#### **REVIEW ARTICLE**



# Breast cancer and chronic pain: a mixed methods review

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#### **Abstract**

**Background** More patients are surviving breast cancer; however, many complain of persistent pain, which significantly impacts on their lives. Studies have predominantly examined risk factors alone. This mixed methods study will systematically compare prospective and retrospective studies of chronic pain following breast cancer treatment. A wider scope than risk factors alone is included in a narrative review element.

Results Common risk factors and themes were identified, and these were compared with some of the retrospective literature available. Several common themes arose in the literature such as common patient demographics, perioperative and postoperative management, treatment modalities and psychological factors. The variation in disease severity, treatment mode and symptom progression between participants in the studies made it difficult to draw conclusions from both the prospective and retrospective literature.

**Conclusion** Chronic pain is common after breast cancer. The literature has focused predominantly on risk factors for the development of chronic pain. It may be more beneficial to focus on chronic pain mechanisms and to consider the patient's narrative and experience of their illness and how this has impacted on the perception and intensity of persistent pain. A shared understanding between the patient and professional is likely to have more beneficial outcomes.

**Keywords** Breast cancer pain · Narrative medicine · Persistent · Review · Therapeutic relationship

# Introduction

Breast cancer is the most prevalent cancer affecting women [1]. In 2011 alone, it was estimated that over 500,000 women died of this illness worldwide (WHO); however, with increased efficacy of treatment, there are more survivors of this disease than ever before [1]. Those who do survive can often be left with a lasting legacy of chronic pain, which has a significant impact on their quality of life [2, 3]. Studies attempt to identify the risk factors leading to the development of posttreatment chronic pain [2, 4–6]. They discuss how persistent pain is neuropathic in nature and list several variables

which appear to be linked to it [1, 7, 8]. Persistent pain is not always neuropathic in nature, and this is perhaps a label applied in the absence of an effective explanation for the symptoms or effective treatments [2, 9, 10].

Published reviews predominantly focus on retrospective studies which ask breast cancer survivors up to 10 years postoperatively to fill out questionnaires regarding their chronic
pain [10, 11]. These studies attempt to make links between the
patient's chronic pain and variables which may have had an
influence on their outcomes, such as age and obesity [10].
Using retrospective studies in reviews is problematic as they
are relying on patient's memory and there is no objective
measurement of pain status or other patient characteristics
prior to the treatment period. As the pretreatment circumstances are not measured at the outset, only a tenuous link
can be made between patient characteristics, intervention
and persistent pain.

Review articles in this field also do not take account of other research agendas such as the patient's sense of injustice, impact on family members and experience of interaction with healthcare professionals [12]. Chronic pain following breast cancer should not be viewed purely in terms of fixed risk



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factors but in combination with the patient's narrative [13, 14]. The patients' narrative is key to understanding their experience of chronic pain [14–17].

This mixed methods study will systematically compare prospective and retrospective studies of chronic pain following breast cancer treatment. A wider scope than risk factors alone is included in a narrative review element. It aims to identify ways of understanding chronic pain and its treatment that have not yet been explored in this setting such as narrative medicine and accomplishing positive patient-physician relationships.

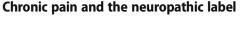
# **Methods**

To compare retrospective and prospective studies, the search engines AHMED (EBSCO Host), PubMed, Science Direct and Google Scholar were searched in January 2016 for English language references; search dates were not limited. Search terms were "breast cancer" and "chronic pain" and "post-surgery" and "post chemotherapy" and "post radiotherapy"; other search terms used were "post-surgery chronic pain breast cancer" and "post chemotherapy chronic pain breast cancer" and "post radiotherapy chronic pain breast cancer" and "breast cancer treatment chronic pain". English language articles, prospective and retrospective, observational, randomised controlled trials and review articles were included.

The authors also emailed other authors whose research was not available and requested their articles. The authors also studied suggested reading lists from Science direct and articles related to the topic suggested by Google Scholar. The combined searches yielded 376 results, filtering for prospective studies produced 79 results. These were carefully examined, and 61 papers were excluded for reasons such as language, incorrect prospective design description, focus on preoperative chronic pain rather than postoperative pain, mixed cohort, e.g. breast cancer and knee arthroplasty and having little relationship with the research question. Eighteen articles remained.

# **Results**

Table 1 gives a synopsis of the prospective studies reviewed. Studies ranged from 17 to 860 participants and together demonstrated an average chronic pain prevalence rate of 32%. Risk factors identified for the development of chronic pain were similar to those found in retrospective studies. These are categorised into headings and outlined in further detail below. The following section compares the common risk categories identified in the prospective and retrospective literature and then outlines patient outcomes described in the literature.



It is widely accepted in the literature that chronic posttreatment pain is neuropathic in nature and defined as pain lasting beyond 3 months of the treatment and differing from the original preoperative pain. The intercostobrachial nerve (ICBN) has been implicated in this outcome as it is frequently damaged during breast surgery [18]. Overall, prospective studies agree with this categorisation reporting that surgery causes injury to sensory afferents, nerve entrapment, axillary haematoma or traumatic neuroma at the affected site [19]. A recent prospective study which assessed patients preoperatively and at several intervals postoperatively found that preservation of the ICBN was actually a risk factor for chronic postsurgical pain [20]. The authors hypothesised that though the nerve might be macroscopically preserved, microlesions may cause spontaneous activity [20].

While retrospective and review studies described the sensations of tingling, electric shock, numbness, tenderness, aching, shooting, tiring-exhausting, stinging, burning and nagging, qualitative prospective literature more effectively illustrated survivor's experience of chronic pain, describing sensations of the scar feeling tight, and having changed sensations around the scar [21, 22]. A pitfall of many prospective studies included in this review, e.g. Meretoja [23], is that they did not perform a detailed clinical investigation to diagnose the type of persistent pain; overall, there was a tendency to accept that persistent posttreatment pain was neuropathic in nature without investigating other causes. Some did identify that patients had musculoskeletal problems pretreatment or shortly afterwards and that the use of aromatase inhibitors exacerbated musculoskeletal symptoms [9, 24]. One prospective study, which focused on the prevalence of musculoskeletal pain, demonstrated that 20% of women reported joint aches and pains and muscle stiffness after the primary cancer surgery but prior to adjuvant therapy [9]. Another study identified that patients with chronic pretreatment pain such as neck or back pain had an increased likelihood of reporting chronic pain due to treatment [2]. One explanation for this may be neurological; central sensitisation and cortical reorganisation occur from long-term exposure to nociceptive input [21].

Perhaps researchers are likely to accept that chronic pain is neuropathic in nature as it is assumed that nociceptive pain due to injury to muscles and ligaments will heal in the same timeframe as the surrounding damaged tissues, whereas neuropathic pain is thought to persist indefinitely [10].

### **Psychological factors**

Prospective studies have mixed results, and therefore, a link cannot be made between psychological predisposition and development of chronic posttreatment pain. There is evidence that patients with higher pretreatment trait anxiety, sleep



 Table 1
 Prevalence of chronic pain post breast cancer treatment

Author	Study	Year	Number	Elapsed time	Prevalence	Risk factors identified
Andersen et al.	Prospective cohort	2015	537	1 year	14%	Age < 65, breast conserving and ICBN conserving surgery, preoperative and postoperative pain, higher preoperative diastolic blood pressure
Pereira et al.	Prospective cohort	2015	503	1 year	30.8%	Adjuvant RT, CT and postoperative pain control
Sherman et al.	Prospective	2015	106	3 months	Not given	Mental health—focusing on health-related threats and tendency to report somatic symptoms
Fenlon et al.	Prospective cohort	2014	543	12 months	28%	No risk factors identified. Study looked at postoperative MSK pain prevalence only
Bruce et al.	Epidemiological prospective	2012	362	9 months	63%	Intraoperative nerve handling, mental health, younger age, ALND, severity of acute postoperative pain
Miaskowski et al.	Prospective longitudinal	2014	398	6 months	34.8%	Youth, BMI, higher pretreatment pain scores, higher number of biopsies and lymph nodes removed, neoadjuvant CT mental health, race, low income, unrelieved postoperative pain
Meretoja et al.	Prospective	2014	860	12 months	50% mild, 15% moderate to severe	Chronic preoperative pain, ALND, RT, adjuvant CT
Albi-Feldzer et al.	Prospective double blind randomised	2013	236	3 months-1 - year	33%	Postoperative analgesia does not influence on chronic pain outcome
De Oliveira et al.	Prospective observational cohort	2014	300	26 months	37%	Youth and ALND
Miaskowski et al.	Prospective longitudinal	2012	95	6 months	31.7% (11.6% severe)	Younger age, less education, non-white, lower income
Jain et al.	Prospective	2012	69	3 months	Not given	Use of dexmedetomidine (sedative/analgesic/anxiolytic) perioperatively is protective
Bokhari et al.	Prospective longitudinal	2012	17	3 months	23%	Age < 50, severity of surgery, acute postoperative pain, reduced use of analgesics
Alves Nogueira Fabro et al.	Prospective	2012	174	50 days– 8 months	52%	Age < 40, preoperative subjective sensation of lymphedema, > 15 lymph nodes removed, sentinel node biopsy
Torres Lacomba et al.	Prospective	2010	116	1–12 months	44% (at 12 months)	Post ALND myofascial pain
Poleshuck et al.	Prospective	2006	95	3 months		Young age, invasive surgery, RT, intensity of postoperative pain
Kairaluoma et al.	Prospective	2006	60	1 month −1 year	43%	Preincisional paravertebral block is protective
Millar et al.	Prospective	2005	371	Up to 1 year	4.3	Psychological distress
Legeby et al.	Prospective	2002	110	37–50 months	25%	Axillary dissection, postsurgical management

ICBN intercostobrachial nerve, RT radiotherapy, CT chemotherapy, MSK musculoskeletal, ALND axillary lymph node dissection, BMI body mass index

disturbance and depression have higher chronic pain scores then their less distressed counterparts [6]. Other evidence suggests that altered mental health status such as depression, anxiety, anguish or preoperative emotional functioning does not correlate with experience or intensity of chronic pain [25, 26]. Correspondingly, while "psychological robustness", i.e. the capacity to adopt positive coping strategies in the face of external threats, was noted to be protective against pain in the



early recovery trajectory, this was not a significant finding 9 months postoperatively [5].

Retrospective studies link psychological disposition with chronic pain more readily, noting that anxiety, depression, sleep disturbance, somatisation, catastrophising and perceived stress were all significantly associated with persistent post-mastectomy pain [2, 4]. However, retrospectively, it is impossible to decipher the patient's premorbid psychological functioning and its influence on patient's posttreatment well-being. Other evidence links higher education levels to increased post-treatment chronic pain [27]. Perhaps those who are more educated are able to identify and express their distress with greater efficacy. This study provided no evidence of the participant's pain over the timeline of their illness [27].

## **Treatment modality**

There are several treatment modalities available for breast cancer patients in terms of surgical procedures and adjuvant or neoadjuvant therapies. The decision regarding which treatment or combination of treatments to use depends on several factors revolving around the characteristics of the patient's individual illness. In addition to other risk factors, it is assumed that recovery trajectory and persistent pain are linked to the choice of therapy used (Fig. 1).

Prospective studies have noted a large increase in likelihood of chronic pain following lymph node dissection [5, 18, 23, 28–30]. There is some evidence to suggest that adjuvant therapy such as radiotherapy (RT) does not influence chronic pain prevalence, but other evidence reports a high incidence of chronic pain, chemotherapy-induced peripheral neuropathy and phantom breast syndrome [6, 31]. In addition,

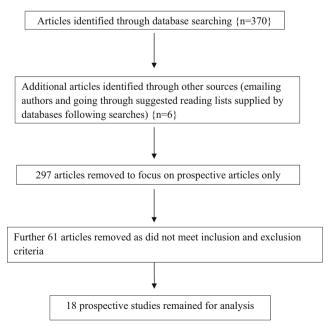


Fig. 1 Flow chart of the inclusion and the exclusion procedure



cognitive decline has been reported postchemotherapy when compared with baseline cognitive functioning [31]. The overall inconsistent findings in relation to adjuvant therapy might reflect variance in treatment practices involving estimation of dosages and administration practices resulting in variable incidence of chronic pain [28].

Retrospective study findings are extremely mixed; one investigated women who were treated up to 3 years previously and found no association between persistent postmastectomy pain (PPMP) and type of surgery performed, e.g. total mastectomy, axillary dissection or reconstruction [4]. There are several such studies which investigate patients several years postoperatively for persistent pain not accounting for the women's experiences in the interim [2, 32]. In agreement with the prospective data, several retrospective studies have found that women who were treated with axillary lymph node dissection reported significantly more pain than the women who had sentinel node biopsies alone [2]. However, those women had also received other therapies in combination with this treatment; therefore, it is impossible to conclude one treatment caused pain more than the other. Chemotherapy-induced peripheral neuropathy is reported to be a disabling side effect of antineoplastic agents [2, 33]. Radiation therapy can produce plexopathies and osteoradionecrosis and is thought to be a major predictor of development of chronic pain in breast cancer survivors [34]. Highest levels of chronic pain have been reported with combined chemotherapy, radiotherapy and axillary lymph node dissection [35]. Novel evidence has emerged that patients treated prophylactically with granulocyte colony-stimulating factor (G-CSF) while receiving chemotherapy had reduced bone pain and treatment emergent adverse events [36].

### **Patient demographics**

Several demographics appear in the prospective literature which link factors such as race, obesity, age, income and relationship status with incidence of chronic pain [6, 8, 25, 26]. Prospective evidence also suggests that survivors who are overweight or lead more sedentary lifestyles have significantly higher pain [37]. However, studies such as these while taking account of premorbid functioning are biased in that they chose factors to focus on instead of investigating in an explorative manner what factors actually appear to influence pain.

Overall, there is agreement between prospective and retrospective studies in relation to youth and persistent posttreatment pain [5, 11]. While young age was a highly significant factor in the occurrence of postmastectomy pain, the younger participant's symptoms should also be viewed in combination with their differences in marital status, employment and housing [38]. Also in younger women, the tumour is usually more aggressive and there is increased likelihood of tumour

recurrence, therefore the higher incidence of perceived pain may be related to associated distress or anxiety [2, 39]. One study found that while there was some evidence that youth and obesity correlated with increased pain scores, this was non-significant when adjusted to account for confounding factors [27]. There is less agreement among studies in relation to obesity [5, 26, 39, 40]. Some studies suggested that obesity impacts on the way in which the intercostobrachial nerve is handled during the surgical procedures, thus increasing the potential for neuropathic pain [1].

## Perioperative/postoperative pain management

In their systemic review, Andersen and Kehlet [11] found a link between acute postoperative pain and development of persistent postoperative pain; however, most of the studies included in the review were based on recalled acute pain and therefore were subject to bias. However, most studies in this area are prospective as they measure the perioperative conditions and follow-up on the patients in order to draw a link between patient's overall management and subsequent development of chronic pain. Several studies discuss a combination of analgesics and other medications and the manner in which they are delivered and how this impacts on the persistence of the patient's pain.

The effects of axillary dissection were rendered negligible when patients were given a preincisional paravertebral block perioperatively even up to 1 year postsurgery [41]. Other evidence suggests that the analgesic sparing effects of dexmedetomidine given perioperatively impacts on the occurrence of chronic pain postbreast surgery [19]. Patients who received patient-controlled analgesia (PCA) and were managed by a dedicated acute pain service reported less chronic postsurgical pain (CPSP) then patients who did not receive such a service [32]. However, the patients in this study were not randomised but received PCA if they could afford it; therefore, patient's socioeconomic status could have influenced these results rather than allocation of PCA. In addition, the authors did not consider that it may have been the dedicated and attentive treatment by the specialist team that influenced the pain scores rather than the actual modality of the analgesic. There are other well-designed studies in this area that randomised patients into PCA and nurse-administered analgesic groups, and they have demonstrated that the patients on PCA had better pain control scores but used more analgesics

Postoperatively, patients are at risk of developing adhesions, collections and fistulae; this all has the potential to cause persistent pain. Evidence suggests that those who reported the worst pain had more postoperative complications such as higher than average pain intensity scores which were not effectively treated. They were also more likely to have had a drain in the axilla or in the breast and the axilla [6].

Postoperative analgesia intake is also influenced by other factors such as premorbid chronic pain, anxiety and axillary clearance [42]. It is suggested that effective aggressive management of postoperative pain may reduce the incidence of chronic pain [25].

Blunt and Schmiedel [43] reported that women's chronic postsurgical pain occurring at 4–11 months after their procedure was resolved following aspiration or formal drainage of a hematoma in the axilla. This research highlights the importance of postoperative management in preventing long-term problems. In an unusual study involving only six patients, lymph nodes were harvested from patient's groins and transplanted into the axilla causing resolution of lymphedema and pain, allowing the patients to return to work and daily activities [7]. This small study signifies the importance of novel and alternative ideas in overcoming physical causes of persistent pain instead of dismissing it as neuropathic.

#### Pain treatment outcomes

Chronic postsurgical pain affects every aspect of life such as ability to work, general activities and relationships [28]. Research has noted that physical, emotional and cognitive functioning is influenced by chronic pain [21]. Retrospective evidence has shown that quality-of-life (QOL) scores were lower for patients who experience chronic pain, but the scores tend to improve over time [5]. Retrospective studies are limited by an absence of preoperative QOL assessment; therefore, it is difficult to conclude that there are no other precipitating factors influencing the patient's reduced QOL. Patients in prospective research who reported more pain also reported significantly poorer QOL, but this was the case before they received their medical treatment [6].

Breast cancer survivors experiencing chronic pain are treated with a variety of drugs and non-drug options. The most common drugs are non-steroidal anti-inflammatories and acetylsalicyclic acid, gabapentenoids and antidepressants [34]. All these drugs have side effects on systems including gastrointestinal and cardiovascular, causing problems such as dizziness, somnolence, peripheral oedema and nausea. Opioids are not firstline and have many side effects and a high risk of dependency [3]. Non-drug alternatives include physiotherapy, exercise, transcutaneous electrical nerve stimulation, acupuncture and cognitive behavioural therapy [34]. In one study, 42% of patients living with chronic pain were taking no analgesics at all [21]. A multidisciplinary approach is recommended in treatment of chronic pain with the goal being pain relief and improved function [3].

Several common themes arose in the literature such as common patient demographics, perioperative and postoperative management, treatment modalities and psychological factors. The variation in disease severity, treatment mode and symptom progression between participants in the studies



made it difficult to draw conclusions from both the prospective and retrospective literature.

A deeper understanding of the nature of chronic postsurgical pain is gained when assessed qualitatively. Instead of seeing the chronic pain in terms of risk factors like age or obesity or treatment type, chronic pain was explored in relation to patient's narrative and experience [21]. However, these qualitative studies are rare. The quantitative evidence regardless of design attempts to categorise patients according to risk factors associated with chronic pain without paying enough attention to individual patient characteristics and the different combinations of treatment modalities.

Most of the research in the literature—both prospective and retrospective—did not emphasise the subjective nature of pain. It used questionnaires to categorise pain severity. There is some research emerging which attempts to objectively measure pain, e.g. categorising sensitivity of pain using hot and cold mediums [20, 42]. Research using objective measurements is scarce, but it is a useful direction for future research.

One of the areas focused on in this review was patient's psychological predisposition to developing chronic pain. Both prospective and retrospective studies attempted to identify a type of premorbid mental state such as depression or anxiety, which might render the individual at risk of developing posttreatment chronic pain. However, in doing so, valuable information was not focused on and therefore lost. The authors suggest that psychological status of the individual changes throughout the course of the diagnosis and treatment and does not remain in static categories such as "depressed" or "anxious". Qualitative studies alluded to this when they described the patient's experiences such as mourning their lost breast and loss of social networks causing isolation [13, 22]. This mourning is likely to be transient, but if a quantitative investigator were to analyse this patient at this point, they would surely categorise her as depressed and attempt to link this category to chronic pain. At the very least, it draws negative connotations between chronic pain and the type of patient who experiences this outcome and further diminishes the responsibility of the treating professional to alleviate the pain. Patients are most frustrated with the invisibility of the pain which limits physicians in their recognition, diagnosis and pain management. Without a physical explanation, patients become frustrated at being unfairly branded as having a psychological condition causing shame and guilt, a loss of sense of self and social identity [15]. Postsurgical distress can also influence adjustment up to 1 year after treatment. This can result in patient's becoming more prone to somatic awareness and fearful monitoring of disease reoccurrence. They experience greater pain compared to well-adjusted patients with a similar clinical outcome [10, 16, 17]. The resulting anxiety, fear and helplessness can be ameliorated and compliance with analgesic regimes accomplished if there is good communication between the patients and the treating professionals [17].



Other research agendas not covered in breast cancer chronic pain literature are linked to this suggestion that the patient's experience can influence distress levels and therefore perception of pain intensity [44]. One study investigated chronic musculoskeletal pain in 173 patients and noted that perceived injustice was significantly correlated with pain intensity, depressive symptoms and self-reported disability [45]. The patients reported high levels of anger which increased their sense of injustice and influenced depression and pain intensity levels, causing isolation and loss of positive reinforcement from interpersonal interactions, further exacerbating symptoms. As well as a psychological impact of the perceived injustice resulting from chronic pain, there may also be a neurological impact; anger and depression cause serotonergic and dopaminergic dysfunction and in turn reduced orbitofrontal functioning [45].

Empathy also has a role in professional management of chronic pain. Empathy is lost when there is a conflict between physician and patient over the origin of pain—physical versus psychosomatic, and the power struggle between the dyad which ensues. Lack of empathy towards the patient leads to mistrust and anger causing increased damage to the therapeutic relationship. Chronic pain patients who disagree with their physician on the burden of their disabilities tend to report a greater intensity of chronic pain [14]. Linked to patient empathy and understanding, the professional must also consider the impact of chronic pain on the patient's spousal relationship. This area also requires further investigation, and how this in turn worsens the perception of the pain. Evidence suggests that couples experience greater relationship disruption on days when patients have greater pain levels and lower mood [46].

Acceptance-based interventions may drive the patient towards achieving valued life goals instead of control and avoidance of pain and anger [45]. Cognitive behavioural therapy has also been shown to increase self-awareness and help patients adopt a more optimistic view, while acknowledging that chronic pain has diminished their capacity to realise their goals [13].

Narrative medicine considers the patient's story as integral to their experience of ill health and essential for healing [47]. Through communication, listening and understanding, the physician makes a subjective interpretation of the patient's situation and applies scientific knowledge to that individual case. The importance of teaching medical professionals about relationship techniques and developing a culture that emphasises the patient-doctor relationship is becoming increasingly recognised [36]. Much of the telling of the self is critical, formative and transformative [16]. The doctor-patient relationship seems fundamental to a positive outcome, the physician's most important therapeutic tool that goes beyond any



cure [48]. This way, scientific principles are not applied to each patient on a one size fits all basis, but instead, through dialogue, clinical decisions are made an understanding of the individual and working on the patient's behalf [48]. It diminishes the power differential between doctor and patient outlined elsewhere in the literature [49]. Narrative medicine has been shown to decrease pain intensity and improve sense of well-being in cancer patients [50]. Patients sharing their narratives among other breast cancer patient's results in empowerment, reduced social isolation and increased support network [51].

There is also a well-publicised role for the multidisciplinary team, for example, breast cancer nurse specialists have been shown to reduce anxiety, depression and nurture the patient's capacity to cope by providing counselling, advice and emotional support [52]. Psycho-oncology addresses the psychological, social and behavioural aspects that influence the patient's cancer experience. Australia prides itself on leading psychosocial care for oncology patients and has invested heavily in this area. There is a culture of collaboration among cancer specialists and psycho-oncologists, who come together to share ideas, research and case studies. Collaborations such as this can only lead to a deeper understanding of the holistic issues affecting breast cancer patients and address ways to manage issues such as posttreatment chronic pain in a way that is therapeutic and dignifying for the patients [53]. In comparison, a 2016 study on breast cancer service provision in 32 countries in Europe found that while the states recognised the need for psycho-oncology services in the national cancer plans, few provided detailed strategies on how to obtain such services and even less provided guidelines on allocation of resources and personnel to guide these services [54].

# **Conclusion**

Prospective studies of chronic pain in breast cancer patients allow more convincing conclusions as they illustrate the patient's trajectory from diagnosis to posttreatment well-being. However, much information is lost if prospective studies use a quantitative approach alone as the focus on why it occurs is prescriptive and too narrow. It is imperative when looking at chronic pain that patients are investigated on a case-by-case basis. This is unlikely to be achieved through quantitative analysis of large cohorts as the demographics, disease severity and treatment types are too varied among patients. An alternative focus may be achieved through focusing on narrative and relationship-based medicine and involving other specialities such as psycho-oncology and breast nurse specialists. This is likely to help researchers in establishing a true understanding of the development of chronic pain and also equip the physician with tools to help the patient accept and manage their chronic pain in a way that is cathartic for them.

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## Compliance with ethical standards

**Conflict of interest** The authors declare that they have no conflict of interest.

Research involving human participants and/or animals Not applicable.

**Informed consent** Not applicable.

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