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TITLE

Psychological Factors Influencing Healthcare Utilization in Breast Cancer Survivors with Pain

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ABSTRACT

Introduction:Pain is a prevalent side-effect seen in breast cancer survivors (BCS). Psychological factors are known role-players in pain mechanisms. Both pain and psychological factors contribute to or interact with healthcare use (HCU). However, the association between psychological factors and HCU has never been investigated in BCS with pain, which is aimed in this study.

Methods:Belgian BCS with pain (n=122) were assessed by the Medical Consumption Questionnaire, Injustice Experienced Questionnaire, Pain Catastrophizing Scale, Pain Vigilance and Awareness Questionnaire, Brief Illness Perceptions Questionnaire, and the Depression, Anxiety and Stress Scale. Associations were analyzed using logistic and Poisson regressions.

Results:Opioid use was related to more catastrophizing and less psychological distress. Psychotropic drug was related to more psychological distress. Endocrine therapy related to less vigilance and awareness. Psychological distress related to all types of healthcare provider (HCP), with psychological distress negatively related to physiotherapy, psychology, and other primary HCP visits, and positively with visiting a general practitioner and secondary HCP. Catastrophizing related to more visiting behavior in primary HCP, except to a general practitioner. Perceived injustice related to more general practitioner and other primary HCP visits, but to fewer psychology visits. Illness perceptions are only related to visiting other primary HCP. Vigilance and awareness was related to more psychologist and secondary HCP visits.

Conclusion:Our findings underscore the complex interplay between HCU and psychological factors in BCS with pain. Psychological distress was overall the most important psychological factor related to HCU, whether catastrophizing and perceived injustice were the most relevant related to HCP visits.

Keywords

Breast Cancer; Healthcare Use; Medication Use; Cognitions; Emotions

MANUSCRIPT

1. Introduction

Breast cancer is the most common type of cancer among women [1]. In 2020, 2.26 million individuals were diagnosed with breast cancer, accounting for 11.7% of the total number of cancer cases worldwide [2, 3]. While the number of survivors is rising thanks to improved detection and better treatment [3], there is still no universally accepted definition for a cancer survivor [4]. The European Organization for Research and Treatment of Cancer (EORTC) Survivorship Task Force defines a cancer survivor as 'any person who has been diagnosed with cancer, has completed their primary treatment (excluding maintenance therapy), and shows no evidence of active disease' [4]. This definition stands out for its focus on the patient itself as well as on the clear stage of survival after finishing the curative treatments compared to other definitions.

Long- and late-term side effects of both cancer and its treatment have become more common during the survival stage of cancer [2, 3]. Chronic pain is one of the most reported side effects, with a prevalence of up to 30-50% among breast cancer survivors (BCS) [5, 6]. Pain experience is influenced by psychological and social factors that can both amplify or reduce pain intensity [7-9], requiring a biopsychosocial treatment approach involving biological, psychological, and social aspects of pain [10]. Additionally, pain is one of the leading reasons for healthcare and medication use among people with cancer [11], breast cancer [12] and chronic pain [13, 14], which leads to high costs for both patients and society.

Based on the conceptual model of Andersen, three dynamics (predisposing, enabling, and need factors) determine the use of healthcare resources [15]. In addition to the pain itself [16-18], pain-related cognitions, categorized as predisposing and/or need factors, contribute to healthcare use (HCU) [19]. Taking into account the interindividual differences in pain experience and psychological processes [20], HCU can be seen as a behavioral action [15]. A recent review confirmed the association between a limited selection of pain-related cognitions and HCU outcomes in individuals experiencing pain [21]. However, none of the included studies considered BCS and associations with a large number of psychological factors and HCU outcomes remained un(der)explored.

One such important psychological factor gaining increasing attention in BCS, and pain populations is perceived injustice [22, 23]. Previous research showed us that perceived injustice leads to increased protective pain behavior in early BCS [24], which makes clinicians more likely to prescribe opioids [25]. In addition, pain behavior mediates the association between perceived injustice and opioid prescription in chronic pain [26]. Perceived injustice also predicts opioid use at 1-year follow-up in individuals with a whiplash history [27] increasing the risk of long-term side effects of long-term opioid use [28]. Additionally, more frequent ambulatory transport, emergency department and hospital admissions are seen in long-term opioid users compared to individuals who do not use opioids [29].

Other important psychological factors potentially seen together with pain symptoms, such as pain catastrophizing, pain vigilance and awareness, and psychological distress, may impact the need to use healthcare resources. A recent systematic review of individuals with pain found a positive association between catastrophizing and psychological distress with pain medication use, a positive relationship between anxiety and depressive symptoms with opioid use, and a positive relationship between psychological distress and consulting behavior [21]. Moreover, in accordance with the Common Sense Model of self-regulation, when individuals encounter an illness, they develop personalized models or representations as a mechanism for coping, which can be either adaptive or maladaptive [30]. These psychological representations are influenced by factors such as personality, prior events, observations, and information received about the illness and its symptoms [31]. Consequently, these perceptions of illness can drive subsequent self-management behaviors, including decisions related to healthcare utilization [32].

To the best of our knowledge, the previously mentioned psychological factors have not yet been investigated in relationship with HCU in BCS with pain. However, it is important to unravel which factors could play a role in HCU for survivors. The Institute of Medicine reported that “Healthcare providers should increasingly aim at tailoring pain care to each person’s experience, and self-management of pain should be promoted” [33]. In order to understand the experience of pain in BCS and its related HCU, the biopsychosocial model should be considered [34], which includes psychological factors. This could be the starting point to design targeted interventions for BCS with pain to possibly lower the socio-economic burden related to the late consequences of cancer treatment. Therefore, this cross-sectional study with secondary analyses aims to explore associations between psychological factors and HCU in BCS with pain.

We hypothesize that higher levels of perceived injustice, pain catastrophizing, pain vigilance and awareness, as well as psychological distress, are related to more HCU, and that more favorable illness perceptions relate to lower HCU levels.

2. METHODS

2.1. Study design

This cross-sectional study was written in accordance with the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) recommendations [35]. Participants were initially recruited for a randomized controlled double-blinded trial (registered on ClinicalTrials.gov: NCT04531917) of which only the baseline data were used for secondary analyses in this cross-sectional study. An agreement was obtained by the Ethics Committee of all participating hospitals, with the University Hospital Brussels as the Main Ethics Committee (B.U.N. 1432020000068).

2.2. Setting

Participants were recruited by convenience sampling at the University Hospital Brussels (Belgium), AZ Rivierenland (Bornem, Belgium), AZ Sint-Blasius (Dendermonde, Belgium), Hospital Geel (Geel, Belgium), Imeldaziekenhuis (Bonheiden, Belgium) and AZ Sint-Lucas (Gent, Belgium). Physicians, pharmacies, Flemish patient support groups, occupational health services, and social media were used as additional recruitment channels.

2.3. Participants

Participants were contacted by phone by an independent researcher (A.L.) and screened based on the predefined in- and exclusion criteria: (1) Meeting the definition 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 [36]; (2) Being breast cancer-free and finished primary treatment with curative intent for at least 3 months prior to study participation. Adjuvant endocrine therapy and immunotherapy were tolerated; (3) Reporting a pain severity of ≥3/10 on the pain visual analogue scale (PVAS); and (4) Being able to speak and read in Dutch to give informed consent and complete the assessment tools. The exclusion criteria were as follows: (1) Having a chronic pain pathology, which was unresolved and diagnosed before the cancer diagnosis (e.g., *fibromyalgia, rheumatoid arthritis*);

(2) Suffering from dementia or cognitive impairment (unable to understand the test instructions and/or Mini-Mental State Examination (MMSE) score <23/30. The MMSE was assessed before the baseline assessments.); (3) Suffering from severe psychological or psychiatric diseases (unable to understand the test instructions); and (4) Being diagnosed with new neoplasms or metastases. Written and signed consent was obtained from all participants.

2.4. Outcome measures

All baseline data used in this cross-sectional study were assessed by online self-reported questionnaires using the Qualtrics platform, at one of the study locations: Vrije Universiteit Brussel (Belgium), AZ Rivierenland (Bornem, Belgium), AZ Sint-Blasius (Dendermonde, Belgium), AZ Sint-Lucas (Gent, Belgium), private practice (Geel, Belgium), Imeldaziekenhuis (Bonheiden, Belgium), and Universiteit Hasselt (Belgium).

2.4.1. Demographics

The following demographic characteristics were assessed at baseline: age, ethnicity, body mass index (BMI), marital status, educational level, presence of lymphedema, type of surgery, menopause, and breast cancer treatment plan. In addition, the pain severity was assessed by the Brief Pain Inventory (BPI) [37]. The BPI consists of 14 items to assess the pain severity, the pain interference and pain locations in a cancer patient's daily life. For the analysis of this study, only the pain severity score reported on a scale of 0 to 10 is used [37]. Moreover, we assessed the level of symptoms related to two different mechanistic pain types. For symptoms of central sensitization, the Central Sensitization Inventory (CSI) was used and the Douleur Neuropatique 4 (DN4) was assessed to identify the number of symptoms of neuropathic pain [38-43].

2.4.2. Psychological factors

Perceived injustice was assessed by the Injustice Experienced Questionnaire (IEQ) [44] containing two correlated constructs (1- blame/unfairness and 2- severity/irreparability of loss) [45] and assessing the perceptions of injustice following injury/illness. The total score ranges between 12 and 48, with higher scores being indicative for greater levels of perceived injustice [44]. The IEQ shows adequate internal reliability in chronic pain populations (r=0.90) [45].

The level of pain catastrophizing was measured with the Pain Catastrophizing Scale (PCS), containing 3 subscales: rumination, magnification, and helplessness, with a total score ranging from 0 to 52. Higher scores are representing higher levels of pain catastrophizing. The PCS shows adequate reliability and is considered to be a valid measurement tool with good internal consistency [46, 47].

The assessment of attention to (changes in) pain was assessed by the Pain Vigilance and Awareness Questionnaire (PVAQ). It assesses awareness, consciousness, vigilance, and observation of (changes in) pain [48, 49], with higher scores indicating a higher degree of vigilance and awareness for (changes in) pain [48]. The total scores on the PVAQ range from 0 to 80. The PVAQ has been validated and found to be a reliable assessment tool in patients with chronic pain [48].

Illness perceptions were retrieved from the Brief Illness Perception Questionnaire (IPQ-B), which assesses cognitive illness perceptions, emotional perceptions, illness comprehensibility, and causal perception [50]. Total scores range from 0 to 80 with a higher score reflecting a more threatening view of the illness. Causal perceptions were omitted for this study. The IPQ-B has acceptable psychometric properties [50].

The Depression, Anxiety and Stress Scale–21 Items (DASS-21) was used to assess psychological distress based on three constructs: depression, anxiety, and stress. Each subscale is scored between 0 and 21, with higher scores representing more severe symptoms of psychological distress [51, 52]. The DASS-21 has been validated and was found to be a reliable measurement tool in cancer patients [52-54].

2.4.3. Healthcare use

The Medical Consumption Questionnaire (MCQ) quantifies the patient's total medical consumption behavior, encompassing additional diagnostics, visits, surgery including hospital admissions, physiotherapy, medication, and aids prescribed by the general practitioner as well as medication and aids purchased by the patients themselves in the past 3 months. The questionnaire can be used in different study populations and was made to measure healthcare consumption in a standardized manner [55].

HCU was categorized based on consensus meetings between A.R., E.S., E.R., E.H., and L.L.. Medication use was subdivided into (1) opioids (e.g., *Tradonal, Zaldiar, Tramadol, Contramal, Oxycontin*), (2) psychotropic drugs (e.g., *antidepressants, hypnotics, anti-epileptics*), (3) endocrine therapy (e.g., *Tamoxifen, aromatase inhibitors, protein kinase inhibitors*), and (4) other medication (e.g., *supplements, gastro-intestinal, cardiovascular, urogenital, articular medication*). The BCFI (Belgisch Centrum voor Farmacotherapeutische Informatie) compendium was used to define the types of medication used by the participants in order to correspond the medication to the correct pre-defined category of medication use. All outcomes for medication use are set as dichotomous variables (use (1) or not (0)). Visits with healthcare providers were expressed in count variables including the number of visits to (1) a general practitioner, (2) a physiotherapist, (3) a psychologist, (4) visits with other primary (i.e., *social worker, occupational therapist, dietician, homeopath, acupuncturist, occupational physician*) and (5) secondary healthcare providers (*specialized care in a policlinic, hospital or rehabilitation center; e.g., oncologist, breast surgeon, cardiologist, dermatologist*). Primary and secondary healthcare providers were defined based on the Belgian healthcare system. In addition, the use of emergency first aid or transportation (ambulance) as well as hospital or institutional admissions in the past 3 months were assessed.

2.5. Bias

The risk of sampling bias with convenience sampling is limited using different recruitment strategies, and this study is multicentric in character. Additionally, all questionnaires were validated with a maximum recall of 3 months. In general, recall questionnaires are valid and feasible for a period of up to 6 months [56]. Moreover, all questionnaires were self-administered without an interviewer's assistance. Only in case of difficulties, an independent researcher could be contacted.

2.6. Statistical methods

The statistical analyses were done with R version 4.2.2. Descriptive statistics were performed for the demographical data and all outcome measures. Missing values were imputed using sequential estimation.

The education levels were categorized based on the International Standard Classification of Education (ISCED) 2011 [57]. The categories are low education (including early childhood, primary, and lower secondary education), medium education (including upper secondary, post-secondary non-tertiary, short cycle tertiary education), and high education (including bachelor, master, and doctoral level education or equivalents) [57].

Since the subscales of the DASS-21 are moderately inter-correlated with each other, the three DASS-21 scores were transformed into one total outcome measure summarizing negative emotional symptoms. This was done by first converting each scale score to a z-score (i.e., subtracting the mean and dividing by the standard deviation from the normative data for that scale) to retain a connection to the normative data [51]. For all remaining psychological outcomes, the total scores of the questionnaires were used.

Medication use and visiting behavior were selected for further analysis. The admissions (i.e., use of emergency first aid or transportation (ambulance) and hospital or institutional admissions) were omitted from the analyses due to the low prevalence in the sample. The relationship between the psychological factors (independent variables) and each HCU variable (dependent variables) was investigated separately with the same set of confounders including age, BMI, marital status, education level, lymphedema, menopause, months since cancer diagnosis, type of treatment had, pain severity and symptoms of different pain mechanisms (i.e., DN4 and CSI). The correlational structure between independent variables was checked a priori to see if multicollinearity is present. Moreover, if an independent variable results in hugely inflated standard errors, it is eliminated from the model.

The probability of using specific healthcare services or medication was modelled for all dichotomous outcomes with logistic regression, being (1) whether someone used opioids; (2) psychotropic drugs; (3) endocrine therapy; and (4) other types of medications or not. The frequency of specific HCU was modelled for the remaining outcomes using Poison regressions, possibly enhanced with a dispersion parameter, or extended to a zero-inflated Poison model, being (1) the number of visits to a general practitioner; (2) physiotherapist; (3) psychologist; (4) other primary care visits; and (5) secondary care visits.

For each model, the relevance of the predictors was explored with a stepwise (forward-backward) procedure based on the AIC (Akaike Information Criterion). Although not used for selecting the variables, in addition to the estimates and their standard errors, *p*-values are offered for completeness for all variables that remained in the model.

3. RESULTS

3.1. Demographics and descriptives

A total number of 259 female BCS were screened for eligibility from September 2020 to December 2022 of which 137 were excluded due to different reasons (***Figure 1***). Finally, 122 participants were assessed at baseline. Participants had a median age of 54.50 [49.00-59.25] years old, were mainly Blank (n=121, 96.2%), and had a mean BMI of 26.58±5.14 kg/m². Subjects were predominantly married (68.00%; n=83) and 83.60% of them had medium to high education levels (n=102). All participants underwent surgery (100%; n=122). A large portion of the BCS underwent chemotherapy (65.57%; n=80), radiotherapy (87.80%; n=107), and was diagnosed with lymphedema (31.96%, n=39), of which 17 (43.59%) had an axillary lymph node dissection. Up to 85.24% (n=104) of the subjects were currently in their menopause with 59.83% (n=73) being in early menopause, 61.47% (n=75) experiencing hot flushes and/or 56.55% (n=69) experiencing night sweats.

In terms of pain, the included BCS showed a mean pain severity of 4.49±1.75. Most scored above the cut-off point of ≥40/100 on the CSI [42], indicating clinically significant symptoms of central sensitization, with a mean score of 46.39±15.14. In contrast, for neuropathic pain symptoms, the sample scored below the clinical cut-off of ≥4/7 on the DN4 on average (mean: 3.00 [1.00-4.00]) [39].

Regarding the psychological characteristics of the sample, feelings of injustice were relatively low 14.00 [9.00-22.00] [27]. The median score for pain catastrophizing was 18.00 [10.75-26.25] which is largely under the cut-off of >30 for clinically significant levels of pain catastrophizing [46]. Levels of pain vigilance and awareness were also relatively low 30.00 [25.75-39.50]. In contrast, the median illness perception score (48.00 [42.00-55.00]) indicated a moderate experience of threat [58]. For psychological distress, the depression levels were mild (6.00 [2.00-12.00]) and anxiety and stress levels were moderately high (6.00 [2.00-12.00] and 12.00 [6.00-18.00] respectively) [59]. See ***Table 1*** for all the descriptives.

3.2. Probability of using medication

For the odds of using opioids, pain catastrophizing (exp(B)=0.046; p=0.042) and psychological distress (exp(B)=-0.588; p=0.062) were retained as psychological factors in the final model, together with age (exp(B)=-0.040; p=0.098), education level (exp(B)$_{\text{medium education (ref: low education)}}$=-0.471; p=0.450; exp(B)$_{\text{high education (ref: low education)}}$=-1.72; p=0.007), whether someone has lymphedema (exp(B)=0.703; p=0.119), and the number of neuropathic pain symptoms (exp(B)=-0.254; p=0.034) as confounding factors in the model.

The final model for the odds of using psychotropic drugs only contained psychological distress (exp(B)=0.609; p=0.010) as a psychological factor and only whether someone is in menopause (exp(B)=-0.717; p=0.065) as confounding factor.

For endocrine therapy, also only one psychological factor was retained in the final model, namely pain vigilance and awareness (exp(B)=-0.024; p=0.149). However, more confounding factors were kept in the model, including whether someone is in menopause (exp(B)=0.966; p=0.029), months since first breast cancer diagnosis (exp(B)=-0.008; p=0.008), whether someone had chemotherapy (exp(B)=-0.987; p=0.035), and the pain severity (exp(B)=-0.251; p=0.047).

For all other types of medication use, none of the psychological factors seemed to be relevantly related to the odds. Again here, several confounding factors remained in the model, including age (exp(B)=0.058; p=0.031), BMI (exp(B)=-0.106; p=0.078), whether someone has lymphedema (exp(B)=1.19; p=0.081), and whether someone is in menopause (exp(B)=1.06; p=0.040). The results of the probability of using medication are shown in *Table 2*.

3.3. Frequency of visiting healthcare providers

The number of visits to a general practitioner was related to perceived injustice (exp(B)=0.010; p=0.179) and psychological distress (exp(B)=0.357; p<0.001), as well as the marital status (exp(B)$_{\text{single/widow (ref: married)}}$=0.074; p=0.756; exp(B)$_{\text{living together (ref: married)}}$=-0.462; p=0.014) as a confounding factor. However, in this sample, no relationship was found between any psychological factors and whether someone visits a general practitioner.

The number of physiotherapy visits was also related to psychological distress (exp(B)=-0.049; p=0.571), together with pain catastrophizing (exp(B)=0.008; p=0.282). Moreover, the pain severity, whether someone is in menopause, and whether someone has lymphedema or not remained also relevant in relationship to the number of physiotherapy visits. However, whether someone visited a physiotherapist or not was only related with psychological distress (exp(B)=-0.930; p=0.224). Again, some confounding factors are also related to whether someone visits a physiotherapist, which were the number of symptoms of central sensitization (exp(B)=-0.039; p=0.105), whether someone has lymphedema (exp(B)=-2.235; p<0.001), and the marital status (exp(B)$_{\text{single/widow (ref: married)}}$=0.398; p=0.637; exp(B)$_{\text{living together (ref: married)}}$=1.656; p=0.005).

The number of visits to a psychologist was related to perceived injustice (exp(B)=-0.021; p=0.083), pain catastrophizing (exp(B)=0.060; p=0.001), pain vigilance and awareness (exp(B)=0.017; p=0.150), and psychological distress (exp(B)=-0.361; p=0.044). In addition to these psychological factors, the number of neuropathic pain symptoms (exp(B)=0.064; p=0.472) and symptoms of central sensitization (exp(B)=0.089; p=0.262), whether someone had chemotherapy (exp(B)=0.466; p=0.076), whether someone is in menopause (exp(B)=-0.027; p=0.254), and whether someone has lymphedema (exp(B)=0.653; p=0.077) were relevant confounding factors in the final model for the number of psychological visits. Whereas whether someone visited the psychologist or not was only related to pain vigilance and awareness (exp(B)=0.081; p=0.014) and psychological distress (exp(B)=-1.170; p=0.003) together with the number of neuropathic pain symptoms (exp(B)=-0.424; p=0.015).

The number of visits to other primary healthcare providers was related to perceived injustice (exp(B)=0.050; p=0.162), pain catastrophizing (exp(B)=0.077; p=0.030), illness perceptions (exp(B)=0.014; p=0.591), and psychological distress (exp(B)=-0.038; p=0.916). Additionally, almost all confounding factors were also included in this final model, including the number of neuropathic pain symptoms (exp(B)=0.003; p=0.973) and symptoms of central sensitization (exp(B)=-

0.067; p=0.002), whether someone had chemotherapy (exp(B)=0.628; p=0.170), whether someone has lymphedema (exp(B)=1.034; p=0.049), age (exp(B)=0.043; p=0.127), and marital status ($\text{exp(B)}_{\text{single/widow (ref: married)}}$=-1.183; p=0.136; $\text{exp(B)}_{\text{living together (ref: married)}}$=-2.039; p=0.002). The same psychological factors, except illness perceptions, are related to whether someone visits other primary care providers (exp(B)=0.045 (p=0.365), exp(B)=-0.007 (p=0.870), and exp(B)=-0.714 (p=0.250 respectively). The confounding factors relevant in whether someone visits other primary healthcare providers are the number of neuropathic pain symptoms (exp(B)=-0.120; p=0.497) and symptoms of central sensitization (exp(B)=-0.066; p=0.864), and age (exp(B)=0.128; p=0.008).

Lastly, the number of visits to secondary healthcare providers was related to pain vigilance and awareness (exp(B)=0.006; p=0.590), and psychological distress (exp(B)=0.083; p=0.672). Here again, the number of neuropathic pain symptoms (exp(B)=232; p=0.002) and symptoms of central sensitization (exp(B)=0.032; p=0.031) seem relevant confounding factors in the model, together with the severity of pain (exp(B)=-0.116; p=0.169) and whether someone is in menopause (exp(B)=0.016; p=0.942). However, visiting a secondary healthcare provider or not was unrelated to any psychological or confounding factors. All the results of the frequency of visits to healthcare providers are presented in ***Table 3***.

4. DISCUSSION

4.1. Discussion of the results

In this cross-sectional study the association between various psychological factors and HCU was investigated in BCS with pain. Due to the low occurrence of certain HCU outcomes, including emergency admissions, ambulance usage, and institutional admissions, these could not be thoroughly analyzed in relationship to psychological factors. Nonetheless, the study revealed significant associations between psychological factors and medication use as well as visiting behavior, showing the importance of psychological factors in BCS with pain. For the psychological factors retained in the final models, the direction of the associations with the healthcare use outcomes was overall in line with the hypothesis (i.e., *higher levels of perceived injustice, pain catastrophizing, pain vigilance and awareness, as well as psychological distress, are related to more HCU, and that more favorable illness perceptions relate to lower HCU levels*).

However, for psychological distress in relationship with opioid use and visiting a physiotherapist, psychologist, and other primary healthcare providers the hypothesis could not be confirmed. The negative association of pain vigilance and awareness with endocrine therapy, and perceived injustice with the number of psychological visits were neither as hypothesized.

First of all, **opioid use** was found to be related to higher levels of pain catastrophizing and lower levels of psychological distress. Pain catastrophizing is the magnification of pain-related negative thoughts impacting the disability levels on the long-term [22]. By targeting pain catastrophizing during psychological treatments, improvements in the interference of pain can be achieved [60, 61]. When looking into cancer, pain catastrophizing was found associated to increased pain symptoms [11] possibly leading to more opioid use. Knowing that pain catastrophizing is strongly related to perceived injustice in the pain experience of BCS [22], and that both cognitive appraisals increase the risk of long-term disability and aggravate pain-related distress through maladaptive behavioral responses [22], the unfounded association of perceived injustice with **opioid** use is surprising. Especially knowing that feelings of injustice related to pain may result in enhanced pain behavior, which in turn increases the chance of being prescribed opioids [62]. The prescription of opioids could validate the pain behavior of people with perceived injustice and makes it not easy to break out of this pattern [25]. However, prescription behavior varies across countries and continents, as well as across different types of populations with pain, which makes it difficult to compare with our study. Since BCS mostly suffer from different type of side-effects and/or comorbidities, the prescription of opioids can be considered differently compared to other populations with only pain.

On the other hand, the negative association found between **opioid use** and psychological distress is also unexpected. The presence of depression can decrease the responsiveness to opioids to alleviate chronic pain, possibly leading to more and stronger opioid use and increased opioid prescription [63]. Moreover, long-term opioid use increases the risk of depression onset and recurrence as well as worsening of depression [64-66] leading to the expectation that opioid use would be related to more psychological distress. However, low doses of buprenorphine, found in opioids, may have antidepressant effects mediated through its action on the mu, delta, and kappa opioid receptors in the short term [67]. Based on the results of our study we do not know how many opioids and days of opioids were taken in the past 3 months to conclude if the opioids were taken in the long- or short-term.

Psychological distress is a significant issue among cancer survivors [68], which is not related to the cancer itself but is rather a logical consequence of having completed cancer treatment and survived the disease. In our results, psychological distress was positively associated with the chance of using psychotropic drugs. This is not surprising given that psychotropic drugs are used to treat a wide range of mental health conditions, including anxiety, depression, and stress [69]. These medications adjust the levels of neurotransmitters in the brain to help manage symptoms and improve overall well-being [69]. Moreover, psychological distress affects pain experience over time [70] leading to increased medication use in BCS with pain [71]. Furthermore, in any stage of the breast cancer journey, psychotropic drugs (e.g., *antidepressants*) can be used as adjuvant medication in the management of different types of pain [72, 73] making it a potential kind of medication to use when experiencing chronic pain as a cancer survivor.

The use of endocrine therapy was found to be associated with lower levels of pain vigilance and awareness. It is known that BCS with hormone-positive cancers, who need to take endocrine therapy during the survival stage, may experience side effects like pain [74, 75], anxiety and depression [76] due to endocrine therapy . Since this is a common problem and generally known by BCS, it is possible that BCS who are under endocrine therapy, do relate their pain to the endocrine therapy decreasing the threat of pain and thus be less vigilant and aware of their pain complaints [77]. In accordance, the results of our study showed that the pain severity was also found to be less in the BCS taking endocrine therapy possibly showing that the perception of pain is possibly different between those taking endocrine therapy or not. In addition, based on precision medicine [78], endocrine therapy is recommended in regard to the type of cancer and its hormone receptor status [79]. Whether it is prescribed, depends on menopausal status, the specific type of hormone receptor-positive breast cancer, and the risk of cancer recurrence [79]. It seems also logical that endocrine therapy is related to being in menopause due to its endocrine suppression effect [80]. Psychological factors are thus not influencing the prescription but may be related to the side effects of the endocrine therapy.

Visiting healthcare providers in general did relate to most of the psychological factors, except illness perceptions. The only type of visiting behavior for which illness perceptions remained significant was the number of visits to primary healthcare providers (i.e., *social worker, occupational therapist, dietician, homoeopath, acupuncturist, occupational physician*). For individuals with maladaptive illness perceptions, visiting a healthcare provider may reduce worry about their illness [81]. However, our population included BCS with an average of 44.00 [22.00-85.75] months since the first time of breast cancer diagnosis, which still falls under the regular supervision by the oncologist and other members of their healthcare team in the next 5 years after treatment completion [82]. A previous study showed that negative illness perceptions among endometrial cancer survivors were associated with higher HCU with more prominent associations among long-term survivors compared to short-term survivors [81]. It is thus possible that the illness perceptions of our study population do not relate to HCU in their stage of survivorship but may in long-term survivors.

The positive association between visiting a general practitioner and perceived injustice and psychological distress (i.e., *depression, anxiety, and stress symptoms*) in BCS with pain was not surprising, knowing that psychological distress is one of the psychological factors possibly increasing the intensity of pain and its related disability [83-85]. From previous research on BCS, it is known that strong disease identity, anxiety about the disease, and emotional distress are associated with higher HCU in general [32]. In cancer survivors, psychological distress was found to be associated with lower quality of care and an increase in the number of healthcare visits [86]. Another aspect of psychological distress, pain-related anxiety, often drives patients into safety-seeking behavior such as frequent visits with healthcare practitioners [87].

When looking to the visits to other primary healthcare providers (i.e., *physiotherapist, psychologist, other primary healthcare providers*), psychological distress was found negatively associated with whether someone visits the healthcare provider as well as the number of visits to the healthcare provider. This is surprising since it was hypothesized that the chance of visiting these healthcare providers would be related to higher levels of psychological distress. However, it may be possible that the levels of psychological distress are lower thanks to possible treatment effects, which is less the goal when visiting a general practitioner [88]. Our study only includes cross-sectional data which makes it difficult to define the causal association between the psychological and the healthcare use outcomes [89]. It is thus possible that visiting a physiotherapist, but also a psychologist, and other primary healthcare providers decreases the levels of psychological distress and are even lower compared to those who are not visiting one of the respective healthcare providers.

In contradiction to the overall primary healthcare provider visits, a positive association of psychological distress was found with the number of visits to secondary healthcare providers, including oncologists. It should be noted that visiting healthcare is normal and necessary for BCS. In general, BCS see their oncologist and other members of their healthcare team regularly in the next 5 years after treatment completion [82], since the vast majority of recurrences of breast cancer occur within this period [90]. The frequency of visiting healthcare ranges from 1-4 times a year, depending on the individual's situation (e.g., *use of aromatase inhibitor, age, family history, stage of disease at diagnosis*) [82]. During the survival phase, the oncologist is often seen as their primary healthcare contact. In other situations, although Belgium does not employ an official gatekeeper system, the general practitioner is often the starting point for additional care prescriptions [91]. This is thus not necessarily the case for individuals in the survival stage after breast cancer and could also explain why none of the psychological factors are associated with whether visiting a general practitioner.

So far, research on healthcare visiting behavior and its relationship with perceived injustice is lacking. In this study, a positive association was found between perceived injustice and the number of visits to a general practitioner. What is generally seen in clinic, is that general practitioners are often visited for various health problems related to the physical side-effects (i.e., *acute symptoms, sleep problems, chronic diseases*) and the psychological side-effects during the survival stage of breast cancer (i.e., *difficulties within their family/couple, discussing work disability/planning the re-uptake of work*) [92], which are potential triggers for feelings of injustice [93] in BCS with pain. This could be why the number of visits to a general practitioner are seen together with higher levels of both, perceived injustice and psychological distress.

Further, no association was found between the number of physiotherapy visits and perceived injustice, however, we did for pain catastrophizing. Due to worse perceived well-being, people are more likely to use primary care and physical therapy [94]. On the other hand, perceived injustice, rather than pain catastrophizing, has been found to be a mediator between pain and quality of life in BCS highlighting its potential role in healthcare-seeking behavior in primary healthcare [23]. This shows that the severity/irreparability construct of perceived injustice, seen as an important similarity to pain catastrophizing, is more important in defining the number of visits to a physiotherapist, rather than the blame/unfairness construct of perceived injustice which seems to be less important [44].

However, both, perceived injustice and pain catastrophizing, were associated with the number of visits to a psychologist as well as visits to primary healthcare providers. However, perceived injustice was negatively associated with the number of visits to a psychologist which contrasts with pain catastrophizing being positively associated. In this case, it could be possible that BCS with pain with higher levels of unfairness/blame may not be open to go to a psychologist regularly since they perceive their losses as undeserved as a result of another one's actions [93]. A psychologist does work on personal perception, which a person with perceived injustice may not perceive as necessary to work on by blaming others for their losses. In line with this, more visits to other healthcare providers (i.e., *social worker, occupational therapist, dietician, homoeopath, acupuncturist, occupational physician*) are observed alongside higher levels of perceived injustice and pain catastrophizing. This pattern may indicate "medical shopping" behavior, where individuals seek help while catastrophizing and feeling victimized. Consequently, this behavior increases the frequency of visits to other primary healthcare providers.

Finally, in terms of pain vigilance and awareness, positive associations were also found with visits to a psychologist and secondary healthcare providers. In individuals with chronic pain, the perceived pain intensity is associated with attention to pain [48]. Someone vigilant to pain tends to attentionally prioritize pain and pain-related cues which is associated with emotional aspects of pain [48]. This attention to pain can be linked to the need to take action, and to fear and anxiety [7], being present in BCS [95]. The heightened focus on pain may lead to seek additional medical attention, including secondary healthcare, to address their pain and its emotional impact [96]. For instance, patients may seek help from a psychologist who can help by providing support, guidance, and interventions to manage their pain and related emotions [97].

Overall, the Belgian healthcare system is well organized and regulated by the federal government through the Federal Public Service Social Security, the National Institute for Sickness and Disability Insurance (INAMI), and the Dutch-, French-, and German-speaking communities' Ministries of Health [98]. To access public healthcare, Belgian residents must register with a sickness fund of their choice. The sickness funds provide reimbursements of 50-75% of medical costs. Prescription drugs are partially reimbursed, with patients paying 20-50% of the cost. During the study period, physiotherapy and psychological care needed to be prescribed by the physician. In general, after breast cancer surgery, every patient has right to two prescriptions of 30 sessions of physiotherapy. In case of lymphedema, more physiotherapy sessions are possible for manual lymphatic drainage. The results of this study show a median of 6 physiotherapy sessions in the past 3 months for BCS with a mean of 44 months of time since diagnosis. It is thus plausible, that the BCS who visited a physiotherapist, went for lymphatic drainage in case of complaints since the period for the physiotherapy prescription after surgery was already passed. This can be confirmed since both, lymphedema and pain, are also one of the factors related to the number of visits to a physiotherapist.

Psychologist visits are also covered by up to 20 sessions by insurance in Belgium. It is not standardly advised after cancer but can be done if indicated [99]. Almost 1 out of 4 of the BCS included in this study went to a psychologist, however, the median number of visits was still 0. It is thus clear that visiting a psychologist is not standard care during the survival stage. This is not surprising seeing the psychological characteristics in this population being overall relatively low compared to the cut-off levels of the questionnaires to indicate clinically relevant levels of the psychological outcome (see description in results of descriptives). Although the relatively low levels of the psychological outcomes do not mean they are not relevant. The results of this study still show important relationships between the selected psychological outcomes and healthcare use outcomes, as well as clinically high levels of pain (BPI=4.49±1.75) with a high number of symptoms of sensitization (CSI=46.39±15.14), asking for a biopsychosocial approach in BCS with pain [10].

4.2. Implications

The estimates from our study results help the clinic to inform medical decision-making, the guidance of future treatment strategies, and especially enhances the understanding of relationships between the variables for clinical context. Important to note is that the results of this study only provide a preliminary insight into understanding the underlying mechanisms, and future research is needed to investigate whether focusing on psychological factors in BCS with pain could potentially decrease HCU to decrease the related healthcare costs. Therefore, large randomized controlled trials focusing on HCU are needed to make conclusions about the causal interaction between HCU and psychological factors in BCS with pain. The preliminary results of this study can be the starting point for the development of innovative therapy approaches targeting psychological factors related to excessive HCU or management policies for BCS with pain. Up to now, the management of pain complaints in BCS is rather biological in nature instead of biopsychosocially oriented. The results of this study may trigger future research into causal mechanisms and potentially the development of interventions addressing modifiable factors related to HCU (e.g., psychological factors) in an attempt to maintain HCU at an optimal level. The management of BCS with pain is complicated due to the complexity of the mixed underlying pain disorders. Moreover, exploring these associations in other geographical areas with different healthcare systems than Belgium is needed, knowing that every country has its healthcare system influencing the way people use healthcare resources.

4.3. Strengths and limitations

This study is the first to explore associations between HCU and psychological factors in BCS with pain. Moreover, this is the first study to explore the association of perceived injustice with HCU in a pain population in general. The validity of the results is supported by the use of well-established analyses and outcome measures. However, when interpreting the study's findings, some limitations should be considered. The sample comprised a baseline sample of a large multicenter randomized controlled trial (n=122), implying that the present research comprises a secondary analysis of the respective data. Therefore, the results should be interpreted with caution. Furthermore, the study was conducted in Belgium (research centres in Flanders and Brussels), which may limit the possibility of extrapolating the results to healthcare systems outside of Belgium. However, the current analyses are informative for future research questions on this matter. Due to the cross-sectional design, no causal interactions between psychological factors and HCU could be assumed as both are simultaneously assessed at baseline [100, 101]. For example, it is not clear if visiting a healthcare provider or using any type of medication is a consequence of the psychological factor or is it the healthcare use outcome that results in the decrease/increase of the psychological factor? Moreover, HCU carries many aspects, which, in fact, should all have been tested and calculated separately, but there is still too little known in the literature to properly subdivide HCU into different types of (pain) populations.

5. CONCLUSION

The results give a better understanding of factors associated with healthcare-seeking behavior and medication use in BCS with pain highlighting the attention of a biopsychosocial point of view of pain in BCS. Psychological distress was found to be the most important psychological factor related to most of the included HCU outcomes. Pain catastrophizing and perceived injustice were the most important factors in the relationship with healthcare visiting behaviour. However, the direction of the associations was not always as hypothesized in advance. Therefore, further research on the causal relationship between HCU and psychological factors within this population is needed.

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6.2. Competing Interests

The authors have no relevant financial or non-financial interests to disclose.

6.3. Author contributions

All authors contributed to a significant part of the study. All authors read and approved the final manuscript.

- *Conceptualization: Eva Roose and Eva Huysmans*
- *Material preparation: Astrid Lahousse*
- *Data collection: Astrid Lahousse*
- *Recruitment: Astrid Lahousse, Marian Vanhoeij, Christel Fontaine, Eva Roose*
- *Methodology: Eva Roose, Eva Huysmans, Wilfried Cools, Laurence Leysen, David Beckwée, Astrid Lahousse*
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- *Funding acquisition: Jo Nijs and Laurence Leysen*
- *Supervision: Eva Huysmans and Astrid Lahousse*

6.4. Data Availability

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

6.5. Ethical approval

"This study was performed in line with the principles of the Declaration of Helsinki. An agreement was obtained by the Ethics Committee of all participating hospitals, with the University Hospital Brussels as the Main Ethics Committee (B.U.N. 1432020000068).

6.6. Consent to participate

Written informed consent was obtained from all individual participants included in the study.

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8. FIGURE LEGEND

Figure 1: Flowchart