Palliative and Supportive Care

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Palliative care in the treatment of women with breast cancer: A scoping review

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Review Article

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Abstract

Objectives. Recent studies on the quality of life in women with breast cancer show a high prevalence of signs and symptoms that should be the focus of palliative care (PC), leading us to question the current role they play in addressing breast cancer. Therefore, the objective of this review is to map the scope of available literature on the role of PC in the treatment of women with breast cancer.

Methods. This is a methodologically guided scoping review by the Joanna Briggs Institute and adapted to the PRISMA Extension for Scoping Reviews (PRISMA-ScR) Checklist for report writing. Systematic searches were conducted in 8 databases, an electronic repository, and gray literature. The searches were conducted with the support of a librarian. The study selection was managed through the RAYYAN software in a blind and independent manner by 2 reviewers. The extracted data were analyzed using the qualitative thematic analysis technique and discussed through textual categories.

Results. A total of 9,812 studies were identified, of which only 136 articles and 3 sources of gray literature are included in this review. In terms of general characteristics, the majority were published in the USA (35.7%), had a cross-sectional design (44.8%), and were abstracts presented at scientific events (19.6%). The majority of interventions focused on palliative radiotherapy (13.6%). Thematic analysis identified 14 themes and 12 subthemes.

Significance of results. Our findings offer a comprehensive view of the evidence on PC in the treatment of breast cancer. Although a methodological quality assessment was not conducted, these results could guide professionals interested in the topic to position themselves in the current context. Additionally, a quick synthesis of recommendations on different palliative therapies is provided, which should be critically observed. Finally, multiple knowledge gaps are highlighted, which could be used for the development of future studies in this field.

Introduction

Palliative care (PC) aims to improve the quality of life of patients and their families when they are facing life-threatening situations; therefore, they are essential to improve their well-being and comfort (World Health Organization and Pan American Health Organization 2016). However, despite its described relevance, the World Health Organization (WHO) (World Health Organization 2020b) and the Worldwide Palliative Care Alliance estimate that only 14% of people who need PC receive it, leaving annually more than 40 million people with unmet need for PC, of whom 78% live in low- and middle-income countries (LMICs; Organización Mundial de la Salud [World Health Organization] 2020b; Worldwide Hospice Palliative Care Alliance 2021; Worldwide Hospice Palliative Care Alliance and World Health Organization 2020).

Along with this unfavorable statistic, it is also important to rate the advances that the area has had; for instance, it is increasingly possible to talk about PC in a health context far from the stereotype of death, in addition to its inclusion in university curricular programs (DeCoste-Lopez et al. 2015; Ibrahim et al. 2022). All these advances, although slow, acquire relevance in the current scenario of chronicity that we find ourselves in, where diseases such as hypertension, diabetes, or cancer are increasingly prevalent, making PC necessary in their therapeutic approach (Instituto Nacional de Câncer 2018; Lopes-Júnior et al. 2020, 2021).

In relation to cancer, world statistics are alarming, ranking in 2020 as one of the main causes of mortality worldwide with close to 10 million deaths, and in that same year, among the most common cancers, breast cancer ranked first place with 2.26 million cases (International Agency for Research on Cancer and World Health Organization 2022). From the biopsychosocial point

of view, breast cancer diagnosis negatively impacts women' lives, in whom the appearance of feelings of fear and suffering is common throughout the entire disease process (Abrahão et al. 2019; Lopes et al. 2018).

Despite the fact that breast cancer is one of the most treatable cancers when detected early, different treatment modalities can trigger undesirable side effects that compromise the quality of life of patients and their families (Organización Mundial de la Salud [World Health Organization] 2020b; Worldwide Hospice Palliative Care Alliance 2021; Worldwide Hospice Palliative Care Alliance and World Health Organization 2020), scenario in which PC become relevant, helping to alleviate symptoms and managing the disease, thus achieving a balance between progression and discomfort caused by treatment for curative purposes (Drageset et al. 2021).

In the update of the clinical guidelines for PC integration in standard cancer care produced in 2017 by the American Society of Clinical Oncology (Ferrell et al. 2017) and other studies (Kokkonen et al. 2019), the inclusion of patients with cancer is recommended – whether hospitalized or outpatient – to specific PC programs from the beginning of the course of advanced disease (stage IV). However, recent studies address the importance of including early PC in standard oncological practice along with curative treatment, within 8 weeks (Bouleuc et al. 2019; Gärtner et al. 2019; Smith et al. 2018; Zimmermann and Mathews 2022). As a result of these divergences found, the recommendations are not always followed, causing referral to PC services to generally occur in the last few weeks (Zimmermann and Mathews 2022), leading to untreated symptoms, patient distress, and unnecessary aggressive end-of-life (EoL) treatments (Jordan et al. 2020).

In breast cancer, the scenario of PC is similar, where despite the strong degree of recommendation to include PC from the beginning of treatment, with recent studies that assess quality of life in women with breast cancer including advanced stages (Guerra et al. 2020; Haddou Rahou et al. 2016; Lima and Silva 2020; Lopes et al. 2018; Mokhatri-Hesari and Montazeri 2020; Salibasic and Delibegovic 2018; Villar et al. 2017). The existence of a high prevalence of symptoms, such as pain, anxiety, fear, depression, fatigue, insomnia, dyspnea, sexual dysfunction, etc., that should be treated interdisciplinary in PC services is striking. These disagreements lead us to question the current role that PC plays in breast cancer treatment, the way in which it is being addressed in this population, and the impact it has on the lives of these women.

Under this questioning, a quick search was carried out in the main databases with the objective of identifying similar review studies on the subject, not being possible to find any study with the same objective. However, 2 systematic reviews (Drageset et al. 2021; Oostendorp et al. 2011) were found close to the topic addressed, although with differences in terms of scope. One study reviewed the quality of life of women living with metastatic breast cancer (MBC) receiving PC (Drageset et al. 2021), while the other assessed the current knowledge on the efficacy and safety of palliative single-agent chemotherapy drugs used in daily clinical practice (Oostendorp et al. 2011).

In this regard, since there is no broad scoping review on this subject, this study becomes relevant, in addition to being aligned with Sustainable Development Goal 3, which is premised on guaranteeing a healthy life and promoting well-being for all in all ages (World Health Organization 2020a). It is important to mention that this review is part of a master's thesis (Velasco Yanez 2023) and represents the initial phase of a protocol that encompasses the scoping review and a stakeholder consultation exercise (Velasco Yanez et al. 2023).

Objective

To map the scope of available literature on PC role in the treatment of women with breast cancer.

Methodology

Design and protocol

This is a scoping review conducted according to the methodological recommendations proposed by Joanna Briggs Institute (JBI) (Peters et al. 2020) and adapted to the PRISMA Extension for Scoping Reviews (PRISMA-ScR) guideline for reporting scoping reviews (Tricco et al. 2018) (Appendix A). The review protocol was registered on the Open Science Framework platform under registry osf.io/yqubp.

Literature review question

To construct the review question, the Population, Concept, Context (PCC) strategy proposed by JBI (Peters et al. 2020) was used (P – young women, adults and older adults; C – PC; and C – breast cancer), giving rise to the question: What is the scope of available literature on PC in the treatment of women with breast cancer?

Inclusion criteria

All studies without restriction of methodological design, date, and language of publication that addressed the variables of acronym PCC were included (Fig. 1). To review studies in languages other than English, Spanish, and Portuguese, digital translators and speakers of the language in question were consulted.

Type of participants

All studies that included women from a young age according to the age classification proposed by the WHO were included. The WHO considers the young age, from 25 to 44; the middle age, from 44 to 60; the advanced age, from 60 to 75; the senile age, from 75 to 90; and longevity, after 90 years (Dyussenbayev 2017). This distinction was made because the highest incidence of breast cancer occurs in women $\geq$40 years of age (Coughlin 2019).

Concept

Studies that presented interventions, treatments/therapies, reflections, or comments aligned with the definition of PC described by the WHO (Organización Mundial de la Salud [World Health Organization] 2020b) were included. PC is an approach that improves the quality of life of patients (adults and children) and their relatives when they face problems inherent to a life-threatening disease. They prevent and alleviate suffering through early identification, assessment, and correct treatment of pain and other problems, be they physical, psychosocial, or spiritual.

Context

To include research that presents recommendations on PC either in the advanced stage (Ferrell et al. 2017; Kokkonen et al. 2019) or

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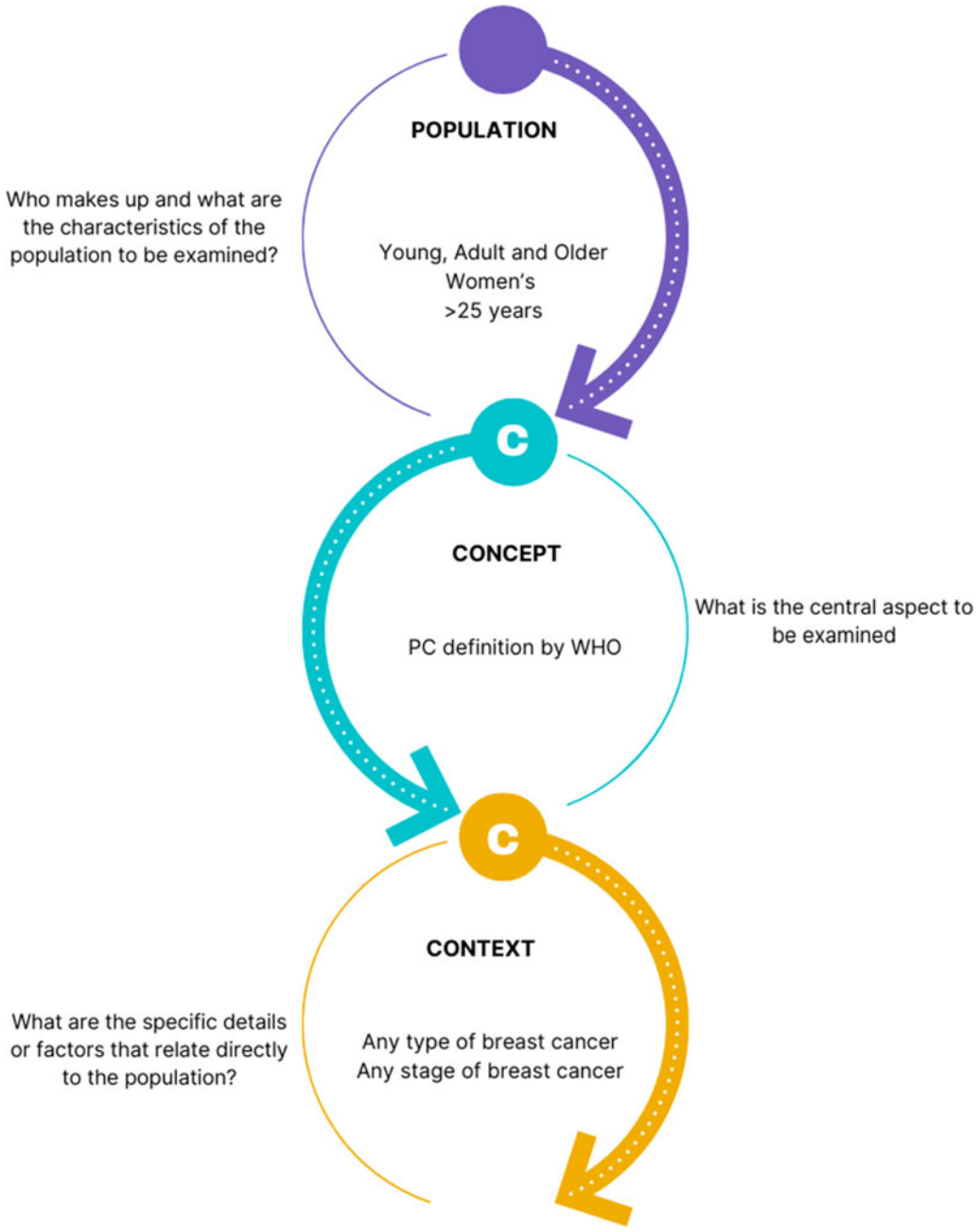

Figure 1. Inclusion criteria – PCC strategy.

from diagnosis (Bouleuc et al. 2019; Gärtner et al. 2019; Smith et al. 2018; Zimmermann and Mathews 2022), all studies treating breast cancer were included, without restriction of cancer type, molecular classification, or stage.

Exclusion criteria

Studies in which participants had breast cancer diagnosed with other types of cancer or other pathologies and are receiving concomitant PC for them as well as studies presenting palliative interventions specific to the breast cancer metastatic site and studies conducted in survivors were excluded. Studies on PC and breast cancer developed in the COVID-19 pandemic context were not included, since there is a scoping review carried out in this context (Velasco Yanez et al. 2022).

Search strategy

The literature search was carried out systematically in 8 electronic databases: MEDLINE (Via PubMed); Embase (Excerpta Medica dataBASE); Cochrane Library; Web of Science; Scopus; Epistemonikos; CINAHL (Cumulative Index to Nursing and Allied Health Literature); LILACS (Latin American and Caribbean Literature in Health Sciences); and the electronic repository SciELO (Scientific Electronic Library Online). For this, a search limited to the main descriptors of acronym PCC was initially

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carried out in 2 databases (MEDLINE/PubMed and LILACS) with the objective of analyzing the words contained in the title and abstract of articles retrieved as well as the terms indexing used to describe articles. Then, search commands were created with the words retrieved together with the descriptors of central issues (PCC) obtained from controlled vocabularies (MeSH, DeCS, Emtree, and CINAHL indices), including their synonyms and keywords according to their relevance. These terms were combined using the Boolean operators "AND" and "OR." An individual search strategy was designed for each database (Appendix B). Descriptors, synonyms, and keywords were limited to the languages of Spanish, English, Portuguese, and French. Regarding differences from the published protocol (Velasco Yanez et al. 2023), it was decided not to include the JBI Evidence Synthesis database as all retrieved articles were indexed in Medline/PubMed.

Due to the flexibility of including gray literature in scoping reviews (Peters et al. 2020) and the importance of mapping all available literature on the subject, searches were also conducted in other secondary sources, such as The British Library, Google Scholar, Preprints for Health Sciences [medRXiv], Open Grey, ProQuest Global Dissertations and Theses, and ClinicalTrials.gov. Moreover, the reference lists of included primary studies, from which no relevant studies were found, were also manually reviewed.

Final search commands were reviewed and approved by a librarian. For the articles that did not have free access, the strategy of requesting the study directly from the author or buying it was proposed. The searches were carried out on August 23, 2022.

Source of information selection

For proper management and selection of retrieved studies, the Rayyan Systems Inc (RAYYAN) (Ouzzani et al. 2016) software was used, detailed in the following steps: Initially, all articles from the general search were deposited in RAYYAN, and duplicate articles were later removed. Before beginning the reading process, the selection agreement percentage between the 2 reviewers was assessed, and for this, a random sample of 25 articles was chosen to be analyzed, obtaining an agreement percentage of 84%, adapting to the JBI recommendations (Peters et al. 2020).

After this phase, all articles were analyzed in title and abstract by 2 independent researchers with the aim of identifying potentially eligible articles and any uncertainty regarding the inclusion of a study was resolved by another reviewer. Subsequently, the same reviewers independently reviewed the full manuscripts that passed the first selection stage, and any decision conflicts were resolved by a third reviewer, thus finally obtaining a list of studies that were included in the review. The selection process flow is presented through the PRISMA 2020 flowchart (Page et al. 2021) (Fig. 2).

Data collection

Data were collected using a form designed by the main author, adapted to the JBI data extraction template (Appendix C), in addition to forms from other previously published review studies (Velasco Yanez et al. 2022). To verify that the form extracts all the

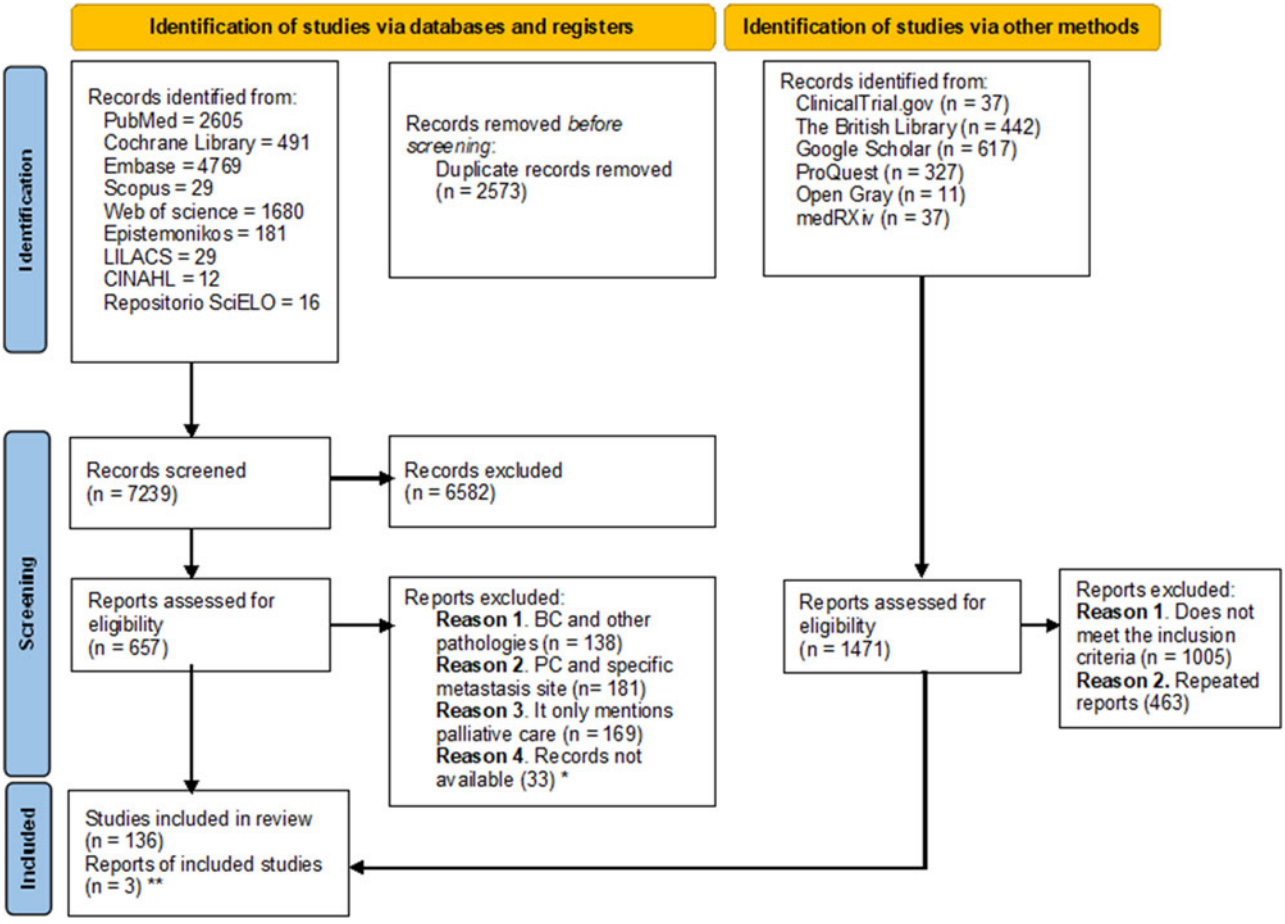

Figure 2. PRISMA flowchart. Search process and selection of literature included in the review (Page et al. 2021).

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relevant results, a pilot test was carried out (Peters et al. 2020) in which 2 reviewers individually extracted the proposed data from 2 articles already included, verifying the relevance of the form. It was finally assessed and accepted by a third reviewer.

The information was extracted by 2 reviewers and included (a) study identification and objectives; (b) study population and baseline characteristics; (c) study design; (d) sample size; (e) type of PC; and (f) main key points.

Data analysis and presentation

For the analysis of information extracted from the articles, the qualitative thematic analysis technique proposed by Braun and Clarke (2014; Horntvedt et al. 2018) was used, with the 6 phases as follows: In phase 1 (Data Familiarization), the author became familiar with extracted data, then interesting features of studies were coded and collated into potential themes in phase 2 and 3 (Initial Code Generation and Theme Search); subsequently, in phase 4 (Theme Review), the recoding and discovery of new themes were carried out, and in phase 5 (Theme Definition and Naming), the themes were definitively identified, establishing the essentials and elaborating the subthemes, to finally, in phase 6 (Final Report Writing), build the narrative based on data understanding.

Descriptive statistics (frequencies and percentages) were also used to summarize the relevant quantitative characteristics of the set of studies. The main results were grouped according to their baseline characteristics and presented through tables and graphic models. The similarity analysis referenced in the review protocol (Velasco Yanez et al. 2023) was not included due to the significant heterogeneity of the results.

Results

The final search identified 9,812 studies, of which 2,573 were detected and removed as duplicates. In the first phase, the remaining 7,239 articles were analyzed by title and abstract, excluding 6,582 studies because they did not meet the inclusion criteria. Subsequently, the remaining 657 articles were reviewed in full text, with 521 studies being excluded, thus obtaining a sample of 136 articles that were included in the review. From the gray literature search, 1,471 documents were identified on different websites, of which only 3 articles (Google Scholar) were included in the final file (Fig. 2).

Study description

The search process collected a wide scope of literature on PC in the treatment of women with breast cancer. From the general characteristics of included studies, it can be highlighted that the publications occurred in a variety of ways around the world, having a greater concentration in countries such as the USA (35.7%), the UK (7%), and India (6.3%). In Latin America, only Mexico (2%), Brazil (1.4%), and Colombia (0.7%) have published articles on the subject (Fig. 3).

Regarding the years of publication, there is great variability from 1967 to the present date, with the last 6 years (2016–2022) concentrating the largest number of published studies (53.1%). About the methodological design, the majority were cross-sectional studies (44.8%), 51.6% had a retrospective approach and 14% were prospective, followed by case reports (14.7%) and clinical trials (12.6%). Other methodologies such as cohort studies, qualitative studies, literature reviews, quasi-experiments, and opinion articles were also included, although to a lesser extent.

A total of 19.6% were abstracts presented at scientific events, and the 3 journals that published the most articles on the subject were the *Journal of Clinical Oncology* (7.6%), *Breast* (4.2%), and *Journal of Palliative Medicine* (3.5%). Regarding palliative interventions, there was a predominance of palliative radiotherapy (PRT) (13.6%) followed by palliative chemotherapy (PCT) (12.9%). The remaining characteristics are shown in Appendix C.

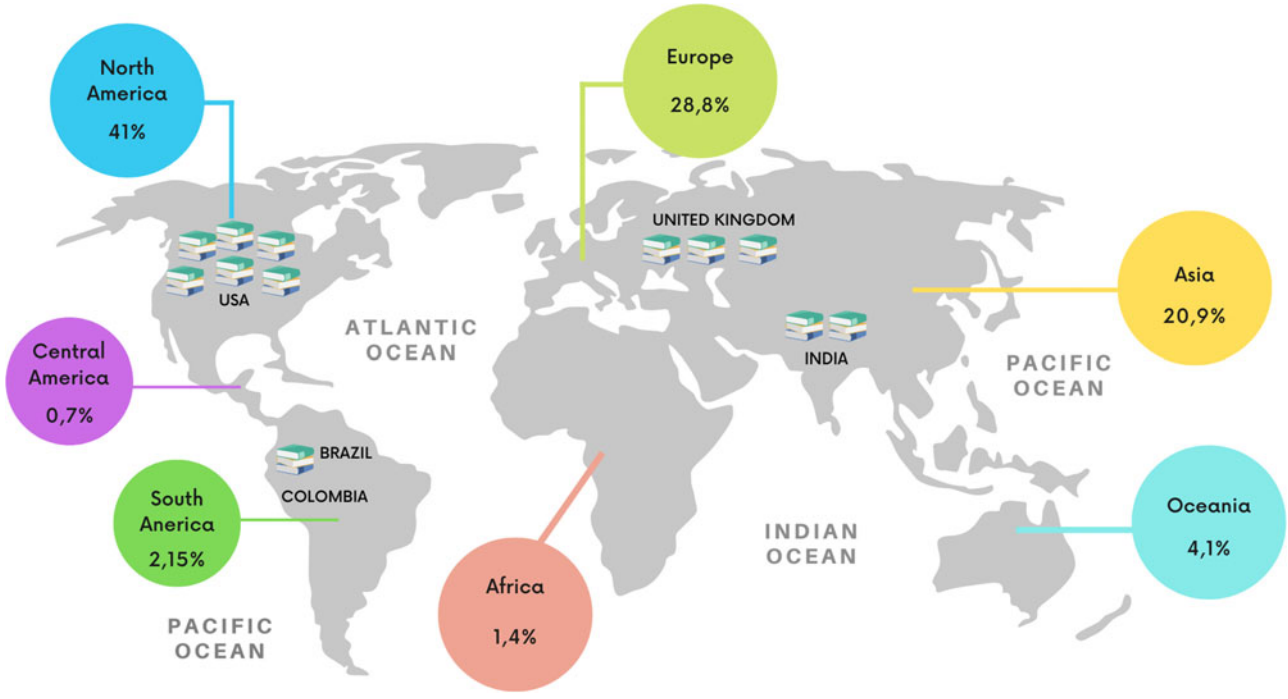

Figure 3. Distribution of continents and countries with the highest number of publications.

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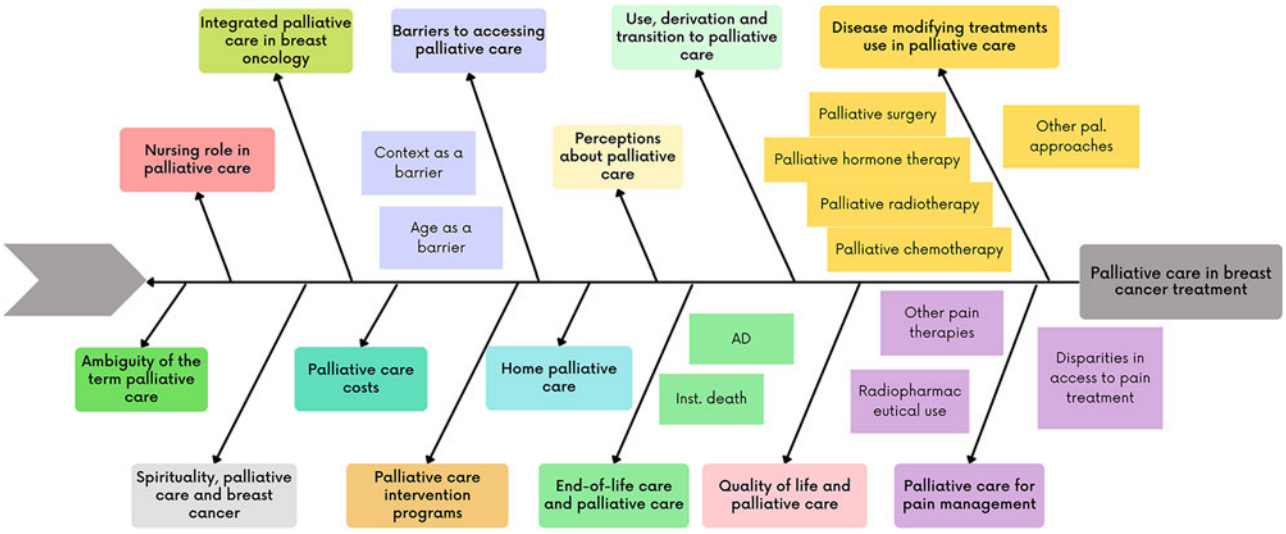

Figure 4. Thematic analysis: theme and subtheme definition.

Following the thematic analysis of the main findings, 14 broad final themes and 12 subthemes were identified that reflect the main results of this review, as detailed in Fig. 4 and described in the following sections.

Disease-modifying treatments use in PC

Based on PC in breast cancer, a study conducted in Germany (Soetekouw et al. 2007) mentions that there are palliative therapies based on systemic antitumor treatment, such as hormone therapy, chemotherapy, radiotherapy, surgery, and targeted therapy. However, in the palliative context, they are intended to manage the disease, and, for this reason, it is important to know the various types of therapy in MBC because palliative treatment is more than just symptomatic treatment.

A study conducted in the USA (Morrogh et al. 2010) on the frequency and duration of palliative procedures performed in the context of MBC concluded that palliative interventions for symptoms are safe and provide lifelong symptom management in 70% of patients. However, another study (Patel et al. 1986) highlighted that, despite the existence of increasingly sophisticated palliative therapies, aggressive palliative modalities do not significantly increase the survival time of patients with MBC.

Palliative chemotherapy. In breast cancer, PCT is an area that has been widely studied over the years, through the development of clinical trials that investigate the efficacy of different combinations of cytostatic drugs (Table 1).

For instance, from the series of studies included in this review, the first trial carried out to assess the efficacy of PCT in MBC palliation using weekly low doses of epirubicin dates back to 1989, a regimen that was well tolerated, effective, and achieved a useful palliation (Jones 1989). Similarly, in Germany (Eichbaum et al. 2007), they assessed the activity of a PCT regimen of mitomycin + folinate + 5-fluorouracil concluding that it is a well-tolerated treatment option in palliative therapy for patients with MBC. Another study conducted in Japan (Wada et al. 2007) concluded that PCT with weekly doses of paclitaxel is a treatment option in patients with MBC from the point of view of palliation.

Studies also show the existence of oral PCT regimens. As an example, a study conducted in Italy retrospectively assessed the efficacy of oral cyclophosphamide or oral cyclophosphamide + oral methotrexate for symptom management in patients with MBC, concluding that oral metronomic PCT achieved management in 54% of cases and may be used in that context (Gebbia et al. 2012).

Table 1. Palliative chemotherapy regimens used over time in included studies

Regimen	Dose	Year
Epirubicin	12 mg/m^2 IV weekly	1989
Cyclophosphamide, methotrexate and 5-fluorouracil (fungal breast cancer)	Cyclophosphamide, 75–100 mg/m^2 + methotrexate IV, 30 and 40 mg/m^2 + 5-fluorouracil 500–600 mg/m^2 IV	1995
Mitoxantrone, 5-fluorouracil, and high-dose leucovorin (NFL) vs cyclophosphamide, methotrexate, and 5-fluorouracil (fungal breast cancer)	1C received mitoxantrone 12 mg/m^2 IV + leucovorin 300 mg IV + 5-fluorouracil 350 mg/m^2 IV 2C received cyclophosphamide 600 mg/m^2 IV + methotrexate 40 mg/m^2 IV + 5-fluorouracil 600 mg/m^2 IV	2000
Vinorelbine	30 mg/m^2/week	2001
Mitomycin + folinate + 5-fluorouracil	4 weeks of mitomycin 8 mg/m^2 IV + folinic acid 500 mg IV + 5-fluorouracil 750 mg/m^2 IV	2007
Paclitaxel	60 mg/m^2, 6 times every 8 weeks	2007
Oral metronomic cyclophosphamide with and without methotrexate	1C received oral cyclophosphamide at 50 mg/day 2C received oral cyclophosphamide at the previous dose + oral methotrexate at low doses of 2.5 mg orally twice weekly	2012
Carboplatin as late-line therapy	1C received carboplatin AUC 5 or carboplatin + trastuzumab 6 mg/kg (8 mg/kg loading dose) 2C received carboplatin AUC 5 on day 1 + gemcitabine 1,000 mg/m^2 on days 1 + 8 in a 3-week cycle	2017

1C = first cohort of patients, 2C = second cohort of patients, AUC = area under the curve, IV = intravenous; mg = milligrams.

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Several lines of chemotherapy treatment can also be offered depending on patients' response to the cytostatic drug. In this regard, 1 study suggests that first-line PCT for MBC confers benefits to a substantial proportion of patients, with about a quarter feeling better after treatment and almost half feeling better or the same 4 to 6 months later (Ramirez et al. 1998). However, sometimes first-line PCT can fail, leading to a change in treatment or dose (Schrama et al. 2003). For this, changes can be made, such as using irinotecan-based regimens after another line of PCT (Lan et al. 2014); Vinorelbine on an outpatient basis when there is failure with anthracyclines and taxanes (Zelek et al. 2001); mitoxantrone, 5-fluorouracil, and high-dose leucovorin (NFL) for patients who have shown poor tolerance to other PCT regimens (Hainsworth et al. 1997); or cyclophosphamide, methotrexate, and 5-fluorouracil (fungal breast cancer) in patients who have relapsed after adjuvant chemotherapy with the same modality (Gerritsen et al. 1995).

There are specific situations in which PCT can be a great palliative for advanced disease management; for instance, carboplatin-based regimens have a promising effect and are well tolerated as late-line therapy in heavily pretreated MBC patients (Rosvig et al. 2018). Additionally, in those breast cancers that spread to the chest wall, a Japanese study demonstrated that using redistributed subclavian arterial infusion chemotherapy may be useful for local control and palliation (Koike et al. 2012), or in the management of symptoms of fungal breast cancer where intra-arterial PCT infusion of mitomycin + fluorouracil + cisplatin + mitozantrone was able to provide effective symptom palliation (Bufill et al. 1994) as well as in patients ≥75 years with MBC where single-agent PCT is feasible and may have clinical benefit (Overgaauw et al. 2020).

Despite all the benefits that PCT can offer in the management of breast cancer symptoms, a recent study in the UK showed that PCT toward EoL is associated with a higher probability of unplanned hospital admissions and hospital death (Bright et al. 2022) contrary to the philosophy of PC. In this scenario, patients' decision to receive or not receive PCT is very important, since studies show that many times the lack of clear communication about diagnosis leads patients and their families to see PCT as a cure option, thus increasing the risk of continued late PCT lines (Bergqvist and Strang 2017, 2019) and a deterioration in quality of life, especially in outpatient settings where there is no adequate follow-up of community PC, as demonstrated by an English study (Little et al. 2020), in which less than half of MBC patients had been referred to PC teams when they started taking eribulin.

Palliative radiotherapy. Regarding radiation doses, a review carried out in the UK (Maher 1992) concluded that 8 to 12 Gy is the highest single dose tolerated by a mean palliative volume without unacceptable acute effects, such as nausea and vomiting. A comparative study conducted in Israel (Jacobson et al. 2021) found that PRT can provide long-lasting palliation, reducing pain and bleeding with minimal and tolerable toxicity, even when administered as a single fraction although fractionated therapy provides a more durable response.

In this scenario of hypofractionated PRT, 2 studies conducted in India assessed the efficacy of a once-dose weekly schedule (Chatterjee et al. 2018; Santosham et al. 2020), concluding that it presented acceptable toxicity, satisfactory local management, and excellent palliation in patients with advanced incurable breast cancer. Similarly, another study identified that hypofractionated PRT in the thorax improved quality of life and offered effective palliation (Basu et al. 2019), and may also be beneficial in safely and effectively relieving symptoms among patients with incurable inflammatory breast cancer (Choi et al. 2019) (Table 2).

Regarding the combination of PRT with other therapies, 5 studies analyzed hyperthermia (HT) + PRT or reirradiation (reRT) use. Two studies (Zee et al. 1988, 1999) identified that reRT with 8 × 4 Gy + HT twice per week is a safe, effective, and well-tolerated method for the palliative treatment of patients with recurrent breast cancer in previously irradiated areas, agreeing with 2 other studies that add that compared to currently available systemic treatment options, reRT + HT is more effective and less toxic (Oldenborg et al. 2015, 2018). Finally, in 2003, a Thai study also reported that the combination of HT + PRT once or twice a week + PRT at 1 dose with or without chemotherapy is an effective treatment for palliation of local symptoms of large, ulcerative, advanced breast injuries in MBC (Lemwananonthachai et al. 2003) (Table 2).

In this same line, the association of PRT + selective inhibitors of cyclin-dependent kinases (CDK) is also an area of growing interest. Two of the studies included in this review address the issue presenting contradictory results, while a study conducted in the USA (Kim et al. 2021) concluded that using PRT within 2 weeks of CDK4/6 inhibitors (palbociclib or abemaciclib) had acceptable low toxicity, high efficacy, and is safe for MBC palliation. A case series investigated in Australia (David et al. 2021) noted increased radiotherapy toxicity when palliative doses of radiotherapy were administered during or before treatment with a CDK4/6 inhibitor (Table 2).

Within the scope of literature, the benefits of PRT in specific situations are also reported, such as in fungal breast cancer, 2 studies reported that PRT achieved high response rates of up to 90% with a median local progression-free survival of 10 months (Chia et al. 2016) and achieved good long-lasting local management and symptomatic relief (Williams and Harvey 2021) as well as in

Table 2. Palliative radiotherapy regimens used over time in the included studies

Regimen	Dose	Year
Electron beam therapy	400 rad once a week for 6 consecutive weeks using 3.5-MeV electrons from a 6-MeV linear accelerator	1979
HT + reRT	reRT with 8 × 4 Gy + HT twice a week	1988 1999
HT + PRT	HT at 43°C once or twice a week + PRT at a dose of 20–70 Gy	2003
PRT in fungal breast cancer	20 Gy in 5 fractions and 65 Gy in 26 fractions	2016
PRT in ulcerative breast cancer	30 Gy in 15 fractions	2016
Hypofractionated PRT	35 Gy in 10 fractions over 2 weeks	2018
Hypofractionated PRT in the chest	30 Gy/ 10#/2 weeks	2019
PRT in incurable inflammatory breast cancer	42.5–55 Gy with 2.5–3 Gy per fraction	2019
Hypofractionated PRT	26 Gy in 5 fractions over 1 week + 6 Gy of simultaneous integrated booster	2020

HT = hyperthermia, MeV = electronvolt, Gy = gray, Rad = absorbed radiation dose, reRT = reirradiation, PRT = palliative radiotherapy.

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ulcerative breast cancer, a study reported that PRT is an effective treatment with minimal toxicity (Vempati et al. 2016). Another survey, although very old, demonstrated that skin subtotal electron beam therapy is an excellent palliative method to treat the progression of recurrent inflammatory breast cancer (Nisce et al. 1979) (Table 2).

Even though the benefits of PRT are widely known, especially because of its low cost, there are studies that report the lack of access of women with breast cancer to this treatment. A retrospective study conducted in Canada (Danielson et al. 2008) reported that factors associated with not receiving PRT for women living outside of cities with radiotherapy facilities were age >75 years, community size >10,000, median income <$47,000, and residence in a regional health authority, compared to those living in the city, where only age >75 years was an important factor. Similarly, in another study, 11.3% of women with MBC did not receive PRT or specialized palliative care (SPC) (Fairchild et al. 2022). Finally, a recent African study (Mushonga et al. 2021) recommended using PRT in resource-limited settings to improve symptom management and overall quality of life.

Finally, although PRT offers many benefits in breast cancer management, the available literature shows that it should be evaluated by a multidisciplinary team to have a complete picture of patients' needs and personalize supportive care (Hill et al. 2022).

Palliative hormone therapy. Of the main drugs used in the palliative scenario of breast cancer, a study in 1989 evaluated the therapeutic efficacy of tamoxifen + medroxyprogesterone acetate to determine whether tamoxifen would increase the progesterone receptor levels, concluding that there is no potentiation by tamoxifen and recommending that both drugs should be administered independently to palliate MBC (Nemoto et al. 1989). Based on these results, in Japan, Okamoto et al. (2016) reported 2 cases of patients with breast cancer who used medroxyprogesterone acetate with palliative intent and demonstrated that this medication in isolation may be a good option as part of PC for patients with end-stage breast cancer, since the 2 patients undergoing treatment improved their appetite and quality of life and became more active than when they had been under aggressive anticancer treatment.

Regarding tamoxifen use, there are no conclusive studies on a possible palliative benefit when administered in isolation. However, in a study carried out in the USA, Harvey et al. (1982) assessed the sequential tamoxifen and aminoglutethimide use in postmenopausal patients with MBC, concluding that these 2 drugs used sequentially are effective forms of palliative hormone therapy (PHT) in MBC. In those cases where MBC is refractory to tamoxifen, another study identified megestrol acetate as an effective agent to palliate advanced breast cancer (Ross et al. 1982).

Palliative surgery. As part of the surgical approach, palliative surgery (PS) is offered in the context of improving patients' quality of life (Takuwa et al. 2017) and helping them enjoy life during their limited time (Vandeweyer et al. 2000) In this regard, there are several types of surgeries available in the palliative context. For instance, a recent study in Japan (Kai et al. 2019) found that palliative mastectomy was beneficial for aggressive symptomatic patients with HER2-positive breast cancer to improve their quality of life and achieve excellent local tumor management. Similarly, in another previous study, the authors reported that radical mastectomy with chest wall defect replacement with a myocutaneous flap is an effective palliation method for ulcerative tumors of advanced or recurrent breast cancer (Sweetland et al. 1995).

In the context of LMICs, a study recommends using "toilet mastectomy" due to a greater number of patients with MBC presenting large ulcerated injuries (Yip 2017) as well as in the case of older women with locally advanced breast cancer who are not candidates for standard therapies. A study recommends that, in terms of survival, mastectomy as palliative therapy can be used in hormone receptor-negative patients (Pan et al. 2019).

On the other hand, the literature shows that not only PS provides an effective palliative in breast cancer but also plastic reconstruction methods should be considered. For this, there are many methods whose choice depends on wound characteristics, extent of resection, and patient comorbidities (Alvarado et al. 2007). In this regard, an Italian study (Veronesi et al. 2007) reported that full-thickness chest wall resection followed by plastic reconstruction is a safe procedure with low morbidity and mortality that can provide good symptom palliation in patients with locally advanced breast. Similarly, in a study conducted in Pakistan, they concluded that myocutaneous flap reconstruction of the latissimus dorsi is a useful and effective palliative method for wound closure after extensive resection of locally advanced breast tumors with complications such as fungification, bleeding, and extensive bad odor (Cheema 2014). Another study conducted in the USA identified that radical resection associated with coverage with pedicled flaps may be a safe and reasonable option in PC of selected patients (Vandeweyer et al. 2000).

Finally, as part of the global evidence mapping, 2 previous studies presenting interesting surgical approaches were included. The first deals with bilateral adrenalectomy as a useful palliative therapy in hormone-dependent breast cancer (Huggins 1967). The second deals with transsphenoidal hypophysectomy use as a substantial possibility of objective and subjective palliation in women with breast cancer (Schwarz et al. 1981). Both studies were conducted in the USA (1967; 1981) and, despite the fact that the studies report some palliative benefit, they are techniques that are currently no longer reported in available literature.

Other palliative approaches. A study conducted in the USA used photodynamic therapy for treating patients with locally recurrent breast carcinoma, resulting in effective local palliative management with minimal complications. Therefore, it could be used in conjunction with chemotherapy, hormonal therapy, surgical excision, and after radiation therapy (Schuh et al. 1987). Similarly, a case report reported using palliative radiofrequency ablation to treat a symptomatic fungal injury of MBC, obtaining effective palliation, improving patients' signs and symptoms and quality of life (vanSonnenberg et al. 2005).

In another case report from Canada, the "lymphocentesis" technique was used for symptom relief in end-stage breast cancer, which the authors found to be a beneficial and low-risk intervention in the PC scope (Liao et al. 2019). In Malaysia, the PC team used the "conscious breathing" technique for treating physical and psychosocial suffering caused by breast cancer and treatment, with the results that patients reported feelings of calm, peace, and relaxation after each session, with decreased suffering, negative emotions and physical discomfort (Tung and Tan 2020). Finally, a review on PC in older women with breast cancer highlighted the importance of using dignity therapy (Laird and Fallon 2009).

Use, referral, and transition to PC

Regarding PC use, a study conducted in Norway identified that women with MBC need PC. However, these were only partially offered, as priority was given to treatments to prolong life and

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alleviate physical symptoms (Drageset et al. 2021). On the other hand, a study carried out in China highlighted a significant increase in the rate of PC use in Intensive Care Units from 2.53% in 2005 to 25.96% in 2014. Despite this, the authors state that usage remains low (Chen et al. 2020).

Thus, several studies address referral patterns to PC services. For instance, in a study carried out in the USA (Small et al. 2016), only 25% of women had received early PC consultation, of which 39.5% had been referred for symptom management and emotional support (Leadbeater 2013), similar to another study, where only 44.8% of patients with MBC were referred to PC (Bushan et al. 2018), and another, where 33% died without referral to a hospice, with only 7% of patients who died without referral had a documented discussion of PC as a treatment option (O'Connor et al. 2015).

Following this same idea, a study carried out in Austria (Jäger et al. 2020) identified that only 58.7% of patients received SPC, who lived significantly less time than patients who were not referred, a result that seems to be contradictory. However, the authors posit late referral (Cabrera-Galeana et al. 2019; Leadbeater 2013) as a plausible justification and also recommend that patients with MBC should participate in an SPC team consultation $\leq$60 days after initiation of systemic palliative anticancer therapy.

In another study on the reasons for hospital admission and the frequency of PC use among women with MBC, only 29% were referred to PC after their last hospitalization and the PC team assessed 57% of those who died at least once during an admission, but only 17% of patients attended an outpatient PC appointment. Furthermore, it concludes that patients hospitalized with MBC are commonly admitted due to uncontrolled symptoms and have a poor prognosis (Shin et al. 2016).

In a qualitative study carried out in Brazil (Telles et al. 2021) on the transition to exclusive PC in women with MBC, several professionals considered the process abrupt, caused by a fragmented structure, and a routine based on the dynamics of transfers between units in which PC is not part of care philosophy from diagnosis, being indicated, for the most part, at EoL, adding that in general women and family members resist referral because they do not have knowledge of PC.

Regarding the decision to refer or not refer patients to PC services, a study carried out in the USA (Li et al. 2018) indicates that it is a complex decision and is linked to specific factors of patients, such as the coordination of additional visits and the fear of EoL conversations as well as why a palliative medicine link is being considered after most acute care options have been exhausted as highlighted by a recent study in India (Arora 2020).

In this context of referral of patients to PC, health professionals also play an important role, as mentioned in a study that shows that oncologists differ widely in their attitudes toward PC thinking of referral only when the Karnofsky index is $<$ 50 and among other reasons because of the "fear of destroying patients' hopes" (Kierner et al. 2010). In addition to that, another study mentions that there is no consensus among oncologists about the most appropriate time to interrupt systemic therapy for disease management and use a palliative approach (Telles et al. 2021). Therefore, physicians must actively participate in this communication process to ensure the smoothest possible transitions to PC (Ashby et al. 1996).

Perceptions about PC: patient, family and multidisciplinary team

Since PC is an area rarely discussed, there are several perceptions that patients have about this approach, the same ones that studies show have been maintained over time. In the USA, in 1998, a qualitative study (Millstein et al. 1998) explored that the perceptions of patients with MBC on PC are summed up by an evident lack of knowledge on the subject. Years later, in the UK, in 2013, another study (Beaumont 2013) was carried out with a similar objective, and the authors reported that the perceptions of women with MBC about PC were negative and only changed after a positive experience that improved their quality of life. In addition, they identified that the factors that influence this perception include the lack of coordinated care, reluctance of health professionals to refer patients to PC, and patients' perception that PC is interchangeable with EoL care. Despite this refusal, a study (Berman 2012) mentions that professionals should be aware of the importance of patient participation in decision-making regarding cancer treatment considering the premise of treating patients not the disease.

Regarding the family, a case report (Ozaki et al. 2017) carried out in Japan reported on the importance of family to achieve PC at home and the participation of family in communication with the medical team, and another study (Camartin 2012) pointed out the importance to take care of family as a fundamental pillar in PC.

On the other hand, it is also important to mention the importance of multidisciplinary care in the context of PC. However, no studies were found that specifically explored the multidisciplinary approach in breast cancer. Despite this, 2 studies (Berman 2012; Camartin 2012) can be cited that include the importance of this approach in their conclusions, and only 1 case report (Binoy 2017) includes the benefits of palliative physiotherapy for postmastectomy lymphedema management.

Barriers to accessing PC

Age as a barrier. Regarding the barriers to access PC in women with breast cancer, several studies present conclusive evidence focused on the disparity of care. For instance, with respect to age, in the USA, a cohort of 2,291 women classified as dying of breast cancer identified that the youngest women were less likely to receive PC than women $>$70 years of age, concluding that a considerable proportion of women with breast cancer do not have access to PC (Gagnon et al. 2004), results that coincide with a cohort of more than 12,000 women with MBC, where it was identified that age influenced the delivery of hospital PC, also noting that young triple negative and older non-triple-negative patients needed more PC in the short term as well as older patients diagnosed outside large centers received less hospital PC in the long term (Frasca et al. 2020).

In contrast to the results of these 2 studies, a recent study reported that older women were less likely to receive PC (Stahl et al. 2020), but that when it comes to choice, younger women tend to choose PC more frequently than older patients as well as married versus single women (Lackan et al. 2003).

Social context as a barrier. In a study carried out in the population of Yamatji women in Australia (Dembinsky 2014), it was identified that they underuse PC services due to misperceptions about what the term implies, such as cultural and structural barriers. Similarly, in the USA, another study reported that White Hispanics, those from the Midwest, the South Atlantic, the West Coast, and uninsured patients were less likely to receive PC (Stahl et al. 2020).

In other studies conducted in the Caribbean region and Iran, the authors point out that there is an urgent need to improve access to PC and pain relief throughout the region, mentioning that the main challenges to improve such access are: insufficient

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health infrastructure to support cancer care; great unmet need for PC; reluctance of patients to participate in clinical care and the widespread complementary medicine use; and alternatives before conventional care acceptance (Khoshnazar et al. 2016; Spence et al. 2018).

Integrated PC in breast oncology

In a recent review study (Kida et al. 2021) on the priorities of supportive care for patients with MBC, the authors concluded that integration of PC and oncology is crucial, noting the importance of including a palliative oncologist with double training within the multidisciplinary team and agreeing with what was reported in another study, where it mentions that the integration of a PC specialist in the breast oncology care team can improve communication between primary and secondary care teams, holistic needs assessment, and individualized care planning (Colbourne and Gibson 2016).

Along the same lines, a study carried out in the USA (Rabow et al. 2018) reported that specialized integrated PC was well received by patients and oncologists, increasing early PC referrals and improving EoL care. Similar to another study, where it was reported that the incorporation and integration of a PC practice in breast oncology resulted in patients being referred early (Small et al. 2016).

Nursing role in PC

In a study carried out in the USA (Griffie et al. 2004), it is detailed that nursing professionals work so closely with patients, families, and other providers that they are the most suitable to direct PC transition communication. In another study carried out in Greece (Lavdaniti and Dimitriadou 2009) on nursing professionals' role in PC of terminal breast cancer, it is highlighted that nurses provide care to patients on a physical, psychological, social, and spiritual level, satisfying the needs in each dimension as well as playing an important role in grief work, using relaxation therapies and timely identifying care needs (Jones 2012).

In a study carried out in Brazil on nursing care management for women with breast cancer in PCT, the results show that nursing professionals play an important role in care management, contributing to a more accurate look at the recognition of needs and prioritizing quality of life. However, the term "palliative" is still perceived by professionals as 1 more phase of the disease (Cirilo et al. 2016), a situation that may be due to the fact that research in nursing area is not yet particularly advanced in PC (Jones 2012).

PC for pain management

Radiopharmaceutical use. Regarding the drugs used to alleviate pain in bone metastases, several studies report radiopharmaceutical use for palliative purposes, such as 4 studies addressing strontium-89 (Sr-89) use at different doses: (a) 2 MBq/kg (118–148 MBq) of 89Sr by intravenous injection (Berna et al. 1995); (b) 4mCi (148 MBq) 89Sr (Iakovou et al. 2014); and (c) 148 MBq 89Sr (Fuster et al. 2000; Sciuto et al. 2001), presenting similar results and concluding that patients with breast cancer with metastatic bone pain can benefit from therapy with 89Sr, since it is an agent effective for pain relief.

Similarly, 4 studies assessed radiopharmaceutical Renium-186 HEDP (186Re-HEDP) use for managing bone pain in breast cancer metastases (Hauswirth et al. 1998; Iakovou et al. 2014; Palmedo et al. 1999; Sciuto et al. 2001), concluding that 186Re-HEDP is safe and effective, presenting even faster pain relief than Sr-89 when used in a dose of 1406 MBq 186Re-HEDP (Sciuto et al. 2001), or it can also be used in a complementary way to analgesic therapy and radiation (Hauswirth et al. 1998).

Other studies also included radiopharmaceuticals such as 186Re-1,1-hydroxyethylidene diphosphonate (etidronate), which showed a 58% response in palliative treatment of metastatic bone pain derived from breast cancer (Han et al. 1999) as well as samarium-153-ethylenediaminetetra-methylenephosphonic acid (153Sm-EDTMP), which was also effective for pain relief (Iakovou et al. 2014).

Other therapies for pain management. Two studies assessed dexmedetomidine use as an analgesic/sedative agent in breast cancer. The first study used it in continuous infusion for refractory pain management in EoL care, obtaining satisfactory results (Byrne et al. 2022). The second study used intranasal dexmedetomidine for procedural sedation in complex wound dressing management (Ferguson and Wilson 2021).

Another study evaluated the feasibility of half-body radiation (8 Gy) in a fraction to treat pain in patients with MBC, obtaining as a result that only 2 of 13 patients had no pain relief in the radiated field with acceptable toxicity (Furlan et al. 2014). Similarly, a study conducted in the USA described the experience of treating patients with painful bone metastases using skin cryoablation, concluding that this procedure can be offered as a safe palliative treatment, since most patients experienced an improvement or resolution of pain (Deipolyi et al. 2018).

Finally, 2 cross-sectional studies described cannabis use. A study was carried out among patients with MBC undergoing adjuvant and PRT, where it was shown that 47% used cannabis during PRT, with pain being the most common reason for consuming (87%), although they also used it for insomnia, anxiety, stress, nausea/vomiting, and anorexia treatment (Weiss et al. 2021). In the other study, an attempt was made to establish cannabis use by age and breast cancer stage, finding that 42% of those surveyed had used medical cannabis to treat symptoms or side effects, especially pain in MBC. Regarding age, although younger patients are somewhat more likely to use this form of palliative treatment, older patients suffer from the same symptoms and its use is almost the same (Weiss et al. 2020).

Disparity in pain care. Despite the fact that pain management is a substantial part of PC for breast cancer, the literature shows us that there are still important gaps to be filled, especially in LMICs where there is a deficient use of morphine. The Breast Health Global Initiative reported in 2014 that morphine consumption among women with breast cancer in Canada was 87.46 mg per person-year, compared to 0.0032 mg per year in Nigeria (Distelhorst et al. 2015), and a Caribbean study adds to this widespread "opiophobia," resulting in limited access to opioids for pain relief in MBC (Spence et al. 2018).

A study conducted in the USA (Halpern et al. 2010) on disparities in access to PC identified that patients with distant or regional stage disease were less likely to receive pain management as well as Black women compared to White women and other ethnic groups (Payne et al. 2003) and also older adult patients. Regarding the latter, a review carried out in the UK concluded that pain management in older adult patients with breast cancer is inefficient due to the existence of other comorbidities (e.g., osteoarthritis), and in turn because they are less likely to report pain (Laird and Fallon 2009).

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In another study conducted in a rural population in India on disparities in access to PC, it was reported that, in the majority of patients with breast cancer, management of pain and other symptoms is grossly inadequate due to lack of properly trained labor (Manna 2017). On these scenarios of disparity of access, the management of pain; symptoms; and psychosocial, cultural, and spiritual issues is of prime importance in the care of these women. For instance, in Uganda, a morphine nurse prescriber program was implemented along with training people from Uganda and other African countries up to degree level in PC with the aim of addressing these disparities (Merriman 2010). Despite the fact that these strategies could provide some benefit, the truth is that, under optimal conditions, pain management should be carried out by a multidisciplinary team, as indicated by a study (Zarrabi et al. 2018).

Quality of life and PC

Since PC is an approach that aims to improve patients' quality of life, its measurement is very important in the context of breast cancer. In a study that assessed the incidence and relevance of depression symptoms and the level of health-related quality of life (HRQoL) among patients with MBC in the PC program, it was identified that depression was incident in 61%. In addition to this, HRQoL was at a very low level, clearly associating MBC in the PC program and depression (Slovacek et al. 2009).

In another study that compared quality of life among patients with breast cancer receiving PC versus ordinary care (Khalili et al. 2020), it was found that the scores in functioning and global health were higher in the PC group as well as higher scores in sexual functioning, body image, future outlook, physical activity, and lower scores in symptom scales, arm symptoms, and hair loss. Therefore, the PC group demonstrated a better quality of life, a result supported by another study (Shankpal 2011) where for the PC group the highest quality-of-life scores were correlated with the lack of sexual dysfunction/pain. This same study concludes that breast cancer patients' life expectancy/quality of life depends on social acceptance and the appropriate PC (Sunilkumar et al. 2021).

Finally, regarding quality-of-life measurement instruments used, they were only reported in 2 studies. In 1 study, the Czech versions of the Zung Self-Rating Depression Scale and the EuroQol EQ-5D generic questionnaire were used (Slovacek et al. 2009). In the other study, the European Organization for Research and Treatment of Cancer quality of life questionnaire (EORTC QLQ-C30), its complementary breast cancer questionnaire (QLQ-BR23) and the International Physical Activity Questionnaire (IPAQ) were used (Khalili et al. 2020). Another study emphasized the nonexistence of a standardized measure of quality of life for African women (Payne et al. 2003).

PC intervention programs

Of the studies that include technology use, a quasi-experimental study conducted in Korea (Park et al. 2011) developed, implemented, and assessed a program based on phone calls called "Hospice Smart Patient" aimed at women with breast cancer who needed PC. The results highlight that there was a significant difference in quality of life and communication skills between the 2 groups after the service was provided, as the experimental group showed better decision-making skills, sense of mastery, and understanding of hospice and PC.

Another quasi-experimental study (Rowe and Schapmire 2020) used social media to assess the impact of The Shady Pink Elephant EOL educational series on the knowledge, attitudes, and behaviors of women with MBC toward PC and EoL desires, concluding that the series improved some aspects of PC, such as the belief that PC is only for those in EoL, the belief that EoL discussions are only important to those in EoL, the comfort of discussing EoL issues, and the confidence that EoL wishes will be honored by attorney health-care power.

Regarding program-based studies, 2 prospective cohort studies were conducted in the USA. The first study assessed the effectiveness of the Advanced Breast Cancer program in women with stage IV breast cancer and concluded that early integration of PC and oncology is feasible and associated with psychosocial benefits (Small et al. 2015). In the second study (Reiser et al. 2019), an interdisciplinary Program of Support, Education and Advocacy (MBC-SEA) led by nurses was assessed for the coordination of supportive care in MBC, demonstrating that it was effective in decreasing symptom distress, increasing general well-being, and purposeful nurse-led assessment for social service and PC needs increases referrals.

Regarding the studies based on PC team interventions, 5 randomized clinical trials (RCTs) were developed on the subject, bringing important conclusions such as: in 2 RCTs (Greer et al. 2022; Temel et al. 2020) on structured visits, patients in the intervention group were more likely to report discussing their EoL care wishes with their physician and to receive PC services compared with usual care patients. Another RCT (Datta et al. 2017) on a palliative intervention in the cognitive function of patients with MBC undergoing chemotherapy determined that PC is an effective therapeutic option to treat mild cognitive impairment and improve quality of life, adding in another RCT (Mendoza-Galindo et al. 2018) that early PC intervention is associated with a reduction in emergency visits and hospitalizations due to uncontrolled symptoms.

Finally, only 1 RCT (Arce-Salinas et al. 2018) presented negative results when concluding that the early PC intervention among patients with MBC failed to demonstrate a benefit in overall survival when compared with those patients who did not receive the intervention.

EoL care and PC

Institutionalized death. Death with dignity in a calm and familiar environment is one of the principles of PC. However, a study conducted in Canada (Gagnon et al. 2004) showed that only 6.9% of women with MBC died at home, while 69.6% of them died in acute care beds. Results were similar to an Australian study (Philip et al. 2016) where 81% of patients died in hospital, although 60% had a PC approach at the time of death. However, this occurred for the first time at final admission for 69%. In the results of another study, only 20.7% of women with MBC were enrolled in hospice before they died (Lackan et al. 2003).

Among the possible justifications for this prevalence of institutionalized death, we found that women who die due to MBC have a late commitment to PC (Philip et al. 2016) as well as there is the existence of an inflexibility of institutionalized death that may be caused by culturally specific perceptions of death and dying (Dembinsky 2014). In this regard, a recent study carried out in Jordan concluded that earlier referral to PC is associated with less aggressive EoL care, leading to less frequent emergency room visits, hospital admissions, and Intensive Care Unit admissions during the last month of life (Abunasser et al. 2021).

On the other hand, patients' decisions about death are the central aspect of care at EoL. For this, a case report reported in the USA (Johnson-Scott 2019) reports on the decisions of a patient with breast cancer about her disease process deciding not to use

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a treatment for curative purposes, especially if follow-up is carried out by a PC team, avoiding institutionalized death.

Advance directives of will. Advance directives (AD) are a means of documenting treatment preferences and care goals for patients when they are unable to make their own decisions due to illness. In a prospective cohort of 32 women with MBC (Ozanne et al. 2009), we examined whether or not patients had AD and, if so, with whom they would discuss written plans for EoL decisions. The results reported that the majority of patients collected information about AD and had made written plans. However, few have discussed these plans with their providers, adding that explicit discussion of AD and patient preferences regarding EoL care is lacking.

In this same idea, in another study on the attitudes of oncologists toward PC in MBC, only 25% discussed AD with their patients (Kierner et al. 2010), results that differ from another study (Bushan et al. 2018), where 76% had some discussion about PC before death. However, only 32% of women with MBC had formal documentation of AD. On the other hand, it is suggested that the referral of patients to a PC service significantly increases the chances of having an AD (O'Connor et al. 2015), and pain management at EoL is one of the main concerns when constructing it (Griffie et al. 2004).

Home PC

Regarding home PC, a prospective study conducted in Japan states that the reasons for providing palliative home care in patients with MBC include management of infiltrating skin tumors (ulcers), pain, home oxygen therapy, and chemotherapy, taking into consideration that the most important part of PC at home is to prevent any physical and psychosocial problem (Ueno et al. 2009). Similarly, another study highlighted the importance of home visits by a group of social workers in MBC care during the last months of life in a group of patients from a rural village in India (Manna 2017).

Spirituality, PC, and breast cancer

From the reviewed literature, a study conducted in India (Shankpal 2011) showed significant correlations between higher spirituality scores with absence of depression among women with MBC. Furthermore, 53% of women stated that religious/community/faith support was the most important factor in helping them cope with breast cancer.

In another Indonesian study on spiritually focused PC to improve the comfort of patients with breast cancer (Nuraini et al. 2018), it was found that PC significantly improved patient comfort by reducing anxiety and depression. Additionally, it demonstrated a significant positive relationship between spirituality and emotional well-being, concluding that PC focused on spirituality is of fundamental importance for patients with breast cancer.

Finally, in a case report reported in Scotland on a patient with breast cancer (Ireland 2010), the need to systematically assess spiritual needs and not be guided by patients' religious approach was highlighted, since, as the case explains, religion seemed to encourage denial of the possibility of death.

PC costs in breast cancer

In a study carried out in Colombia, they concluded that the main cost generator of a hospital was the PC visit, which was used by three-quarters of patients at least once, which represented 68.6% of the total costs (Franco et al. 2019). Despite this, an RCT (Ramirez-Morales et al. 2018) analyzed the cost of emergency visits and hospital days in patients with early PC intervention versus patients treated only with oncological intervention, obtaining that the reduction of hospital stay costs was statistically significant in patients with early intervention of PC, results that agree with another study where it is highlighted that PC represents a significant reduction in the health system costs (Rabow et al. 2018).

Finally, a study emphasizes that PC and health system support resources must be available to manage treatment-related side effects in the short term (during treatment), in addition to long-term treatment-related side effects (after treatment with curative intent) and metastatic disease (Distelhorst et al. 2015), with the aim of avoiding inappropriate PC use resources among patients with advanced cancer (Bushan et al. 2018).

Ambiguity of the term "palliative care"

Several studies use some terms with interchangeable semantic connotations with "PC" that seem to cause confusion. Although the WHO presented a revised concept of PC, the advancement of research in the area has given way to the emergence of other terminologies. For instance, in 2013, the Breast Health Global Initiative consensus (Cleary et al. 2013) presented the difference between "supportive care" and "PC," referring to the former as the prevention and management of adverse effects of cancer and its treatment. Meanwhile, PC is mainly focused on patients with very advanced disease in whom antineoplastic therapies have been withdrawn, concepts supported by the European Association for Palliative Care and the Multinational Association for Cancer Support Care.

In the same way, the terms "hospice care" and "EoL care" enter into this ambiguity of meanings, differing from the previous 2, because they are provided to people who have accepted death and a physician certifies a life expectancy <6 months. Therefore, these are not combined with disease-modifying treatments and are often used interchangeably, with the difference that hospice care is provided in a community setting (Currow et al. 2020).

The interchangeable use of these terms may be due to misperceptions of the term "palliative" by patients, as mentioned in a quasi-experimental study in which the use of these 3 terms had different levels of acceptance among women with breast cancer, who had greater acceptance of the term "supportive care" (Fishman et al. 2018). On the other hand, this erroneous perception also arises from health professionals, as mentioned in a study in which the term "palliative" was understood as 1 more phase of the disease (Cirilo et al. 2016).

Finally, this review also identified studies addressing terms such as "SPC" and "specialized integrated PC." However, no definition or aspects of its approach are presented.

Discussion

This review shows a global overview of PC role in breast cancer. Although it is true, studies carried out before the redefinition of PC's modern philosophy by Saunders were included. It is in the last decade where a growing interest in the area is denoted, but in Latin America there are still few studies developed on the subject. On the other hand, as there is a greater proportion of cross-sectional studies within the scope of the literature, one can argue about the lack of more robust research outlines that can offer guidance in clinical decision-making in this area.

In the palliative treatment scenario, PCT could be cited as one of the areas that has made the greatest progress in breast cancer thanks to the development of increasingly safer, less toxic, and mainly effective cytostatic regimens to manage disease progression. Some RCTs on the use of different lines of PCT, which showed some kind of palliative benefit in women with breast cancer, were included

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in this review. However, no studies were found that address using PCT concomitantly with other palliative therapies. Another aspect to take into account is the unnecessary use of aggressive PCT lines at EoL, even when their benefit is less than patients' suffering, causing a deterioration in their quality of life and false expectations of cure (Bright et al. 2022; Ikander et al. 2021). No studies were found regarding the use of fractionated QTP or new strategies of antibody–drug conjugates.

PRT is another area that has made great strides in breast cancer management. With the support of technology and the development of new RCTs, hypofractionated radiation regimens are being used retaining the palliative benefits offered by high-dose regimens, adding to this fewer adverse effects and fewer hospital visits. On the other hand, studies also show that PRT can be effective when combined with other therapies such as HT or CDK4 and CDK6 drugs. Although regarding the latter, the results included in this review are contradictory in terms of their benefit, which is why more studies are required in the area.

Regarding PHT, studies on its use in the palliative context are still few and old, with tamoxifen being the drug most studied on its own or in combinations with other drugs. No studies related to aromatase inhibitors, the role of combined CDK4/6 therapy, and the impact of each of these on quality of life were retrieved. Additionally, no associations were found between PHT and other types of palliative therapy. In the field of PS, the included studies present various surgical approaches that demonstrate some type of palliative benefit in patients' quality of life, especially in those types of breast cancer with ulcerative and exudative wounds. It is also important to highlight the "toilet mastectomy" recommendation as an effective approach in LMICs as well as the importance of adding reconstructive surgeries to a surgical plan. It should be noted that no studies were found regarding the use of PS in combination with other palliative therapies or the stabilization of fractures or impending fractures in bone metastases. Regarding the use of other palliative approaches included in this review, more rigorous studies are needed to demonstrate their true efficacy.

With respect to PC use, their underuse is still a trend that is maintained in reviewed studies. However, this dynamic is given by a multifactorial problem, where health professionals (late referrals, idiosyncrasies, lack of knowledge), patients, and relatives (negative perceptions, ignorance) are part of the problem. Regarding family inclusion in PC and the importance of a multidisciplinary approach, only 2 studies explored these dynamics succinctly; therefore, research is needed on this area, since both components are fundamental pillars of PC. In regard to the referral to PC services, there is a need for studies addressing the variable of breast cancer's natural history as a modifying factor at the time of referral.

In addition to these factors, the literature also points to other barriers that hinder access to PC, including the social context (geographical location, ethnicity, or economic situation) and age. Regarding the latter, the studies seem to be contradictory, so more research is required to analyze this association, taking into account factors such as the type of cancer and stage. Despite the existing barriers, it is important to highlight as a strength the integration of PC in breast oncology, in addition to the recommendation that oncologists themselves become PC specialists. In this integration scenario, nursing also plays a very important role in PC. However, there is little existing evidence, suggesting the need for more studies focused on these professionals.

Regarding pain, its proper management is one of the main pillars of the palliative approach in breast cancer with metastasis to the skeletal system. Of the drugs used for bone pain treatment, the majority were studies on radiopharmaceuticals (Sr-89, 186Re-HEDP, etidronate, 153Sm-EDTMP). However, it should be noted that none were carried out in the last 7 years. Using other analgesic therapies such as dexmedetomidine, HIB, and cannabis was also explored. No studies on morphine use were found. Despite this, some results place "opiophobia" as one of the main factors for disparities in pain management, added to age (older adult), ethnicity (Black race), and structural characteristics of health systems, resulting in a deterioration in quality of life.

Regarding quality of life, its assessment is also a way of understanding the real impact of PC. Despite this, only 3 studies reported results on this subject showing significant associations between PC use and a better quality of life among patients with breast cancer. Of the instruments used to assess quality of life, no study used specific questionnaires for the palliative setting, such as the EORTC QLQ-C15-PAL questionnaire, recommended for presenting high sensitivity and specificity to identify clinically important symptoms and functional health impairments in patients receiving PC (Pilz et al. 2021).

Another important aspect of PC is EoL care, which is often misused to refer to PC in a general way despite the different connotations of each term. In this sense, few were the studies that presented evidence on care at EoL in breast cancer, which mostly dealt with the low proportion of women who have access to PC before and during the death process as well as inefficient AD use, in addition to the small number of studies that addressed this issue.

In the context of home PC for breast cancer, only 2 studies included any results on the subject, which is striking, since some palliative therapies can be administered at home. Therefore, they must be followed up by a PC team, in addition to caring for the family, which is another important aspect. In the same way, only 3 studies addressed spirituality in PC and, despite the fact that the results are satisfactory in improving patients' quality of life, it is still an area that needs more research.

Concerning PC costs, the little evidence available shows that it is an area that generates high health costs. However, it presents a good loss/benefit ratio by saving on emergency visits and hospital admissions. It is also highlighted that among patients with breast cancer there is still ambiguity regarding the term "PC" use, a situation that may be caused by a confusion with the concepts of "support care," "hospice care," and "EoL care." Therefore, some updated international consensus is necessary to regulate the context of use of each term, as can be seen in a review on the PC concept evolution (Souza et al. 2022).

With regard to the identification of knowledge gaps, throughout the discussion some have been cited in relation to the issues addressed. However, the lack of studies on issues such as sexuality in the palliative context of women with breast cancer can also be highlighted, namely integrative therapy (yoga, acupuncture, etc.) use for managing symptoms derived from the disease or treatment; studies on quality of life using specific measurement instruments and in different scenarios such as PCT, PRT, PHT, or SP; family inclusion in PC programs; individualized multidisciplinary team role; use of technologies in the palliative setting; and family follow-up in the mourning process. Furthermore, returning to the 4 main pillars of PC (management of signs and symptoms, patient/family support, multidisciplinary, and communication), it can be noted that no studies in the field of communication were included.

As limitations, despite having carried out an extensive literature search, there is the possibility that some relevant study has not been included, a situation that could modify part of results of this review. However, to reduce this bias, the search included

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8 databases, 1 repository, and gray literature as well as a broad strategy with the support of a librarian. It can also be pointed out as a limitation the nonrecovery of 33 potentially eligible studies despite the fact that all resources for their recovery were exhausted; however, due to their age, only the title was available.

Conclusions

The scope of available literature on PC in breast cancer is extensive. However, most studies tend to show an interventionist approach, leaving aside PC comprehensiveness, thus generating the contradiction of identifying PC as 1 more phase of the disease or treatment for curative purposes. There is little evidence on PC use since breast cancer diagnosis, pointing to its greater use in the final stages of the disease. Added to this, the predominance of studies restricted to a few countries and with not very rigorous designs that do not allow guiding clinical decision-making places PC as an area that, although of growing interest, requires special attention to make adequate use of its potential.

Implications for practice

This review offers a global map of evidence on PC in breast cancer treatment and, despite not performing an assessment of the methodological quality of included studies, the results of this review could guide health professionals interested in the subject to situate themselves in the current context of the subject. Furthermore, it offers a quick summary of recommendations on different palliative therapies that should be critically observed according to the methodological scope of this study. Finally, this review also highlights multiple knowledge gaps, which could be used by other researchers to develop future studies in this field.

Supplementary material. The supplementary material for this article can be found at https://doi.org/10.1017/S1478951523001840.

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