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Systematic Review

Nutrition/Dietary Supplements and Chronic Pain in Patients with Cancer and Survivors of Cancer: A Systematic Review and Research Agenda

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Background: Chronic pain is one of the most often seen, but often undertreated, sequelae in survivors of cancer. Also, this population often shows significant nutritional deficiencies, which can affect quality of life, general health status, and even risk of relapse. Given the influence of nutrition on brain plasticity and function, which in turn is associated with chronic pain in the population with cancer, it becomes relevant to focus on the association between pain and nutritional aspects in this population.

Objective: To identify relevant evidence regarding nutrition and chronic pain in patients with cancer/survivors of cancer.

Study Design: Systematic review.

Methods: PubMed, Embase, and Web of Science were systematically searched for interventional and experimental studies that included patients with cancer /survivors of cancer with chronic pain, a nutrition-related observation/examination, and a pain-related outcome. Studies that complied with the inclusion and exclusion criteria were screened for methodological quality and risk of bias by using the Qualsyst (standard quality assessment criteria for evaluating primary research) tool.

Results: The 2 included studies entailed uncontrolled trials which examined different nutritional supplements usage in various patients with cancer (breast, gastrointestinal and gynecological cancers). One study evaluated the effects of vitamin C, but did not report a change in pain outcomes. The other study, looking at the nutritional supplements glucosamine and chondroitin, found an improvement in pain after 12- and 24 weeks.

Limitations: The limitations to the generalization of these results include the insufficient amount of eligible studies and diversity in therapeutic interventions and participant groups.

Conclusion: The association between nutrition and chronic pain in patients with cancer / survivors of cancer is not well documented. The available studies are uncontrolled, and are therefore limited to draw firm conclusions. Additional research is highly needed, and a research agenda is proposed within this paper.

Key words: Survivors of cancer, chronic pain, nutrition, diet

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A patient with cancer is a person who is receiving medical treatment for a malignant growth or tumor. A survivor of cancer is defined as a person who has been diagnosed with cancer but has finalized his/her primary treatment (except from maintenance therapy, like immune and

hormone therapy) and has no mark of active disease (1). Both groups (patients with cancer and survivors of cancer) struggle with various cancer-related problems.

Pain is one of the primary and most troublesome symptoms related to cancer and depending on the disease stage, it affects up to 40% to 70% of the cancer (survivor) population (2). Pain might occur because of the tumour itself or related treatments (i.e., anticancer treatments like chemotherapy, radiotherapy and surgery) or because of comorbid diseases (3). With earlier diagnosis and improvements in treatment, there are more patients with cancer who are living longer (1,4). Therefore, over the last 40 years, the population of survivors of cancer has increased substantially (1). The development of chronic pain is also one of the most often seen sequelae in the survivor of cancer population (5). Chronic pain is described as pain which persists over the usual tissue healing time, or pain which maintains over 3 to 6 months (6). Chronic severe pain, which interferes with functioning, is seen in approximately 5% to 10% of survivors of cancer in the long term and reaches up to even 40% in the early posttreatment phase (first few years after treatment) (7). Currently, pharmacological treatment is the standard approach for cancer-related pain (8). Although guidelines for assessing and managing pain in patients with cancer exist, pain management in clinical settings is often suboptimal and secondary to other cancer-related treatments, leaving many people undertreated (9).

Besides pain problems, people with cancer and survivors of cancer often show significant nutritional deficiencies which crucially affect their quality of life (10). Nutritional requirements change for most people throughout the stages of cancer treatment and survivorship, leading to the need to account for this through dietary changes or dietary supplements (11). Even before treatment initiates, cancer may lead to profound metabolic and physiological changes that may affect the nutritional requirements for protein, carbohydrate, fat, vitamins, and minerals (11). In addition, all of the crucial cancer treatment modalities (surgery, radiation, and chemotherapy) may remarkably affect nutritional needs, change normal eating habits, and adversely influence how the body digests, absorbs, and utilizes food (11). In general, the relationship between nutrition and chronic pain has been merely partially investigated (6). However, it has been proposed that nervous and immune system sensitization can mediate the relation between a poor nutrition status and chronic pain (6).

Even though feeding is a major component of life, it is just lately that the influence of nutrition on brain plasticity and function has been investigated, showing that specific nutrients (like curcumin and salmon) are significant modifiers of brain plasticity and may have an influence on the central nervous system's health and disease (12). Sensitization of the nervous system, brain perception, and psychosocial factors play a crucial role in the persisting pain experience (13). Given the role of the central nervous system and central sensitization in cancer-related pain, it becomes relevant to focus on the association between pain and nutritional aspects in this population (14-16). Moreover, poor eating behaviors were discovered to be highly prevalent in patients with chronic pain who experienced long-term opioid therapy (17), and a recent meta-analysis found that nutritional interventions (such as altered dietary pattern [vegan, vegetarian, Mediterranean diet], or altered specific nutrient intake [reducing total fat intake, changes in fiber/protein intake]) reduce pain scores significantly in patients suffering from chronic (non-cancer) pain problems (13). This supports the idea that dietary factors may be useful for pain management in cancer-related pain as well (12).

There is increased attention on dietary and nutritional factors related to chronic pain, not only for abdominal pain, but also for chronic (somatic) pain disorders including postcancer (18). Because of the importance of both pain and nutritional aspects in survivors of cancer and the increasing focus on the link between nutritional factors and chronic pain, it becomes relevant to investigate the mutual association between pain and nutrition in this population. To date, no clear literature overview exists on the relation between chronic pain and nutrition in patients with cancer/ survivors of cancer. This is an important gap in the scientific literature, as such a systematic overview can assist clinicians and researchers working in the field of survivors of cancer. Therefore, the aim of this systematic review is to identify relevant evidence regarding the possible association between dietary and nutritional factors and chronic pain in patients with cancer/survivors of cancer. This systematic review can then provide guidance for future research and clinical implementations in this field.

Methods

This systematic review was conducted following the Preferred Reporting Items for Systematic review and Meta-Analysis (PRISMA) guidelines (19) (Appendix A). The review protocol was registered in the PROSPERO database (registration No. CRD42019126630).

Search Strategy

This study was conducted to identify published studies investigating the association or interaction between nutrition (i.e., behavioral and dietary) and chronic pain symptoms in patients with cancer/ survivors of cancer. To identify relevant studies, a systematic search in PubMed, Embase and Web of Science was conducted by using a comprehensive search string. In PubMed, the search strategy was based on Title/ Abstract (TIAB) for all terms and Medical Subject Headings (MeSH) terms for some terms. For other databases, the search strategy was based on Topic and, Title and Abstract in Web of Science and Embase, respectively. Additionally, wildcards were used in all databases for plural, other spelling, and to cover British and American English equivalents. For all databases, the used search terms and the detailed search strategy can be found in Appendix B.

Eligibility Criteria

Databases were searched until January 2020 (first search: February 25, 2019; last update: January 16, 2020). More detailed information of eligibility criteria can be found in Table 1.

Table 1. Eligibility criteria

Study Selection/ Risk of Bias Assessment:

Study selection was carried out by 2 researchers independently (STY and ÖE). After checking for duplicates in Endnote (Clarivate Analytics, Philadelphia, USA), Rayyan (Qatar Computing Research Institute, Data Analytics, Doha, Qatar) was used to screen the papers for eligibility.

In a first step, titles and abstracts were screened for eligibility. If the study's eligibility was ambiguous based on title and abstract, it was included for the next step of study selection, i.e., the full-text screening for inclusion and exclusion criteria. Additionally, the reference lists of eligible studies and previous relevant systematic reviews (backward search) were screened to find relevant studies, whereas the "cited by" function in the used databases was used to perform a forward search. Authors of possible eligible publications were contacted in case of doubts, missing information, or when the full text was not available. The response time from the contacted authors was determined as maximally 2 weeks. If no response was received after 2 weeks, these studies were excluded.

Risk of bias was assessed by 2 independent investigators (STY and ÖE), using the Qualsyst (standard quality assessment criteria for evaluating primary research) tool (for nonrandomized controlled trials and uncontrolled clinical trials).

Consensus meetings were arranged between the 2 researchers after each step defined above to discuss any doubts and disagreements. In case of disagreements, other members of the research team (AM, IC, and TD) were consulted for a final decision.

Data Extraction

Relevant data from eligible studies were presented in a descriptive evidence table (Table 1), including study design, sample characteristics, sample size – age – gender, description of pain, intervention, duration/ follow-up, pain measurements, analgesic use at baseline and findings.

Table 1. *Eligibility criteria*.

	Inclusion Criteria of Studies	**Exclusion Criteria of Studies**
Population	Human studies; Cancer patients and cancer survivors (i.e. former cancer patients who have finalised their primary treatment and who do not have any mark of active disease) suffering from chronic pain (i.e. at least three months)	All other studies (e.g. animal studies)
Exposure	Including at least 1 nutritional component or (behavioural) dietary intervention	Others
Comparison	Comparison between diets, comparison with healthy, pain-free people or non-comparison	Others
Outcome	Outcomes assessing pain (frequency, intensity or severity) either as a primary or secondary outcome	All other outcomes
Study types	Experimental/ Interventional (randomised, controlled, non-randomised, uncontrolled) studies, observational (cross-sectional, longitudinal, case-control, cohort, case series) studies Full text available	Non-clinical studies (review, systematic review, meta-analysis); Full text not available (abstracts, posters, letter to the editor) Methodological papers, congress proceedings
Language	English	All other languages

Results

Study Selection

In the initial search, 6,162 publications were found in total. After removing the duplicates and excluding the publications after title/ abstract review based on our eligibility criteria, 63 articles remained for full-text review. Sixty-one of the 63 articles were excluded because of irrelevant study design and/or outcome. So, finally, 2 studies (20,21) were identified for inclusion. Figure 1 illustrates the search process of eligible studies in detail.

Study Characteristics

One of the selected studies was conducted in Australia (20), and the other study in the United States (21). Both studies were uncontrolled clinical trials.

Table 2 shows the characteristics and findings of the included studies.

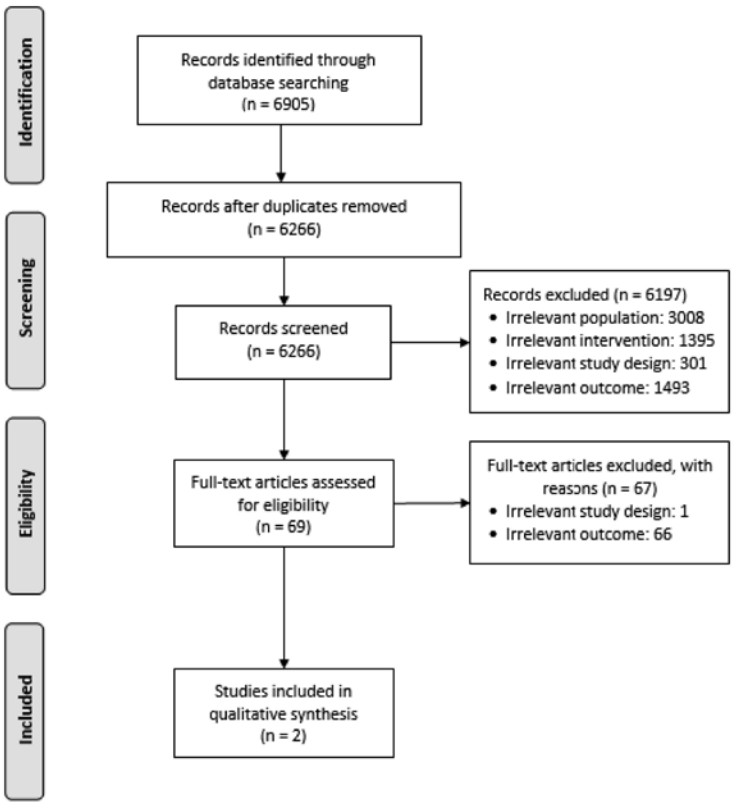

Fig. 1. *Flow chart of the systematic review examining possible associations between dietary and nutritional factors and chronic pain in cancer patients/ survivors.*

Risk of Bias

As there were 2 uncontrolled clinical trials included in the present review, the Qualsyst tool was used to assess the risk of bias of the studies. According to this tool, the study by Pinkerton et al (20) was rated 54% whereas the study by Greenlee et al (21) was rated 81% when expressed as a percentage of the maximum quality score. The details of the risk of bias assessment for each study as well as the explanation of the quality calculation of the Qualsyst score are reported in Table 3.

Patient Characteristics

One of the studies (20) included 24 patients (65% women) who had chronic pain secondary to a range of malignancies like gastrointestinal, gynecological, and breast cancers and/or their treatments. Seven of the patients dropped out of the study because of unstable pain, disease progression, loss of eligibility, and noncompliance. The ages of the patients were between 50 and 80 years.

In the second article (21), 53 postmenopausal women with breast cancer (stages I-III) were enrolled in the study. Thirty-seven of these women were retained in the study until the end. The burden of taking 6 capsules per day, uncontrolled pain, and headaches were the major reasons for dropping out. The patients' ages were between 40.7 and 83.2 years.

Pain Descriptions

The study conducted by Pinkerton et al (20) did not provide a detailed pain definition, but specified it as chronic. Greenlee et al (21) described pain as "self-reported knee and/or hand joint pain and/ or stiffness for ≥ 3 months prior to study entry; ongoing musculoskeletal pain/stiffness in hand and/or knee joints (≥ 4 on a ten-point scale assessing worst joint pain/stiffness in the past 7 days) that started or increased since initiating aromatase inhibitor therapy and has been present for ≥ 3 months."

Intervention Details

Pinkerton et al (20) investigated the efficacy of oral vitamin C as an opioid-sparing agent when used in conjunction with opioids and standard adjuvant therapy in the management of chronic pain. They applied vitamin C 1 g twice daily and orally for 2 days in the run-in phase and 3 days during the study.

The second study (21) investigated the effect of 24 weeks usage of glucosamine plus chondroitin on aromatase inhibitor-associated joint pain in women with breast cancer. Daily doses of 1500 mg glucosamine and 1200 mg chondroitin were applied. Patients could take either 2 capsules 3 times daily or 3 capsules 2 times daily. They made follow-up clinic visits at 6 weeks, 12 weeks and 24 weeks and a phone call follow-up at 18 weeks.

Information concerning who delivered the interventions and their qualification of the providers was not explained in either of the studies.

Table 2. *Study characteristics and findings.*

Study	Design	Sample Characteristics [Sample size (n), age, gender (F/M)]	Pain description	Intervention	Duration/ Follow-up	Pain Measurements	Analgesic use at baseline (%)	Findings
Pinkerton et al (20) Australia	Uncontrolled clinical trial	n = 24 (dropout = 7) Age = 50-80 years 65% Females-35% MalesHospital in or out-patients with pain secondary to various cancer patients (breast, gastrointestinal and gynaecological) and/or its treatment. Receiving opioids. BPI[1] average pain score of ≥ 3/10.	Chronic pain	Vitamin C, 1 g twice daily, orally	Following a 2-day run-in phase, participants received vitamin C for 3 days	Oral morphine equivalents (OME) dose	100% of patients	The OME dose was relatively unchanged over the study period, except for one patient who reported a 40% reduction
Greenlee et al (21) USA	Uncontrolled clinical trial	n = 53 (droupout = 16) Age: 40.7- 83.2 years 100% Females Postmenopausal Previous diagnosis of stage I-III breast cancer with no evidence of metastatic disease Current use of aromatase inhibitor for ≥ 3 months Able to speak Spanish/ English	Self-reported knee and/or hand joint pain and/or stiffness for ≥ 3 months prior to study entry Ongoing musculoskeletal pain/ stiffness in hand and/or knee joints (≥ 4 on a ten-point scale in the past 7 days) for ≥ 3 months	A daily dose of 1500 mg glucosamine and 1200 mg chondroitin	Patients were measured at baseline, 6, 12 weeks(12w) (clinic visits), 18 weeks (phone call) and 24 weeks (24w) (clinic visit)	OMERACT-OARSI[2] WOMAC[3] M-SACRAH[4] BPI[1] -Short Form	47.5% of patients	38.5% (12w, 15 of 39) and 46.2% (24w, 18 of 39) of participants met the OMERACT-OARSI criteria related to WOMAC and/or M-SACRAH. Improvement in WOMAC index for pain at 12w (mean change (mc)=-9,6) and at 24w (mc=-10.7). Improvement in M-SACRAH index for pain at 12w (mc=-14.4) and 24w (mc=-13.8). Improvement in the BPI(12w) for pain severity (mc=-0.7) and worst pain (mc=-0.9) and the BPI(24 w) for pain interference (mc=-1.0) and worst pain (mc=-1.2).

[1]Brief Pain Inventory; [2]Outcome Measure in Rheumatology Clinical Trials and Osteoarthritis Research Society International criteria; [3]Western Ontario and McMaster Universities Osteoarthritis Index; [4]Modified Score for the Assessment and Quantification of Chronic Rheumatoid Affections of the Hands

Table 3. *Risk of bias assessment of the included studies (n = 2).*

Qualsyst Quality Assessment Criteria	Pinkerton et al (20)	Greenlee et al (21)
1- Question / objective sufficiently described?	1	1
2- Study design evident and appropriate?	1	2
3- Method of subject/comparison group selection or source of information/input variables described and appropriate?	2	1
4- Subject (and comparison group, if applicable) characteristics sufficiently described?	2	2
5- If interventional and random allocation was possible, was it described?	N/A	N/A
6- If interventional and blinding of investigators was possible, was it reported?	N/A	N/A
7- If interventional and blinding of subjects was possible, was it reported?	N/A	N/A
8- Outcome and (if applicable) exposure measure(s) well defined and robust to measurement / misclassification bias? Means of assessment reported?	1	2
9- Sample size appropriate?	0	1
10- Analytic methods described/justified and appropriate?	2	2
11- Some estimate of variance is reported for the main results?	0	2
12- Controlled for confounding?	1	1
13- Results reported in sufficient detail?	1	2
14- Conclusions supported by the results?	1	2
Total Sum The Qualsyst Score	12 0.54	18 0.81

The Qualsyst score has 14 questions which can be answered as "yes" (2), "partial" (1), "no" (0) and "N/A". This score is calculated as total sum ((number of "yes"(2)+(number of "no"(1)) divided by total possible sum (28-(number of "N/A"(2)) (Kmet et al., 2004).

Description of the Outcomes

Total opioid dose (oral morphine equivalents [OME], including breakthrough doses) was used as primary outcome by Pinkerton et al (20). They recorded total opioid dose daily for each run-in and study days. They used an opioid conversion application, which calculates a combination of total baseline and breakthrough opioids, to calculate daily OME dose. The Edmonton Classification System for Cancer Pain (ECS-CP) was used for pain classification.

In the study of Greenlee et al (21), the primary outcome was aromatase inhibitor-induced joint pain. The Western Ontario and McMaster Universities Osteoarthritis (WOMAC, to measure hip and knee joint pain) index, the Modified Score for the Assessment and Quantification of Chronic Rheumatoid Affections of the Hands (M-SACRAH, to measure hand joint pain) and the Brief Pain Inventory Short Form (to measure pain interference, severity of pain and worst pain) were used to assess pain at baseline, and after 12 and 24 weeks. Additionally, the Outcome Measures in Rheumatology Clinical Trials and Osteoarthritis Research Society International (OMERACT-OARSI) criteria were used at 12 and 24 weeks to assess treatment response. The data for using pain medication was collected at baseline and each follow-up week. Moreover, joint stiffness, function, quality of life (functional/physical well-being), grip and pinch strength, and safety of aromatase inhibitor use (serum total estradiol and adverse events) were secondary outcomes, which were also measured in this study.

Adverse Events

Pinkerton et al (20) assessed adverse events daily, and reported several adverse events which were somnolence, cold sores, diarrhea, depressed level of consciousness, anxiety, and hot urine. They considered that none of the adverse events was related to the vitamin C supplementation. Also, none of these effects caused study withdrawal.

Greenlee et al (21) assessed adverse events and toxicities at every clinical encounter. The most frequently reported adverse events, which were leastways possibly related to the study drug, were grade 1 headaches, grade 1 dyspepsia, and grade 1 nausea. Nausea, heartburn, gastrointestinal disorder, headache, fatigue and an allergic reaction were reported as associated or possibly associated grade 2 toxicities.

Results for Pain

Pinkerton et al (20) found nociceptive pain as the most common ECS-CP feature. Additionally, they claimed that over the study period, the OME dose was relatively unchanged, except for one patient (with mixed nociceptive/ neuropathic pain) who reported 40% reduction.

Greenlee et al (21) showed improvements in the mean scores in the WOMAC index for pain (mean difference from baseline = -9.6, $P = 0.03$), in the M-SACRAH index for pain (mean difference from baseline = -14.4, $P < 0.01$) and in the BPI for pain severity (mean difference from baseline = -0.7, $P = 0.05$) and worst pain (mean difference from baseline = -0.9, $P = 0.02$) at week 12 when compared to baseline. Similarly, compared to baseline, there were improvements at week 24 mean scores in the WOMAC index for pain (mean difference from baseline = -10.7, $P = 0.02$), in the M-SACRAH index for pain (mean difference from baseline = -13.8, $P < 0.01$) and in the BPI for pain interference (mean difference from baseline = -1.0, $P < 0.01$) and worst pain (mean difference from baseline = -1.2, $P = 0.02$). At week 12, 38.5% of the patients (15 of the 39) and at week 24, 46.2% of the patients (18 of the 39) met the OMERACT-OARSI criteria for self-reported joint pain symptom improvements related to WOMAC and/or M-SACRAH. No differences were reported in analgesics usage from baseline to week 12 or 24.

Discussion

Pain is one of the most extensive and persistent problems that patients with cancer/survivors of cancer report (8). Yet, pain during, and particularly after, cancer treatment continues to be underestimated and undertreated (22). In the rehabilitation following cancer treatment, nutrition is one of the areas that could benefit from further attention, given its effect on brain plasticity and therefore its possible influence on pain (12,23). Therefore, this review investigated the possible association between nutrition and chronic pain in patients with cancer/survivors of cancer. To our knowledge, this is the first review analyzing this relationship. In the present systematic review, only 2 studies complied with the a priori defined inclusion criteria, underscoring the need for more research in this area. These 2 included studies entailed uncontrolled trials that examined different nutritional supplements usage in various patients with cancer (breast, gastrointestinal, and gynecological cancers). In one study, a positive effect of glucosamine and chondroitin on chronic pain was reported in women with breast cancer, while in the other study, no clinically significant benefit of vitamin C was found in pain relief in patients with cancer.

Pinkerton et al (20) did not demonstrate any meaningful change in pain-related outcomes following oral vitamin C supplementation in a range of malignancies. Yet, another systematic review reported an effect of intravenous vitamin C on cancer- and chemotherapy-related fatigue, quality of life, and nonchronic pain in patients with cancer (24). Given that hypovitaminosis C is common in patients with cancer (25,26), and anti-cancer therapies (like immunotherapy) could potentially exacerbate depleted vitamin C status in patients with cancer (27), the rationale to examine associations between chronic pain and vitamin C supplementation remains and further high-quality research is recommended.

The benefit of vitamin C is also studied for other populations unrelated to cancer. For example, a systematic review shows that perioperative vitamin C supplementation reduces postoperative pain for many diseases (like laparoscopic cholecystectomy and ambulatory otolaryngologic surgery) and shows a relative safe side-effect profile in comparison to opioids and nonsteroidal anti-inflammatory drugs usage (28). Although the vitamin C analgesic action mechanism is unclear, it is considered to be due to vitamin C's neuromodulatory functions (29). Vitamin C plays a role as a cofactor in neurotransmitters' synthesis (i.e., norepinephrine, dopamine, and serotonin) (30) and in neuropeptide hormones (like oxytocin) (31). Vitamin C also presents anti-inflammatory properties, supplying marked reductions in inflammation markers like C-reactive protein and pro-inflammatory cytokines (e.g., tumour necrosis factor, interferon, and interleukins) (27). Still, the lack of meaningful changes in pain following oral vitamin C usage on pain-related outcomes in a range of malignancies (20) refutes its use in these patients. A positive result in a proof of concept study is needed prior to initiating a randomized clinical trial.

In the included glucosamine and chondroitin study, some improvements were found for pain outcomes in women with breast cancer (21). Glucosamine and chondroitin are compounds that occur naturally in the body (32). They are the main substrates in the biosynthesis of proteoglycan, a compound necessary for the maintenance of cartilage integrity (32). Combined glucosamine hydrochloride plus chondroitin sulfate usage is common for joint pain and does not have any known side effects (33).

In the literature, there are controversial results published about glucosamine and chondroitin's influence on chronic pain in other conditions like osteoarthritis. For osteoarthritis, a recent systematic review showed that glucosamine plus chondroitin usage indicated no significant effect on pain (measured by a 10 cm visual analog scale (VAS) with a 2 cm change interpreted as clinically significant) in comparison to placebo (effect size (ES), 1.980 cm [95% CI, -0.0740 to 4.700 cm]), and claimed that oral chondroitin alone affects pain-related outcomes better compared to placebo (ES, -0.540 cm [95% CI, -0.900 to -0.0178 cm]) (34). Another review in osteoarthritis proposed that glucosamine alone and chondroitin alone do not provide a meaningful reduction in pain in the short- and long-term (35). In knee osteoarthritis, another recent review proposed that global pain evaluated by VAS (0-100 mm) showed a significant decrease after treatments with glucosamine (weighted mean difference (WMD) –7.41 mm, [95% CI –14.31 to –0.51]) and chondroitin sulfate (WMD –8.35 mm [95% CI –11.84 to –4.85]), but not when both are combined (WMD –0.28 mm [95% CI –8.87 to 8.32]) (36). However, in the same study, with respect to the WOMAC index, none of the 3 oral supplements demonstrated a remarkable benefit in the WOMAC pain subscale. Given the mixed results found for glucosamine/chondroitin in osteoarthritis, and that the study of Greenlee et al (21) is the only available study in survivors of cancer, which was limited by the uncontrolled design, we cannot draw any firm conclusions. So, further high-quality research is needed to confirm or dispute these findings.

The results of the present systematic review should be considered in the light of the following limitations. The included studies all showed relatively small sample sizes, and often did not provide a sample size or power calculation. This leaves us wondering whether they had sufficient power to draw solid conclusions. Moreover, in the vitamin C study, which also had a heterogenous sample group, blood vitamin C concentration, which is an important confounder, was not measured before or after the vitamin C administration. Other limitations of this review include the insufficient amount of eligible studies, with moderate to high quality scores (54% and 81%), and diversity in therapeutic interventions and patient groups. Furthermore, there was no information on dietary pattern or dietary intake from nutritional sources, there was paucity of data for supplement usage, and there were no studies in survivors of cancer.

The main strength of this study is that we revealed a major knowledge gap regarding chronic pain and nutrition in survivors of cancer in the literature. This review exposes the lack of evidence about this issue while providing a crucial starting point for researchers upon which to continue building knowledge. Therefore, the authors are including a research agenda, with ideas for further research.

Research Agenda (Final Considerations and Future Research Directions

This systematic review highlights an important lack of studies on the link between nutrition/dietary supplements and pain in survivors of cancer. However, when looking at this link from a broad perspective, preclinical studies indicate that poor nutrition could influence underlying mechanisms of pain in survivors of cancer through various mechanisms (18) such as vagal nerve afferent activation (37), peripheral inflammation (38), changes in gut microbiota (39), oxidative stress, necrotic cells, and tissue damage (40). Therefore, nutrition might be an important treatment target for clinicians when providing chronic pain management in patients with cancer/survivors of cancer. Yet, many questions remain to be addressed, and the following issues regarding nutritional status and interventions in patients with cancer/survivors of cancer having chronic pain require thorough scientific studying.

- The possible interactions and mechanistic pathways between nutrition and chronic pain in patients with cancer/survivors of cancer should be explored. Therefore, cross-sectional and longitudinal (observational) cohort studies are needed.
- The effectiveness of nutritional interventions on chronic pain in patients with cancer/survivors of cancer require experimental testing using randomized clinical trials. Security (causation studies) and the feasibility of such nutritional interventions for patients with cancer/survivors of cancer having pain requires testing as well.
- Once all this evidence becomes accessible, it should be fully understood and ensured to integrate them into clinics and patients' behavior.

To follow this path, first, future studies should focus on subpopulations, such as patients with head and neck cancer (41); patients with prostate cancer (42); and survivors of breast cancer (7) or survivors of childhood cancer (43) who have a high prevalence of chronic pain within the survivors of cancer population. Within these patients, the relationship between pain

outcomes and outcomes related to nutrition and diet should be investigated. Looking for the link between dietary behaviors and pain, or focussing more in detail on specific macro/micronutrients and their effect on pain could be good starting points. Moreover, clinical studies can be performed in this population by starting from nutritional and dietary interventions that are known to be associated with or effective to alter pain in populations without cancer like the Mediterranean diet (44,45), omega 3 fatty acids (46,47) or vitamin D (48,49).

Conclusion

The present systematic review investigated the relationship between chronic pain and nutrition in patients with cancer and survivors of cancer. There were only 2 uncontrolled clinical trials that met the inclusion criteria. The first study showed that glucosamine and chondroitin improved moderate-to-severe aromatase inhibitor-induced chronic joint pain in women with breast cancer, whereas the second study illustrated that vitamin C did not relieve pain in severe and more complex pain in patients with cancer (with a range of malignancies). The association between nutrition and chronic pain in patients with cancer/survivors of cancer is not well documented and requires further in-depth and high-quality investigation.

Author Contributions

All authors contributed to the concept/idea of the study. The systematic review was performed by STY and ÖE, including selecting and screening of the articles, and assessing risk of bias. AM, IC and TD were consulted to discuss any doubts and disagreements during the study. STY wrote the initial draft of the paper. The manuscript was critically reviewed and the last version of it was approved by all authors.

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Appendix A *(PRISMA 2009 Checklist)*

Section/topic	**#**	**Checklist item**	**Reported on page #**
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	1-2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	2-3
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	4
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	4
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	4
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	4
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	19-24
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	5
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	5
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	5
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	5
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I2) for each meta-analysis.	5

Appendix B

For PubMed:

Population;
("Cancer" [TIAB] OR "Neoplasms" [MeSH] OR "Neoplasm" [TIAB] OR "Neoplasms" [TIAB] OR "Tumor" [TIAB] OR "Tumour" [TIAB] OR "Tumors" [TIAB] OR "Tumours" [TIAB] OR "Cancer survivors" [MeSH] OR "Cancer survivors" [TIAB]) AND
Exposure;
(Nutrition* OR "Nutrition" [TIAB] OR Diet* OR "Diet" [TIAB] OR "Eating behavior" [TIAB] OR "Eating behaviour" [TIAB] OR "Food" [MeSH] OR Food* OR "Food" [TIAB] OR "Foods" [TIAB] OR Macronutrient* OR "Macronutrient" [TIAB] OR "Macronutrients" [TIAB] OR Micronutrient* OR "Micronutrient" [TIAB] OR "Micronutrients" [TIAB] OR "Fat intake" [TIAB] OR "Fat consumption" [TIAB] OR "Fat consumers" [TIAB] OR "Consuming fat" [TIAB] OR "Fat absorption" [TIAB] OR "Fat supplement" [TIAB] OR "Fat supplements" [TIAB] OR "Supplementary fat" [TIAB] OR "Fat supplementation" [TIAB] OR "Fat supplementations" [TIAB] OR "Lipid intake" [TIAB] OR "Lipid consumption" [TIAB] OR "Lipid supplement" [TIAB] OR "Lipid supplements" [TIAB] OR "Lipid supplementation" [TIAB] OR "Fatty acid intake" [TIAB] OR "Fatty acids intake" [TIAB] OR "Fatty acid consumption" [TIAB] OR "Fatty acids consumption" [TIAB] OR "Fatty acid consumers" [TIAB] OR "Consuming fatty acids" [TIAB] OR "Fatty acid absorption" [TIAB] OR "Fatty acids absorption" [TIAB] OR "Fatty acid supplement" [TIAB] OR "Fatty acids supplement" [TIAB] OR "Fatty acid supplements" [TIAB] OR "Fatty acids supplements" [TIAB] OR "Fatty acids supplementary" [TIAB] OR "Fatty acid supplementation" [TIAB] OR "Fatty acid supplementations" [TIAB] OR "Omega 3 intake" [TIAB] OR "Omega 3 consumption" [TIAB] OR "Absorption of omega 3" [TIAB] OR "Omega 3 supplements" [TIAB] OR "Omega 3 supplementation" [TIAB] OR "Omega 3 supplementations" [TIAB] OR "Omega 6 intake" [TIAB] OR "Omega 6 supplements" [TIAB] OR "Omega 6 supplementation" [TIAB] OR "Omega 6 supplementations" [TIAB] OR "Protein intake" [TIAB] OR "Protein consumption" [TIAB] OR "Consuming protein" [TIAB] OR "Protein absorption" [TIAB] OR "Protein supplement" [TIAB] OR "Protein supplements" [TIAB] OR "Protein supplementation" [TIAB] OR "Protein supplementary" [TIAB] OR "Supplementary protein" [TIAB] OR "Protein drink" [TIAB] OR "Amino acid intake" [TIAB] OR "Amino acid consumption" [TIAB] OR "Consuming amino acid" [TIAB] OR "Amino acid absorption" [TIAB] OR "Amino acid supplement" [TIAB] OR "Amino acid supplements" [TIAB] OR "Amino acid supplementation" [TIAB] OR "Supplementary amino acid" [TIAB] OR "Carbohydrate intake" [TIAB] OR "Carbohydrate consumption" [TIAB] OR "Consuming carbohydrate" [TIAB] OR "Carbohydrate absorption" [TIAB] OR "Carbohydrate supplement" [TIAB] OR "Carbohydrate supplements" [TIAB] OR "Carbohydrate supplementation" [TIAB] OR "Sugar intake" [TIAB] OR "Sugar consumption" [TIAB] OR "Consuming sugar" [TIAB] OR "Sugar absorption" [TIAB] OR "Sucrose intake" [TIAB] OR "Sucrose consumption" [TIAB] OR "Sucrose absorption" [TIAB] OR "Glucose intake" [TIAB] OR "Glucose consumption" [TIAB] OR "Glucose absorption" [TIAB] OR "Fructose intake" [TIAB] OR "Fructose consumption" [TIAB] OR "Consuming fructose" [TIAB] OR "Fructose absorption" [TIAB] OR "Fibre intake" [TIAB] OR "Fibre consumption" [TIAB] OR "Fibre supplement" [TIAB] OR "Fibre supplements" [TIAB] OR "Fibre supplementation" [TIAB] OR "Supplementary fibre" [TIAB] OR "Fiber intake" [TIAB] OR "Fiber consumption" [TIAB] OR "Fiber supplement" [TIAB] OR "Fiber supplements" [TIAB] OR "Fiber supplementation" [TIAB] OR "Supplementary fiber" [TIAB] OR "Starch intake" [TIAB] OR "Starch consumption" [TIAB] OR "Starch absorption" [TIAB] OR Vegetable* OR "Vegetables" [MeSH] OR "Vegetable" [TIAB] OR "Vegetables" [TIAB] OR "Fruit" [MeSH] OR "Fruit" [TIAB] OR "Fruits" [TIAB] OR "Vegans" [MeSH] OR "Vegan" [TIAB] OR "Vegans" [TIAB] OR "Vegetarians" [MeSH] OR "Vegetarian" [TIAB] OR "Vegetarians" [TIAB] OR Omnivor* OR "Omnivorous" [TIAB] OR Carnivor* OR "Carnivorous" [TIAB] OR "Meat" [MeSH] OR "Meat" [TIAB] OR "Fish" [TIAB] OR Legume* OR "Legume" [TIAB] OR "Legumes" [TIAB] OR "Spice" [TIAB] OR "Spices" [TIAB] OR "Nut" [TIAB] OR "Nuts" [TIAB] OR "Seeds" [MeSH] OR "Seeds" [TIAB] OR "Seed" [TIAB] OR "Whole grain" [TIAB] OR "Whole grains" [TIAB] OR "Dairy" [TIAB] OR "Milk" [MeSH] OR "Milk" [TIAB] OR "Soy" [TIAB] OR "Cheese" [TIAB] OR "Yogurt" [TIAB] OR "Egg" [TIAB] OR "Eggs" [TIAB] OR "Olive" [TIAB] OR "Calorie" [TIAB] OR "Calorie intake" [TIAB] OR "Caloric intake" [TIAB] OR "Energy intake" [MeSH] OR "Energy intake" [TIAB] OR "Sweetened beverage" [TIAB] OR "Soft drink" [TIAB] OR "Soda" [TIAB] OR "Alcohol" [TIAB] OR "Wine" [TIAB] OR "Caffeine" [TIAB] OR "Coffee" [TIAB] OR "Tea" [TIAB] OR "Water" [MeSH] OR "Water" [TIAB] OR "Vitamin intake" [TIAB] OR "Vitamin consumption" [TIAB] OR "Consuming vitamin" [TIAB] OR "Vitamin absorption" [TIAB] OR "Vitamin supplement" [TIAB] OR "Vitamin supplements" [TIAB] OR "Vitamin supplementation" [TIAB] OR "Vitamin drink" [TIAB] OR "Mineral Intake" [TIAB] OR "Mineral consumption" [TIAB] OR "Mineral absorption" [TIAB] OR "Mineral supplement" [TIAB] OR "Mineral supplements" [TIAB] OR "Mineral supplementation" [TIAB] OR "Mineral drink" [TIAB] OR Antioxidant* OR "Antioxidant" [TIAB] OR "Antioxidants" [MeSH] OR "Antioxidants" [TIAB]) AND
Outcome;
("Chronic pain" [MeSH] OR "Chronic pain" [TIAB] OR "Neuropathic pain" [TIAB] OR "Central nervous system sensitisation" [MeSH] OR "Central nervous system sensitisation" [TIAB] OR "Central nervous system sensitisation" [TIAB] OR "Central sensitisation" [TIAB] OR "Central sensitisation" [TIAB] OR "Peripheral sensitisation" [TIAB] OR "Peripheral sensitisation" [TIAB] OR "Cancer-related pain" [TIAB] OR "Cancer-related chronic pain" [TIAB] OR "Hyperalgesia" [MeSH] OR "Hyperalgesia" [TIAB] OR "Allodynia" [TIAB] OR "Hypersensitivity" [MeSH] OR "Hypersensitivity" [TIAB] OR "Pain sensitivity" [TIAB] OR "Persisting pain" [TIAB] OR "Persistent pain" [TIAB] OR "Post-surgery chronic pain" [TIAB] OR "Post-surgical chronic pain" [TIAB] OR "Post-operative chronic pain" [TIAB] OR "Post-mastectomy chronic pain" [TIAB] OR "Post-surgery pain" [TIAB] OR "Post-surgical pain" [TIAB] OR "Post-operative pain" [TIAB] OR "Post-mastectomy pain" [TIAB] OR "Post-treatment pain" [TIAB] OR "Post-treatment chronic pain" [TIAB] OR "Neuropathy" [TIAB] OR "Plexopathy" [TIAB] OR "Joint pain" [TIAB] OR "Arthralgia" [MeSH] OR "Arthralgia" [TIAB]) NOT ("Terminal" [TIAB] OR "End stage" [TIAB] OR "Palliative" [TIAB] OR "Hospice" [TIAB])

For Web of Science:

Population;
TS=(Cancer OR Neoplasm* OR Tumo$r)
AND
Exposure;
TS=(Nutrition* OR Diet* OR "Eating behavio$r" OR Food* OR Macronutrient* OR Micronutrient* OR "Fat intake" OR "Fat consum*" OR "Fat absor*" OR "Fat supplement*" OR "Supplementary fat" OR "Lipid intake" OR "Lipid consum*" OR "Lipid supplement*" OR "Fatty acid* intake" OR "Fatty acid* consum*" OR "Consuming fatty acids" OR "Fatty acid* absor*" OR "Fatty acid* supplement*" OR "Omega 3 intake" OR "Omega 3 consum*" OR "Absor* of omega 3" OR "Omega 3 supplement*" OR "Omega 6 intake" OR "Omega 6 supplement*" OR "Protein intake" OR "Protein consum*" OR "Consuming protein" OR "Protein absor*" OR "Protein supplement*" OR "Supplementary protein" OR "Protein drink" OR "Amino acid intake" OR "Amino acid consum*" OR "Consuming amino acid"

Appendix B *(continued)*

OR "Amino acid absor*" OR "Amino acid supplement*" OR "Supplementary amino acid" OR "Carbohydrate intake" OR "Carbohydrate consum*" OR "Consuming carbohydrate" OR "Carbohydrate absor*" OR "Carbohydrate supplement*" OR "Sugar intake" OR "Sugar consum*" OR "Consuming sugar" OR "Sugar absor*" OR "Sucrose intake" OR "Sucrose consum*" OR "Sucrose absor*" OR "Glucose intake" OR "Glucose consum*" OR "Glucose absor*" OR "Fructose intake" OR "Fructose consum*" OR "Consuming fructose" OR "Fructose absor*" OR "Fibre intake" OR "Fibre consum*" OR "Fibre supplement*" OR "Supplementary fibre" OR "Fiber intake" OR "Fiber consum*" OR "Fiber supplement*" OR "Supplementary fiber" OR "Starch intake" OR "Starch consum*" OR "Starch absor*" OR Vegetable* OR "Fruit" OR Vegan OR Vegetarian OR Omnivor* OR Carnivor* OR "Meat" OR Fish OR Legume* OR Spice OR Spices OR Nut OR Nuts OR "Seeds" OR "Whole grain" OR "Whole grains" OR Dairy OR "Milk" OR Soy OR Cheese OR Yogurt OR Egg OR Eggs OR Olive OR Calorie OR "Calori* intake" OR "Energy intake" OR "Sweetened beverage" OR "Soft drink" OR Soda OR Alcohol OR Wine OR Caffeine OR Coffee OR Tea OR Water OR "Vitamin intake" OR "Vitamin consum*" OR "Consuming vitamin" OR "Vitamin absor*" OR "Vitamin supplement*" OR "Vitamin drink" OR "Mineral intake" OR "Mineral consum*" OR "Mineral absor*" OR "Mineral supplement*" OR "Mineral drink" OR Antioxidant*) AND
Outcome;
TS=("Chronic pain" OR "Neuropathic pain" OR "Central nervous system sensiti?ation" OR "Central sensiti?ation" OR "Peripheral sensiti?ation" OR "Cancer-related pain" OR "Cancer-related chronic pain" OR Hyperalgesia OR Allodynia OR Hypersensitivity OR "Pain sensitivity" OR "Persist* pain" OR "Post-surgery chronic pain" OR "Post-surgical chronic pain" OR "Post-operative chronic pain" OR "Post-mastectomy chronic pain" OR "Post-surgery pain" OR "Post-surgical pain" OR "Post-operative pain" OR "Post-mastectomy pain" OR "Post-treatment pain" OR "Post-treatment chronic pain" OR Neuropathy OR Plexopathy OR "Joint pain" OR "Arthralgia") NOT
TS=(Terminal OR "End stage" OR Palliative OR Hospice)

For Embase:
Population;
(Cancer OR Neoplasm* OR Tumo?r) AND
Exposure;
(Nutrition* OR Diet* OR "Eating behavio?r" OR Food* OR Macronutrient* OR Micronutrient* OR "Fat intake" OR "Fat consum*" OR "Fat absor*" OR "Fat supplement*" OR "Supplementary fat" OR "Lipid intake" OR "Lipid consum*" OR "Lipid supplement*" OR "Fatty acid* intake" OR "Fatty acid* consum*" OR "Consuming fatty acids" OR "Fatty acid* absor*" OR "Fatty acid* supplement*" OR "Omega 3 intake" OR "Omega 3 consum*" OR "Absor* of omega 3" OR "Omega 3 supplement*" OR "Omega 6 intake" OR "Omega 6 supplement*" OR "Protein intake" OR "Protein consum*" OR "Consuming protein" OR "Protein absor*" OR "Protein supplement*" OR "Supplementary protein" OR "Protein drink" OR "Amino acid intake" OR "Amino acid consum*" OR "Consuming amino acid" OR "Amino acid absor*" OR "Amino acid supplement*" OR "Supplementary amino acid" OR "Carbohydrate intake" OR "Carbohydrate consum*" OR "Consuming carbohydrate" OR "Carbohydrate absor*" OR "Carbohydrate supplement*" OR "Sugar intake" OR "Sugar consum*" OR "Consuming sugar" OR "Sugar absor*" OR "Sucrose intake" OR "Sucrose consum*" OR "Sucrose absor*" OR "Glucose intake" OR "Glucose consum*" OR "Glucose absor*" OR "Fructose intake" OR "Fructose consum*" OR "Consuming fructose" OR "Fructose absor*" OR "Fibre intake" OR "Fibre consum*" OR "Fibre supplement*" OR "Supplementary fibre" OR "Fiber intake" OR "Fiber consum*" OR "Fiber supplement*" OR "Supplementary fiber" OR "Starch intake" OR "Starch consum*" OR "Starch absor*" OR Vegetable* OR "Fruit" OR Vegan OR Vegetarian OR Omnivor* OR Carnivor* OR "Meat" OR Fish OR Legume* OR Spice OR Spices OR Nut OR Nuts OR "Seeds" OR "Whole grain" OR "Whole grains" OR Dairy OR "Milk" OR Soy OR Cheese OR Yogurt OR Egg OR Eggs OR Olive OR Calorie OR "Calori* intake" OR "Energy intake" OR "Sweetened beverage" OR "Soft drink" OR Soda OR Alcohol OR Wine OR Caffeine OR Coffee OR Tea OR Water OR "Vitamin intake" OR "Vitamin consum*" OR "Consuming vitamin" OR "Vitamin absor*" OR "Vitamin supplement*" OR "Vitamin drink" OR "Mineral intake" OR "Mineral consum*" OR "Mineral absor*" OR "Mineral supplement*" OR "Mineral drink" OR Antioxidant*) AND
Outcome;
("Chronic pain" OR "Neuropathic pain" OR "Central nervous system sensiti#ation" OR "Central sensiti#ation" OR "Peripheral sensiti#ation" OR "Cancer-related pain" OR "Cancer-related chronic pain" OR Hyperalgesia OR Allodynia OR Hypersensitivity OR "Pain sensitivity" OR "Persist* pain" OR "Post-surgery chronic pain" OR "Post-surgical chronic pain" OR "Post-operative chronic pain" OR "Post-mastectomy chronic pain" OR "Post-surgery pain" OR "Post-surgical pain" OR "Post-operative pain" OR "Post-mastectomy pain" OR "Post-treatment pain" OR "Post-treatment chronic pain" OR Neuropathy OR Plexopathy OR "Joint pain" OR "Arthralgia") NOT
(Terminal OR "End stage" OR Palliative OR Hospice)