

A Comprehensive Analysis of the Cancer Chronic Pain Experience: A Narrative Review

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Abstract: Cancer-related chronic pain (CP) represents a critical clinical issue through the disease, severely compromising the quality of life (QoL) of patients and the family environment. The current review employed a narrative method to synthesize the main results about the impact of cancer-related CP on QoL, adopting a multidimensional and threefold vision: patients, caregivers, and patient-caregiver perspective. Evidence emphasizes the importance of considering a bidirectional perspective (patient-caregiver) to understand better the pain experience throughout the cancer continuum and its consequences on QoL of patients and caregivers. Moreover, a holistic and multidimensional approach to cancer-related CP and its impact on QoL of patients and caregivers is still needed, in which the interconnection between physical, psychological, and social factors should be analyzed. Theoretical and methodological issues for orienting future social and family research initiatives were discussed.

Keywords: chronic pain, cancer, quality of life, personality, social support, decision-making

Introduction

Cancer-related chronic pain (CP) represents a critical clinical issue through the disease pathway (from diagnosis to long-term survivorship), affecting about 40–70% of patients with a cancer diagnosis.¹ Specifically, Bennett et al² reported that between 33% and 40% of long-term cancer survivors suffer from CP, while 66% of patients with advanced cancer experience pain. Moreover, CP has been demonstrated to seriously compromise their Quality of Life (QoL), adherence to the treatments, and survival rate.³ Nevertheless, notwithstanding this incidence in the cancer population through the whole cancer continuum, CP is neglected, and its knowledge remains inadequate.^{4,5}

According to the International Association for the Study of Pain (IASP),⁶ pain is defined as

An unpleasant sensory and emotional experience associated with or resembling that associated with, actual or potential tissue damage (p.1977)

Consistently to this definition, cancer-related pain is a complex physical and psychological phenomenon in which pain perception results from physical and psychosocial processes. From a *physical perspective*, cancer-related pain depends on several physiological, biological, and clinical processes, as well as the type and the staging of the tumor, grade, presence of metastasis, anticancer treatments (chemotherapy, radiotherapy, biological and hormonal therapy), and consequences of the surgery (both demolitive and non-demolitive ones).⁷ On the other hand, from a *psychosocial perspective*, the IASP's revised definition empathizes pain as a more “subjective experience”, in which psychological and social factors influence pain perception and are not necessarily a consequence of tissue damage.⁶ Moreover, the transition from acute (pain that lasts or recurs for less than three months) to CP (pain that lasts or recurs for more than three months)⁸ is known to be catalyzed and maintained by psychological, cognitive, and social factors.^{9–12} For example, CP is mainly associated with psychological distress, poor social functioning, inadequate beliefs, negative coping strategies (eg, catastrophizing thinking style), unmet expectations,^{11,12} and personality features.¹³ Concerning psychological distress, a higher level

of anxiety and depression were demonstrated to be associated with more intense pain, worry, rumination, and fear.^{11,12} Likewise, higher pain perception was associated with decreased social activities, social functioning, support, and resilience.¹² Moreover, Petraşcu et al¹³ explained the link between personality features and the experience of CP (according to Cloninger's psychobiological model of personality^{14,15}). For example, harm avoidant patients are prone to adopt avoidant behaviors when they are confronted with aversive stimuli such as the experience of pain. This exposure also increases the feeling of negative emotions (eg, depression, worries, fear), altering the representation of their disease. Likewise, patients with lower scores in reward dependence and cooperativeness, who have difficulty expressing their emotions and asking for help, tend to feel more pain.¹³ Overall, these psychosocial factors are demonstrated to modulate pain perception and affect the outcome of the treatments and patients' QoL.^{11,16,17}

Notwithstanding, considering only the individual features is insufficient to understand the CP experience and its consequences on health status and QoL. In line with the biopsychosocial paradigm,^{18,19} in which health status has been defined as the result of interconnection between physical, psychological, and social dimensions, many factors might contribute to defining the CP experience and QoL in cancer patients, including the *family context* and *personal relations*. Mainly, illness represents a challenge for the patient and his/her family: the disease onset and its development provoke a profound transformation in the family system and its members' roles.^{20,21} Furthermore, the behavioral and emotional reactions of each member are strictly interconnected. As supported by the Systemic Transactional Model (STM), the interdependence between partners plays a pivotal role in stress management and adjustment,²² also in the cancer field.²¹ Consistently, stressors may affect directly or indirectly both partners in a close relationship, and the intrapersonal resources of one partner could expand the resources of the other (or vice versa), creating a new synergy and acting as *dyadic coping*.^{21–23} Therefore, how pain is perceived and handled by both patients and caregivers influences the maintenance, exacerbation, and reduction of patients' pain experience and QoL.^{20,24}

Despite these pieces of evidence, none have still revised the literature focusing on cancer-related CP and its impact on QoL, adopting a multidimensional and threefold vision: patients, caregivers, and patient–caregiver perspective. To our knowledge until now, studies have investigated how CP modified QoL in patients considering predominately the general domains affected (respectively, physical, emotional, functional, social, and/or family wellbeing), without investigating in-depth the alterations in specific functions (eg, self-esteem, beliefs about the pain, pain coping strategies) and their consequences on patients' QoL. In addition, few studies are available on the sub-domains of QoL impaired by CP experience (eg, anxiety, depression, pain catastrophizing, attachment styles, social support, sexuality, employment status and/or returning to work), the potential interactions between them and the significant others involved in the care process, such as primary caregivers.

Coherently, the aims of the current narrative review were: *i*) collecting evidence about the impact of cancer-related CP within a threefold vision (patients, caregivers, patient–caregiver perspective); *ii*) analyzing the impact of cancer-related CP in a more comprehensive and multidimensional approach, considering the general domains and sub-domains of QoL, and interactions between them. Data collected was narratively discussed taking in mind the definition of QoL proposed by the World Health Organization:²⁵

An individual's perception of their position in the life, in the context of the culture in which they live and in relation to their goals, expectations, standards, and concerns. (p.1405)

A narrative approach following guidelines given by Demiriz et al²⁶ without a strict protocol for search strategy was implemented. The search was conducted up to August 2021.

Cancer-Related Chronic Pain and QoL Patients' Perspective

An essential set of studies^{4,5,27–35} in the cancer field has investigated the CP experience, focusing on how CP may affect patient QoL, referring prevalently to an analysis of the general QoL domains (physical, emotional, functional, social, and/

or family wellbeing). Notwithstanding, only a subset of them^{4,5,27–29} with the addition of other two studies^{36,37} investigated more in-depth the influence of CP on specific sub-areas of patients' QoL. See Table 1.

Overall, CP was demonstrated to be a crucial issue that impaired all patients' QoL across different cancer syndromes, both during the active phase of the treatments and the following phase of the survivorship.^{4,5,27–35}

In breast cancer patients, accruing evidence highlights that women compared to men experienced more pain,^{5,28,32} greater pain severity,^{5,32} and higher depression symptoms,⁵ suggesting a gender difference in the pain experience. Caffo et al³³ also demonstrated that women who experienced continuous pain had significantly worse physical health, psychological well-being, and autonomy scores than patients with intermittent CP. Similar results were found considering widespread CP after surgery³² rather than a regional one in breast cancer patients.

A gender difference was also observed in rectal cancer patients.^{34,35} For example, Faddern et al³⁴ demonstrated that a higher frequency of CP (eg, more than once a month) due to the radiotherapy and chemotherapy severely affected all dimensions of QoL (in particular, global health status, emotional and social functioning) differently in men and women. In addition, female patients reported lower emotional functioning, a higher degree of constipation, and sleep disturbances than males, while male patients experienced lower scores on physical and role functioning, a higher level of fatigue, and dyspnea. Moreover, a difference was found in rectal cancer patients based on the treatments received³⁵ revealing that patients treated with chemotherapy reported more often neuropathy symptoms (eg, trouble hearing, trouble opening jars or bottles, troubling walking stairs or standing up), especially sensory ones (eg, tingling toes/feet, numbness, aching or burning) compared to patients not treated with chemotherapy. These symptoms also had negative repercussions on all domains of QoL.

Sub-Domains of QoL

A subassembly of studies^{4,5,27–29,36,37} has investigated specific sub-domains of the QoL that seem to play a key role in the patients' pain experience. These studies stressed the impact of CP on sexuality, employment and/or returning to work, and psycho-emotional (eg, anxiety, depression, pain catastrophizing, attachment styles) and social (eg, social support) factors. As discussed by Gonçalves et al²⁷ for example, long-term cancer survivors who experienced CP had not only a worse overall QoL but also showed a decline in other functionalities: family/home responsibility, recreation, support activities, occupational status, self-care, social activities, and sexual behavior. The authors suggested that this impairment may even be superior to the impact caused by a cancer diagnosis and that only thirty-eight (45%) out of 85 patients were followed up for appropriate long-term pain surveillance.

Sexuality. CP has been demonstrated to substantially impact romantic partners' intimacy and compromise sexuality in the ill partner. For example, Pühse et al³⁷ showed that patients with testicular cancer had poorer sexual desire, erectile dysfunction, and/or ejaculation disorders, damaging intimacy with their romantic partner. Likewise, Monga et al³⁶ demonstrated that all domains of sexuality (arousal, behaviors, orgasm, and relationship satisfaction) were afflicted, except for sexual fantasy. Moreover, the authors found a negative correlation between sexual functioning and psychological factors, specifically: higher levels of depression correlated with lower scores of sexual behaviors, orgasm intensity, and drive; higher levels of distress with lower scores of sexual behaviors and drive; higher levels of pain catastrophizing with lower scores of sexual behaviors and orgasm; finally, passive coping strategies with lower scores of orgasm intensity and sexual drive. However, these psychological factors were also demonstrated to be strong predictors of sexual functioning in terms of protective or risk factors. For example, a positive control appraisal over pain and life, coping self-statement, internal locus of control, engagement in household chores and outdoor activities predicted more sexual fantasy, arousal, behaviors, and drive (in other words, they act as protective factors). Otherwise, passive coping strategies and solicitous responses were inversely correlated with sexual fantasy, orgasm intensity, and drive (in other words, act as risk factors).

Psycho-emotional and social factors. Psychological and social factors represent other principal sub-domains of QoL that seem to modulate the experience of CP. Smith et al²⁹ highlighted that attachment styles and catastrophizing pain play a pivotal role as moderators of the CP experience. The authors reported that breast cancer patients who underwent cancer treatments were more likely to account for higher anxious attachment style and catastrophizing thoughts. Conversely, avoidant women were less likely to report pain, which might also be related to the restriction in expressing negative emotions. Both attachment styles negatively impaired overall QoL, particularly the social dimension. Moreover, a negative association between

Table 1 Descriptive Characteristics of the Studies Included on Patients' Perspective

Authors, Year	Study Design	Participants [†] n, M (SD)	Type of Chronic Condition	Question Relevance	Measures of QoL	Main Results
Gonçalves et al, 2020	Retrospective (quantitative design)	20, 65.3 (NE)	Different cancer syndromes: Digestive, Head/Neck, Breast, Genitourinary, Bone, CNS, Synchronous	QoL, Functionality	<ul style="list-style-type: none"> EQ-5D-3L PDI 	Negative relationship between CP and total QoL, specifically CP has decreased daily and social activities, physical well-being, psychological well-being, family/home responsibility, recreation, life-support activities, occupation, and sexual behaviors.
Cox-Martin et al, 2020	Cross-sectional (quantitative design)	1702, NE	Breast Cancer and others (NS)	QoL, Employment status	HRQoL module of the BRFSS	Negative relationships between <i>uncontrolled</i> CP and all QoL domains (physical well-being, psychological well-being, daily activities).
Hamood et al, 2018	Cross-sectional (quantitative design)	305, 63.8 (13.9)	Breast Cancer	QoL, Employment status	SF-36	Negative relationships between CP and all general QoL domains (physical and mental health, physical and social functioning, emotional and physical role, vitality), CP and work re-entry and/ or maintenance.
Smith et al, 2018	Cross-sectional (qualitative design)	128, 57.5 (8.9)	Breast Cancer	QoL, Attachment	FACT-B	Negative relationships between attachment styles (anxiety, avoidance) and total QoL, attachment styles and social well-being; attachment anxiety also predicted worse functional and emotional well-being.
Barrett et al, 2017	Cross-sectional (quantitative design)	121, 63.2 (13.3)	Different cancer syndromes: Breast, Lung, Head/Neck, others (NS)	QoL	FACT-G, Version 4	A better total QoL was predicted by higher school education, having a caregiver, lower level of psychological distress, lower level of pain intensity and interference.
Feddern et al, 2015	Cross-sectional (quantitative design)	426, NE	Rectal Cancer	QoL	EORTC-QLQ-C30	Negative relationships between CP and total QoL, CP and all QoL domains (social, emotional, and physical functioning).
Mols et al, 2013	Cohort (quantitative design)	1643, 69.4 (9.4)	Colorectal Cancer	QoL	EORTC-QLQ-C30	Patients with many chronic neuropathy symptoms (upper 10%) reported worse scores in all QoL domains (general health, physical, role, cognitive, emotional, and social functioning) and more additional symptoms.
Peretti-Watel et al, 2012	Cohort (qualitative and quantitative design)	10, 48.6 (20.5)	Breast Cancer	QoL	WHOQOL-BREF	Living daily with CP has decreased total QoL, specifically the satisfaction in everyday activities and the activity limitation.
Pühse et al, 2012	Cohort (quantitative design)	238, 35.2 (9.3)	Testis Cancer	Sexuality	<ul style="list-style-type: none"> BSFI IIEF-5 	Negative correlation between chronic testicular pain and sexual dysfunctions.

Green et al, 2011	Cross-sectional (quantitative design)	40 (current CP) 80 (CP since diagnosis), NE	Different cancer syndromes: Breast Prostate, Colorectal, Lung, Others (NS), Multiple Myeloma	QoL, Depression, Functionality	<ul style="list-style-type: none"> • EORTC-QLQ-C30 • PDI • CES-D 	<p><i>Current</i> CP has decreased several domains of QoL (general health, physical, social, and role functioning); while additional symptoms and financial difficulties were increased.</p> <p>CP <i>since diagnosis</i> has decreased all QoL domains (general health, physical, role, emotional, cognitive, and social functioning; while depression, additional symptoms, and financial difficulties were increased.</p>
Burckhardt et al, 2005	Cross-sectional (quantitative design)	23, 56.8 (5.5) patients with regional pain 58.7 (8.6) patients with widespread pain	Breast Cancer	QoL	<ul style="list-style-type: none"> • FACT-B • SF-36 	<p>Poorer scores on all QoL domains (physical, emotional, functional well-being, additional concerns) in patients with <i>widespread</i> CP compared to patients with <i>regional</i> one.</p>
Caffo et al, 2003	Retrospective (quantitative design)	210, NE	Breast Cancer	QoL	QoLQ	Poorer scores on all QoL domains (physical, social, and psychological well-being, physical autonomy).
Monga et al, 1998	Cross-sectional (quantitative design)	70, 49.9 (NE)	Different types of chronic illness: Cancer, Arthritis, Neuralgia, Headache, Diabetic Neuropathy	Sexuality, Depression	<ul style="list-style-type: none"> • DISF • CES-D • HSCL-21 	Negative correlations between CP and sexual functioning (drive, arousal, behaviour, orgasm, drive), except for fantasy. More sexual problems were experienced in patients with depression, distress, and those who adopted passive coping strategies than patients with active ones.

Note: †with chronic pain.

Abbreviations: NE, not estimable; NS, not specified; CP, chronic pain; CNS, central nervous system; QoL, quality of life; QoLQ, Quality of Life Questionnaire; FACT-B, Functional Assessment of Cancer Therapy-Breast; FACT-G, Functional Assessment of Cancer Therapy-General; WHOQOL-BREF, World Health Organization Quality of Life; EQ-5D-3L, European Quality of Life Five Dimensions Questionnaire; PDI, Pain Disability Index; EORTC-QLQ-C30, European Organization for Research and Treatment of Cancer – 30-item Quality of Life Questionnaire; IIEF-5, International Index of Erectile Function; BSFI, Brief Sexual Functioning Inventory; DISF, Derogatis Inventory of Sexual Functioning; CES-D, Center for Epidemiological Studies Depression Scale; HSCL-21, Hopkins Symptom Checklist.

attachment avoidance and perceived effectiveness of pain management was found (ie, avoidant patients were more likely to report less effectiveness in handling their pain) when age and pain catastrophizing were taken under control.²⁹

Additionally, Green et al⁵ showed that experienced CP (both current and since diagnosis) is related to greater depressive symptoms, poorer functioning, financial difficulties, and more physical symptoms (ie, fatigue, discomfort, trouble sleeping, appetite) in patients with a different cancer diagnosis. By contrast, as Barrett et al³⁰ stressed, some protective factors bolster the conservation of a better QoL. For instance, the authors³⁰ emphasized factors strictly related to pain (ie, lower intensity and frequency), personal features (ie, higher education level, lower current psychological distress), and social context (ie, receiving support from a caregiver or, in general, a good social/relational wellbeing) as valid predictors of good QoL.

Employment and/or returning to work. The experience of CP was demonstrated to temporarily affect the status related to work and the possibility to return to work. For example, Cox-Martin et al²⁸ revealed that uncontrolled CP, especially in women, decreased employment odds due to the interference of neuropathy or lymphedema to job performance. These results are coherent with a previous study⁴ in which CP was demonstrated to be an independent predictor of the downgrade transition to work. In particular, women who worked full-time jobs were downgraded to part-time jobs, while women who worked part-time quit, retired to, or lost their work after the treatment.

Caregivers' Perspective

The experience of CP impairs not only patients' QoL but also caregivers. Frequently, caregivers of cancer patients are at risk of stress adjustment problems, including physical, psychological, social health impairments and disruptions in family dynamics.³⁸ However, studies retrieved were based on the evaluation of general domains, without considering specific areas such as the relationship between patients and caregivers and neglecting the synergic interrelations between all the domains and sub-domains of QoL involved.³⁹⁻⁴¹ Only a few of them revealed the principal themes and sub-themes related to caregivers' QoL⁴⁰ and the protective factors that may reverse the experience of CP.³⁹ These studies seem to investigate the sub-dimensions of QoL impaired within caregivers' perspectives.

Overall, CP was a crucial issue that affected all caregivers' QoL who lived with a person with cancer pain.³⁹⁻⁴¹ As observed by Ferrell et al⁴¹ for example, cancer-related CP negatively impacted all domains of caregivers' QoL: social wellbeing (with more prevalence of distress from chronic illness, lower engagement in housework activities, more financial burden, lower support perceived from others, and more interferences with employment); psychological wellbeing (with more difficulties to cope with chronic illness, anxiety, depression, difficulty to be happy, to feel in control, to be satisfied, concentrate, and to feel useful); spiritual wellbeing (with a higher prevalence of uncertainty, lower engagement in individual spiritual activities, spiritual changes, positive changes in life, sense of hopefulness, engagement in group religious activities, and sense to have a purpose); and physical health (with more prevalence of sleep changes, fatigue, appetite, and pain).

Sub-Domains of QoL

West et al⁴⁰ interviewed nine caregivers (mainly romantic partners) of people living daily with CP revealing four principal themes of family changes. The themes were as follows: family losses, life changes, emotional impacts, and future plans' concerns. The first one, family losses, incorporated in the financial and social implications sub-theme, referred to the economic consequences that might move from a minor inconvenience to a catastrophizing life-changing and changes in social and family relationships and activities. Specifically, the family reported lower connections with the other member of their family (eg, parents, children, siblings, aunts, and uncles) and friends and a decreased engagement in social activities. The authors also reported that the lack of social connections experienced by families with one of the members having CP was linked closely to friendships loss. Participants explained that friendships and social interactions were intrinsically linked. For example, the inability to attend social events, such as birthdays and dinners, eventually led to decreased invitations to social activities, which may cause social exclusion. The second theme, life changes, referred to a significant transformation in family roles, relationships, and career prospects within the family readaptation. In particular, role reversals between family members, lower ability to work and take care of their family, including the ill partner, and changes in their emotional and sexual relationships are the prevalent issues enhanced. The last two themes were emotional impacts and concerns about future plans. The emotional impacts referred to self-blame, anger, and fear experienced by the partners. Often, caregivers experience negative emotions associated with CP of their ill partner.

Consistently, caregivers tend to blame the pain for the changes and the deep transformation it caused to their family. Moreover, they disclosed how they felt guilty when they became frustrated or overwhelmed and wanted to have a moment to respite from the pain. On the other side, caregivers reported concerns about the outcomes of illness, the related future plans, and their ability to deal with CP of the ill partner.

Although CP has been demonstrated to affect caregivers' QoL negatively, some protective factors may reverse its negative impact. For example, Kizza et al³⁹ highlighted that positive adaptation and fewer financial concerns could improve caregivers' QoL. Likewise, a higher caregivers' knowledge about pain and self-efficacy for cancer pain management has been demonstrated to be the main determinants for their better QoL. Conversely, in the absence of these protective factors, a poorer caregivers' QoL was explicitly found in the domain of burden (determined by the impact of caregiving on physical wellbeing, patient's pain level, self-efficacy for cancer pain management), disruptiveness (determined by the impact of caregiving on physical wellbeing), and social support perceived (determined by hours of caregiving in a week). See Table 2.

A Systemic and Integrated Perspective

Although the disease is a family concern²⁰ and the experience of CP is determined by the synergic interconnection of biopsychosocial factors,^{18,19} studies that analyze the impact of CP considering the perspective of both patients and their caregivers is still in infancy.

Overall, studies⁴²⁻⁴⁶ retrieved revealed an impairment in the general domains of both patients' and caregivers' QoL. However, all these studies mainly investigated the impact of the pain experience in patients' and caregivers' QoL separately, with little attention on the reciprocal influence between their QoL. Also, only a few of them investigated the impairment in the specific areas of QoL (eg, daily activities, lifestyle changes, burden, emotional distress)^{42,46} and the bidirectional influence between patients' and caregivers' QoL.⁴³⁻⁴⁵ See Table 3.

Table 2 Descriptive Characteristics of the Studies Included on Caregivers' Perspective

Authors, Year	Study Design	Participants [†] n, M (SD)	Type of Chronic Condition	Question Relevance	Measures of QoL	Main Results
Kizza & Muliira, 2020	Cross-sectional (quantitative design)	284, 36 (13.8)	Cancer (NS)	Family	CQoL-I-C	The key determinants of better overall caregivers' QoL were their knowledge and self-efficacy for cancer pain management. Burden, disruptiveness, and support were the most afflicted areas damaged of caregivers' QoL; conversely, positive adaptation and lower financial concerns enhanced their QoL.
West et al, 2012	Cross-sectional (qualitative design)	9, NE	NS	Family	Interviews	The impact of CP is extended on the entire family, resulting in physical, social, and emotional changes. Four themes were captured: family losses; life changes; emotional impact; future plans' concerns.
Ferrell et al, 1999	Quasi-experimental (quantitative design)	231, 21-86	Different cancer syndromes: Lung, Others (NS), Breast, Prostate, Pancreatic, Colorectal, Myeloma, Liver, Bladder, Ovarian, Renal, Melanoma, Uterine/Cervical, Oesophageal	Family	QoLFT	The impact of CP is extended on the entire family, resulting in poorer scores on all caregivers' QoL domains (social, psychological, spiritual, and physical well-being).

Note: [†]with chronic pain.

Abbreviations: NE, not estimable; NS, not specified; CP, chronic pain; QoL, quality of life; QoLFT, Quality of Life Family Tool; CQoL-I-C, Caregiver Quality of Life-Index-Cancer.

Table 3 Descriptive Characteristics of the Studies Included on Patient–Caregiver Perspective

Authors, Year	Study Design	Participants [†] n, M (SD)	Type of Chronic Condition	Question Relevance	Measures of QoL	Main Results
De Laurentis et al, 2019	Cross-sectional (quantitative design)	76 (38 dyads), 58.5 (13.4) patients 54.4 (14.8) caregivers	Different cancer syndromes: Breast, Gastric, Head/Neck Lung, Bones, Dermatologic, Gynecologic, Genitourinary, Hodgkin's Cancer (NS)	Family, Emotional Distress	<ul style="list-style-type: none"> • DT • BEES • BLRI-EUs 	Caregivers' distress level was predicted by patients' pain intensity, caregivers' emotional problems and patients' pain intensity.
Izzo et al, 2019	Cross-sectional (quantitative design)	26 (15 patients), 60.7 (9.5) patients 48.07 (16.07) caregivers	Cancer (NS)	QoL, Family, Burden	<ul style="list-style-type: none"> • EORTC-QLQ-C30 • OARS • ZBI 	CP negatively affected the patients' QoL and their functionality extending this impact also to the family environment. Functional capacity positively correlated with caregivers' overload.
Rigoni et al 2016	Cross-sectional (quantitative design)	60 (30 dyads), 56.6 (NE) patients 45.4 (NE) caregivers	Head and Neck Cancer	QoL, Family	<ul style="list-style-type: none"> • EORTC-QLQ-C30 • ADL • CSI 	Patients and caregivers demonstrated a similar impairment in all their QoL domains (physical health, psychological well-being, daily activities, social activities, changes in health, and overall health).
Ojeda et al, 2014	Cross-sectional (qualitative design)	361 (325 patients), 56.5 (15.2) patients 53.4 (20.1) caregivers	Cancer (NS)	Family, Employment status	Interviews	Both patients and caregivers reported a negative experience of CP on their QoL (daily activities limitations, sadness, anxiety, economic problems, job loss, sleep disturbances, modification in leisure activities).
Kowal et al, 2012	Cross-sectional (quantitative design)	318 (238 patients) 47.1 (9.8) patients 48.7 (10.9) caregivers	NS	Family, Burden, Functionality, Depression, Attachment	<ul style="list-style-type: none"> • SPBS • BCOS-R • FLS • PHQ-9 	Positive correlations between caregivers' burden and patients' anxiety attachment, caregivers' burden and patients' depressive symptoms were demonstrated.

Note: [†]with chronic pain.

Abbreviations: NE, not estimable; NS, not specified; CP, chronic pain; QoL, quality of life; EORTC-QLQ-C30, European Organization for Research and Treatment of Cancer – 30-item Quality of Life Questionnaire; DT, distress thermometer; BEES, balanced emotional empathy scale; BLRI-EUs, Barrett-Lennard Relationship Inventory - Empathy Understanding subscale; OARS, Older Americans Resources and Services; ZBI, Zarit Caregiver Burden Interview; FLS, Functional Limitations Scale; SPBS, Self-Perceived Burden Scale; BCOS-R, Bakas Caregiving Outcomes scale-Revised; PHQ-9, Patient Health Questionnaire-9; ADL, activities of daily living; CSI, caregiver strain index.

Sub-Domains of QoL

The principal sub-dimensions of QoL (ie, daily activities, lifestyle changes, burden, emotional distress) analyzed could be categorized into QoL's social and psychological domains, respectively. Specifically, regarding *daily activities*, Izzo et al⁴² revealed that men, compared to women with cancer-related CP, had a significantly lower degree of independence from their caregivers, mainly in some instrumental (eg, inability to clean the house or perform other housekeeping activities, the need for assistance when shopping) and physical (eg, the need of assistance with eating or maintaining personal hygiene) ones. In addition, the condition of co-dependence on their caregiver increased (from mild to severe) caregivers' *burden*, which in turn may have led to decreased instrumental activities in them, as demonstrated.⁴² Moreover, the *lifestyle changes* due to living with an ill partner negatively affected the caregivers' QoL and significantly increased their *perceived stress*.⁴⁶ Also, Rigoni et al⁴⁶ stressed that the caregivers' stress levels related to taking care were mainly related to their feeling of incapacity, personal plans' changes, and sleep disorders.

A Co-Dependence Effect Behind Patients' and Caregivers' QoL

Studies retrieved do not consider the dyad or the family as the unit of analysis, even though illness is demonstrated to cause an in-depth transformation in the family context and reverberated on all actors involved.^{20,21} Besides this matter of fact, studies seem to suggest a *co-dependence effect* in the pain experience and related QoL between patient and caregiver operating at a physical and psychological level. For example, De Laurentis et al⁴⁵ demonstrated a positive association between the patients' pain experience and the caregivers' emotional distress. Specifically, the authors showed that a higher caregivers' emotional distress is associated with a higher CP experience in cancer patients across four subcategories: sensory, affective, evaluative, miscellaneous. They also reported that caregivers' emotional distress was modulated by the quantity of their personal and social problems: a higher level of burden was observed in caregivers more likely to present depression symptoms, fear, irritability, sadness, and loss of interest in daily activities.

Furthermore, the patients' perceived pain seems to play a central role in affecting the caregivers' emotional burden and distress, as highlighted by Schultz et al⁴⁷ Kowal et al⁴⁴ demonstrated a similar trend. The authors underlined that patients with CP who perceived themselves as a burden to their significant other (eg, romantic partner) were more likely to be insecure and dependent on them and showed more anxiety and depressive symptoms. Thus, the patients' emotional instability adversely influenced the level of distress in caregivers and vice versa.

Nevertheless, patients' and caregivers' perceptions of this influence might not always be concordant. Ojeda et al⁴³ pointed out that patients frequently feel sad and anxious due to the limitation in their daily activities and job performance caused by pain. They also perceived that their pain only moderately impacted their family and leisure activities. Conversely, caregivers considered that the "experience of pain in their loved one" affected more deeply the family system reporting sleep disturbances and modification in leisure activities as the main factors of its impact. Overall, the patients' pain perception might be improved or reduced by how CP is experienced in the family context and vice versa.

Discussion

The current narrative review qualitatively synthesized the impact of cancer-related CP on QoL, adopting a holistic and threefold vision (patients, caregivers, and patient-caregiver perspective) to provide a more comprehensive analysis of the cancer pain experience. While the role of healthcare professionals in pain management is more straightforward,^{48,49} family is often underrepresented as an important source of care in this process; therefore, our goal was to contribute to filling in this gap in the literature.

Overall, the evidence collected pointed out that CP experience radically impaired all domains of patients' and caregivers' QoL (physical, emotional, functional, social, and/or family wellbeing).

However, the evidence accumulated pointed out two main theoretical and methodological issues that should be addressed.

At first, studies retrieved emphasize the importance of considering a bidirectional perspective (patient-caregiver) to understand better the pain experienced through the disease pathway and its consequences on patients' and caregivers' QoL. The patients' pain perception might be improved or reduced by how CP is experienced in the family context and vice versa. For example, the presence of a supportive and collaborative partner that acts as a primary caregiver has been

demonstrated to be associated with a reduction of pain perception and emotional distress in chronic lymphocytic leukemia patients,⁵⁰ metastatic,⁵¹ and nonmetastatic breast cancer patients.⁵² Furthermore, the burden of care may cause caregivers a critical physical, emotional, and social imbalance that drastically reduces their QoL and may exacerbate patients' pain experience. Generally, caregivers' emotional distress may be higher when the dependency of their ill partner increases in correspondence to the deterioration in their autonomy and functionality.²⁰ These results suggest a *co-dependence effect* in the pain experience and related QoL between patient and caregiver. Also, it seems that social and relational determinants play a pivotal role in coping with adversity and promoting positive psycho-emotional wellbeing and health.^{21,53,54} This interpretation is coherent with STM theory,²² which explains how romantic partners' behavioral and emotional reactions are strictly interconnected. The STM theory highlights the role of *dyadic psycho-behavioral patterns* in the reaction to the stress events, such as CP and its management. Also, outcomes from dyadic (or family) relationships depend on the two (or more) individuals' characteristics; for that reason, a dyadic (or family) analysis should be implemented in order to investigate the bidirectional effect from one (or more) individual(s) to another (or others) and vice versa.^{54–58}

Secondly, according to the biopsychosocial paradigm,^{18,19} illness is determined by a synergic interconnection between physical, psycho-emotional, and social factors. For this reason, the interdependence and co-influence of each domain and sub-domain of QoL should be considered. Specifically, impairment in one domain or each specific factor may affect another one (domain or sub-domain) and vice versa, modulating the experience of CP and its related features (in terms of increasing or reduction) in patients, extending the impact also in the family context. However, most of the studies retrieved did not consider and measure the interconnection between each domain and sub-domain of patients' and caregivers' QoL. Hence, a holistic and multidimensional approach of the cancer-related CP and its impact on both patients' and caregivers' QoL is still needed, in which the interconnection between physical, psychological, and social factors should be analyzed.^{59–61} This approach may boost cancer pain management and related decision-making processes about care options.

Concluding, we argued that relational factors play a pivotal role in coping with adversity and promoting positive psycho-emotional wellbeing and health in cancer patients with CP. These latter elements may shape the experience of pain and/or support patients during the active phase of the treatments, survivorship, and decision-making process. Therefore, it would be beneficial that clinical and psychological interventions for managing cancer-related CP should consider both patients and significant others (eg, romantic partner).^{62–64} Indeed, a stable and caring relationship for assistance with responsibilities is immensely beneficial^{54,65,66} since they may promote not only better strategies to cope with adversity but also adjustment and a better QoL.^{21,53,54} For that reason, increasing awareness and knowledge about all physical and psychosocial factors involved in cancer pain and how cancer pain affects both patients' and caregivers' QoL is of crucial importance as it serves to guide all healthcare professionals for better cancer pain management.

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Disclosure

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