)	3 (75%)	8 (72.7%)	7 (100%)	
Pain medication									0.1
No		15 (88.2%)	20 (87%)	11 (78.6%)	9 (60%)	2 (50%)	9 (81.8%)	4 (57.1%)	
Yes		2 (11.8%)	2 (8.7%)	3 (21.4%)	6 (40%)	2 (50%)	1 (9.1%)	3 (42.9%)	
Missing		/	1 (4.3%)	/	/	/	1 (9.1%)	/	
SF-36 physical functioning (mean $\pm$ SD)	54.5 $\pm$ 26.1	56.4 $\pm$ 19.2	62.9 $\pm$ 22.4	46.7 $\pm$ 31.2	39.9 $\pm$ 30.2	46.3 $\pm$ 32	68.9 $\pm$ 15	62 $\pm$ 22.8	0.07
SF-36 emotional well-being	68.9 $\pm$ 19.4	64.6 $\pm$ 18.4	80.7 $\pm$ 14.2	67.1 $\pm$ 23.1	67.4 $\pm$ 22.6	58 $\pm$ 23.2	69.8 $\pm$ 11.7	59.3 $\pm$ 16.7	0.12

(mean ± SD)									
SF-36 general health (mean ± SD)	51.7 ± 18.1	53.9 ± 16.7	62.9 ± 15.6	47.9 ± 20	48.9 ± 14.2	42.5 ± 26.6	47 ± 16	40 ± 18.7	0.04*
SF-36 energy/fatigue (mean ± SD)	55.1 ± 19.2	55.36 ± 16.8	65 ± 17.8	53.6 ± 21.3	53.2 ± 22.5	50 ± 18.7	49.4 ± 11.8	45.8± 22	0.31

**Abbreviations:** n, sample size; CS, Central Sensitization; VAS, Visual Analogue Scale; SD, Standard Deviation; DN-4, Douleur Neuropathique 4 Questionnaire; CSI, Central Sensitization inventory; SLNB, Sentinel Lymph Node Biopsy; ALND, Axillary Lymph Node Dissection; SF, Short Form; \*, p-value < 0.05 (One-Way ANOVA); \*\*, p-value < 0.05 (Kruskal-Wallis); +, p-value < 0.05 (Gabriel’s Post-Hoc Procedure); #, p-value < 0.05 (Gabriel’s Post-Hoc Procedure); \$, p-value < 0.05 (Mann-Whitney Test)

### Algemene Vragenlijst

**Naam:**

**Geslacht:**

**Geboortedatum:**

- Wat voor kanker is er bij u gediagnosticeerd?
- Wanneer is de kanker bij u gediagnosticeerd?
- Wat voor behandelingen heeft u gehad?
  - Chirurgie
    - Wat is er weg gehaald?
  - Chemotherapie
  - Bestraling
    - Welke gebied is er bestraald?
- Wanneer hebben de bovengenoemde behandelingen plaats gevonden?
- Is er sprake van uitzaaiingen?
- Is de kanker al eens terug gekeerd?
- Neemt u nu nog medicijnen of ondergaat u nu nog behandelingen die in verband staan met de kanker die u gehad heeft?

- Accepted Article
- Wilt u hieronder aan kruisen waarvoor u nu nog medicijnen slikt.
    - Ik slik geen medicijnen
    - Pijnstillers
    - Hart en bloedvaten
    - Diabetes Mellitus ( suikerziekte)
    - Hormoontabletten
    - Schildklier
    - Osteoporose
    - Anders.....
  - Werd er bij u in het verleden zenuwschade vastgesteld of bent u op consult geweest bij een neuroloog?
  - Bent u verder nog in behandeling bij een arts of specialist? Zo ja, waarvoor?
  - Heeft u op dit moment nog pijn, die ontstaan is na of tijdens de behandeling van uw kanker?
    - Ja
    - Nee



