Pain prevalence and characteristics in survivors of solid cancers : a systematic review and meta-analysis

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Abstract

Purpose: The latest systematic review on the prevalence of pain in cancer survivors was published five years ago. The current review aims to provide an extended overview on the prevalence of pain, pain mechanisms, pain characteristics and assessment methods in cancer survivors.

Methods: A systematic research was conducted on 17th of April 2020 using Medline, Embase, Scopus, Web of Science and Cochrane looking at studies from 2014 to 2020. Studies had to report pain prevalence rates in cancer survivors with a solid tumour who finished curative treatment at least three months ago. Methodological quality was assessed by two independent reviewers using the Joanna Briggs Institute quality appraisal tool. Characteristics of the included studies, participants and reported pain prevalence rates were extracted. The reported prevalence rates of the individual studies were pooled within a meta-analysis. Meta-regressions were performed to identify possible determinants of the pooled pain prevalence.

Results: After deduplication, 7,300 articles were screened, after which 38 were included in the meta-analysis. The pooled pain prevalence was 47% (95%CI 39 - 55), with a heterogeneity of 98.99%.

Conclusion: Evidence with a low risk of bias suggests that nearly half of cancer survivors report pain after completing curative treatment at least three months ago. However, substantial unexplained heterogeneity warrants cautious interpretation of these results. Meta-regression could not identify influencing factors explaining the high heterogeneity.

Keywords: Cancer-related pain, cancer survivor, pain prevalence, systematic review, meta-analysis, meta-regression

Abbreviations

EORTC -	European Organisation of Research and Treatment of Cancer
QoL -	Quality of Life
NRS -	Numeric Rating Scale
IASP -	International Association for the Study of Pain
PRISMA -	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
RCT -	Randomized Controlled Trial
CIPN -	Chemotherapy-Induced Peripheral Neuropathy
VH -	Vincent Haenen
TdB -	Tom De Baerdemaecker
ME -	Margaux Evenepoel
ADG -	An De Groef
JBI -	Joanna Briggs Insititute
VAS -	Visual Analogue Scale
BPI -	Brief Pain Inventory
NPSI -	Neuropathic Pain Symptom Inventory
EORTC-QLQ-C30 -	European Organization for Research and Treatment for Cancer Quality of Life Questionnaire

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Introduction

Cancer remains a major cause of morbidity and mortality worldwide. With 19.3 million new cases of cancer and 10.0 million cancer-related deaths recorded worldwide in 2020, it is one of the leading causes of death.[1] Although cancer incidence has increased, mortality rates have generally been declining since the 1990s, resulting in more cancer survivors.

Several definitions of cancer survivorship exist.[2–4] This review utilized the European Organisation of Research and Treatment of Cancer (EORTC) Cancer Survivorship Task Force which defines cancer survivorship as “patients who have completed their primary treatment (maintenance treatment can be ongoing)”.[5]

These cancer survivors experience a wide range of side effects, often associated with poorer quality of life (QoL).[6, 7] Cancer-related pain is frequently reported by cancer survivors. A systematic review published in 2016 investigated the prevalence of pain in cancer patients and cancer survivors, in studies published from 2005 to 2014.[8] Van den Beuken-van Everdingen et al. concluded that 39.3% of all cancer survivors experience pain after finishing curative cancer treatment. In addition, pain was rated as moderate to severe by 27.6% of the cancer survivors suffering from pain. Moderate pain was defined as pain ranging from five to six on a numeric rating scale (NRS) from 0-10, whereas severe pain was defined as pain equal or above seven on the NRS.[8, 9] Although the results of this systematic review offer valuable information, clinically relevant insights related to pain during and after cancer treatment could perhaps be improved. In addition, research on pain and cancer has improved substantially since 2014, therefore an update might be due.

The importance of identifying the most dominant pain mechanism has become increasingly present in musculoskeletal pain research. It is postulated that mechanism-based pain management could provide more effective analgesia.[10–12] Four pain mechanisms, defined by the International Association for the Study of Pain (IASP), are widely used in pain research. *Nociceptive pain* is defined as ‘pain due to activation of the peripheral receptive terminals in response to noxious and potentially noxious chemical, mechanical or thermal stimuli’ or as ‘pain arising from actual or threat of damage to non-neural tissue due to the activation of nociceptor’.[13] *Neuropathic pain* is known as pain arising as a direct consequence of a lesion or disease affecting the somatosensory system.[14, 15] *Nociplastic pain* is defined by the IASP as pain that arises from altered nociception, despite that there is no clear evidence of actual or threatened tissue damage causing the activation of nociceptors or evidence for

disease or lesion of the somatosensory system causing the pain.[16] Lastly, the term *mixed pain* can be utilized when multiple pain mechanisms are present simultaneously.[17] Limited amount of studies are available reporting on the prevalence of different pain mechanisms in cancer survivors and currently no systematic overview is available.[18, 19] It is not fully known to which extent nociplastic or mixed pain is present in this population. In addition, even though guidelines have been proposed to assess pain after cancer it seems they are not well adopted.[17] It appears that different criteria and assessment methods are used to assess and define pain. To our knowledge, these different criteria for assessing pain were not considered in previous studies and systematic reviews.

The introduction of a mechanism-based approach to pain, combined with the increased amount of published research on the prevalence of pain during and after cancer treatment warrants a new overview on this topic. Therefore, the goal of this systematic review was to summarize pain prevalence rates for survivors of different solid cancer types who finished curative treatment. In addition, and whenever available, prevalence rates of the different pain mechanisms were presented together with the different pain characteristics and assessment methods for pain.

Methods

This systematic review adhered to the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement (PRISMA), and was registered with the International Prospective Register of Systematic Reviews on 11 November 2020 (PROSPERO reference CRD42016038870).[20]

Search strategy

A systematic search of the literature was conducted on April 17th 2020 for studies published from 2014 and onwards using the databases Medline via Pubmed, Embase, Scopus, Web of Science and Cochrane. Keywords used can be found in Table 1. Search strategies were adapted to the particular database. Grey literature and ongoing studies were not included in the systematic search. Detailed description of the used search strategies can be found in Appendix 1.

Key words	**Medline – MeSH Headings**
Pain	Pain
AND	
Epidemiology **OR** prevalence	Epidemiology Prevalence
AND	
Cancer **OR** neoplasm **OR** neoplastic **OR** tumor **OR** tumour **OR** tumoral **OR** tumoural **OR** tumourous **OR** tumorous **OR** metastatic **OR** metastasis **OR** oncology **OR** oncological **OR** oncologic	Neoplasms Neoplasm metastasis

Table 1: Keywords included in the search strategy for all four databases.

Study selection

Inclusion criteria were defined as followed: original prospective studies (cohort, cross-sectional and randomized controlled trails (RCTs)), studies published between 2014 and 2020, studies that included cancer survivors who finished curative treatment with a minimum of three months after last (adjuvant) treatment modality (endocrine therapy excluded) and from which prevalence data on cancer-related pain could be extracted or calculated, and adult study populations. Included articles had to be published in English, Dutch, French or German. Articles were excluded if they did not differentiate between patients with and without cancer (mixed population), or reported pain during or from childhood cancer (age below 18 years at time of diagnosis). Studies performed at pain clinics were excluded in order to prevent selection bias. Studies investigating advanced cancer stage (stage IV), metastases or palliative status were excluded as these stages are associated with a wide range of

comorbidities. In addition, studies on patients treated with a non-curative intent were excluded as treatment can be presumed as ongoing. Studies that included the following were also excluded: patients suffering from hematological malignancies such as leukemia, lymphoma or myeloma; patients residing in nursing homes; cancer patients reporting cancer-(related)pain before cancer diagnosis or treatment. Studies investigating chemotherapy-induced peripheral neuropathy (CIPN) were excluded as CIPN was considered to be a condition with predominantly sensory symptoms with pain not always being a significant presenting symptom.[21] If prevalence data were pooled (e.g. no pain and mild pain were grouped together) or could not be calculated, studies were excluded. RCTs including cancer survivors that did not provide baseline prevalence data were excluded. Retrospective studies, conference proceedings, editorials, letters, reviews, case studies, congress reports and secondary analyses were excluded. If the disease stage, prevalence data or other data were not present or were unclear, the respective authors were contacted. Studies were excluded if this information remained unclear after contacting the authors.

One reviewer (VH) undertook the searches. Duplicates were identified using Endnote and Rayyan, and were excluded by the same reviewer. Three reviewers independently screened the titles (VH, TdB, ME) and subsequently the abstracts. Two reviewers (VH & ME) independently examined the full texts of the selected articles. Disagreements were discussed and resolved through consensus. A fourth reviewer (ADG) was involved when disagreements were not resolved through consensus.

Data Extraction

The first reviewer (VH) extracted all data using a digital data extraction platform (Covidence). The extracted data was checked by the second reviewer (ME). Extracted data included: author, year of publication, study design, population, continent, sample size, method of data collection (questionnaire, medical record, interview), and prevalence data. The following data regarding patient characteristics were extracted:age, sex, type of cancer, cancer stage, type of treatment, method of pain measurement, follow-up time after last treatment, type of pain, pain severity, pain prevalence and if reported the type of pain mechanism. The primary outcome was the prevalence of pain in cancer survivors at least three months after finishing their curative treatment.

Quality appraisal

Included studies were evaluated for their methodological quality using the critical appraisal tool for prevalence studies developed by the Joanna Briggs Institute (JBI).[22] Before quality appraisal, both reviewers (VH & ME) calibrated the individual criteria of the appraisal tool. The reviewers

independently appraised the methodological quality of each study. A third reviewer (ADG) was involved when disagreements were not resolved through consensus. Each item was given a score of 0 (Yes/Unclear) or 1 (No), and scores were summarized across all items to produce an overall score of quality. The overall score ranges from 0 or low risk of bias to 9 or high risk of bias. Whereas the JBI tool does not provide categories on risk of bias, the similar critical appraisal tool by Hoy et al. does provide categories on the overall score: 7–9: 'high risk of bias', 4–6: 'moderate risk of bias' and 0–3: 'low risk of bias'.[23]

Data synthesis

Before performing the meta-analysis, statistical heterogeneity was evaluated by the between-study variance τ^2, I^2 and Q statistics. In addition, heterogeneity was assessed through visual inspection of forest plots.[24] When outcomes were presented with low statistical heterogeneity, then data were pooled using a fixed-effects model. A random-effects model was adopted when outcomes had moderate or high statistical heterogeneity.[24] The Freeman-Tukey double arcsine transformation was used in an effort to normalize the distribution of the proportions and to stabilize the variance.[25] To compute the pooled estimate of the transformed values, the DerSimonian and Laird method was used.[26] Small-study effects were explored by visual assessment of asymmetry of the funnel plots and calculation of the Egger's test.[24] If a study reported multiple pain prevalence rates on one or several follow-up occasions, the highest reported prevalence rate was used.[27]

Four univariate meta-regression analyses were performed to examine potential causes of heterogeneity: cancer type (breast, lung, gynecological, rectal and prostate), cancer treatment location (localized vs. localized and systemic), pain measurement method (pain specific, not-pain specific, NRS/Visual Analogue Scale (VAS), study specific, not specified and a combination of questionnaires) and follow-up time after last treatment modality (in months: 3, 6, 12, 24, 36, 48, 60+). Analysis was performed with R statistical software version 3.6.2., using the metafor package.[28, 29]

A narrative review was performed if the included studies differed significantly in design, settings, outcome measures or if insufficient data was presented. In addition, available information on pain characteristics (severity and different pain mechanisms) and assessment methods for pain were discussed narratively.

Results

Search results

A total of 7,300 articles were retrieved, with 1.740 eligible for full-text review. The search result and screening process is shown in Figure 1. *Thirty-eight* articles were included for analysis.

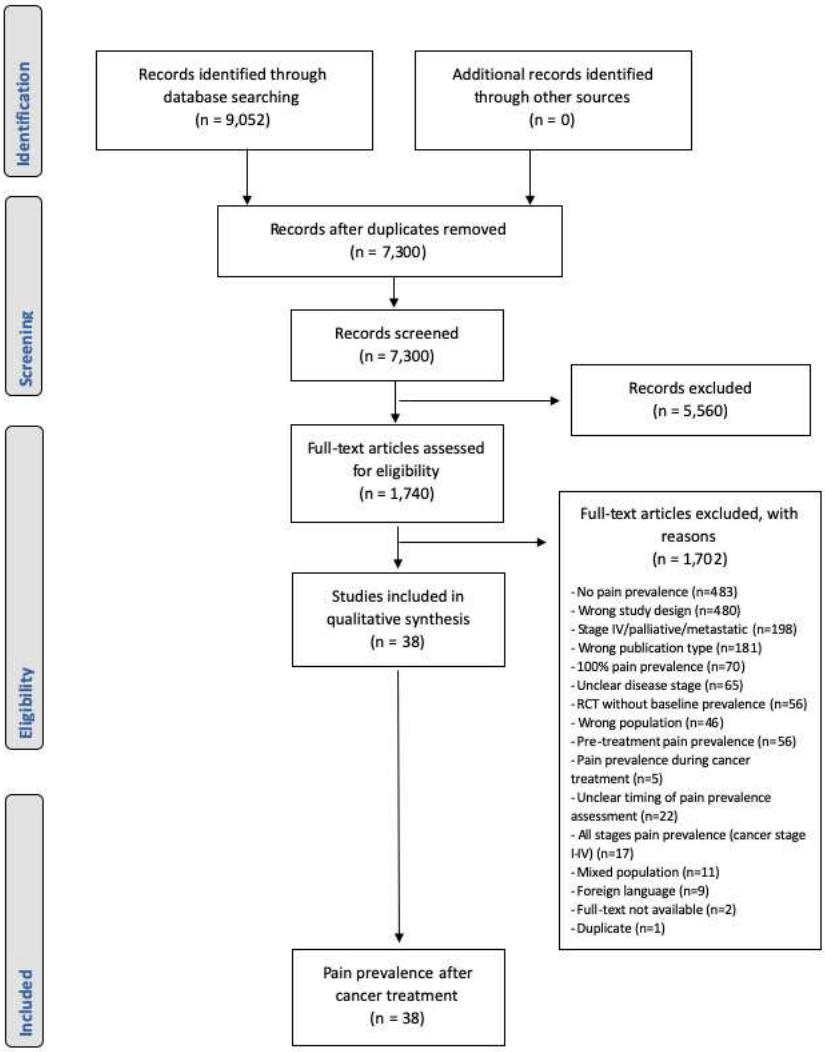

Figure 1: Flow chart

Study characteristics

A total of 14,394 participants were included for this systematic review. The prevalence of pain between the included studies ranged from 2% to 88.2% with a median pain prevalence of 50.3%. The median sample size was 186.5 (range 31 - 2,923), the median age was 59.4 (range 46.3 - 71). Follow-up periods ranged from three months to more than ten years after last cancer treatment modality. The majority of studies (94.8%) were performed in high income countries using a cross-sectional [30–47] or cohort study design [48–66] (Appendix 3).[67] Studies examining pain prevalence in breast cancer survivors were most prevalent (n=30, 80.9%, 11,996 participants).[30–34, 36, 37, 39, 40, 42, 43, 45–47, 49, 50, 53–64, 66, 68] As a result, 84.2% of studies included solely female participant. Other populations consisted of lung cancer (n=3)[41, 52, 65], gynecological cancer (n=3)[38, 48, 51], rectal cancer (n=1)[44] and prostate cancer (n=1)[35] (Appendix 3). Five studies [37, 41, 43, 48, 65] included

solely one type of cancer stage (stage 0: n=1; stage I: n=3, stage III: n =1). Six studies included only survivors of cancer stage I-II [38, 49, 53, 59, 60, 63]. All other studies (n=27) included multiple cancer stages ranging from 0 to III. All studies used a questionnaire to assess pain, with the Brief Pain Inventory (BPI) being the most utilized (23.7%).[31, 33, 41, 42, 47, 52, 60, 64, 65] Different pain definitions and criteria for assessing pain were utilized in all the included studies, see Appendix 3 for further information. Six studies [41, 44, 47, 52, 62, 66] did not specify which type of pain was researched (e.g. arthralgia, arm pain, shoulder pain). Twenty-two studies [31–33, 37, 39, 40, 43, 44, 46, 47, 49–52, 54–56, 59, 63, 64, 66, 68] reported pain severity (Appendix 3). Seven cohort studies [48, 52, 53, 55, 57, 62, 65] provided pain prevalence rates at multiple follow-up occasions. A detailed overview of all included studies can be found in Appendix 3.

Risk of bias

Among the 38 included studies, 12 studies [31, 36, 37, 41, 44, 47, 48, 50, 53, 56, 57, 66] showed a moderate risk of bias on the adapted scale by Hoy et al.[23] The remaining 26 studies showed a low risk of bias. Figure 2 shows the risk of bias assessment for the included studies. For an overview of the used criteria assessing risk of bias, see Appendix 2. Seven studies [36, 37, 41, 44, 45, 65, 66] did not include an appropriate sample frame. No study used random probabilistic sampling as a method of recruitment. Only two studies [45, 59] provided a sample size calculation or an explanation to the obtained sample size. Five studies [30, 38, 52, 54, 65] provided a detailed description of their participants (i.e. age, disease stage and comorbidities). The authors decided to mark all the included studies as unclear on whether data analyses were conducted with sufficient coverage of the identified sample. Seven studies were either unclear [30, 31, 34, 45, 46] or did not seem to use valid methods [48, 57] for the measurement of pain. Three studies [30, 31, 55] were unclear whether the measurement was performed in a standardized and reliable way. All included studies performed an appropriate statistical analysis. Seven studies [30, 31, 47, 48, 50, 53, 56] did not have an adequate response rate, or managed it appropriately.

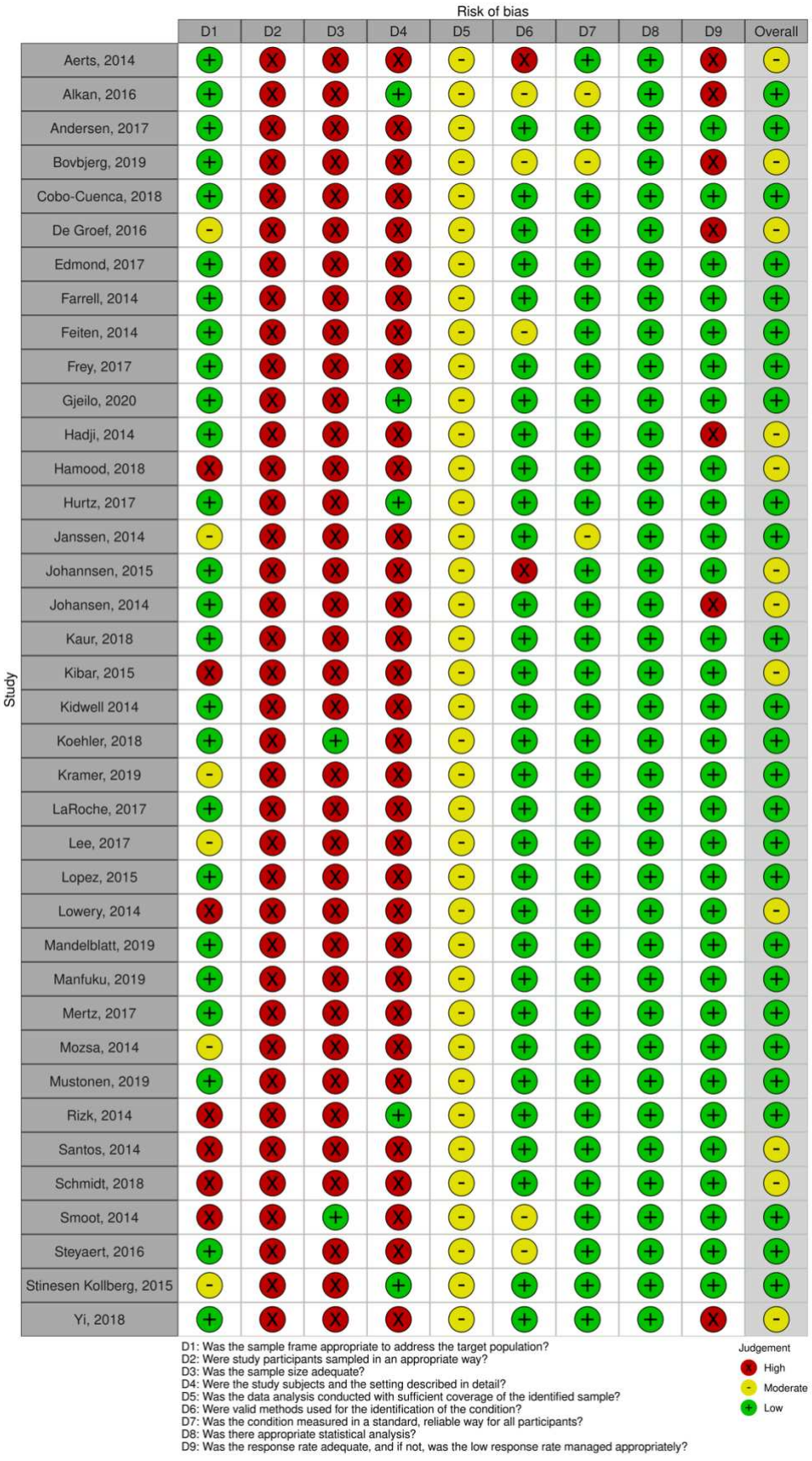

Figure 2: Risk of bias assessment

Prevalence of pain after cancer treatment

Using the highest reported pain prevalence rates, our meta-analysis resulted in a pooled pain prevalence of 47% (95% CI 39 - 55%) with a heterogeneity of (I^2=98.99%) (Figure 3). Pain prevalence rates per population can be found in Figure 3.

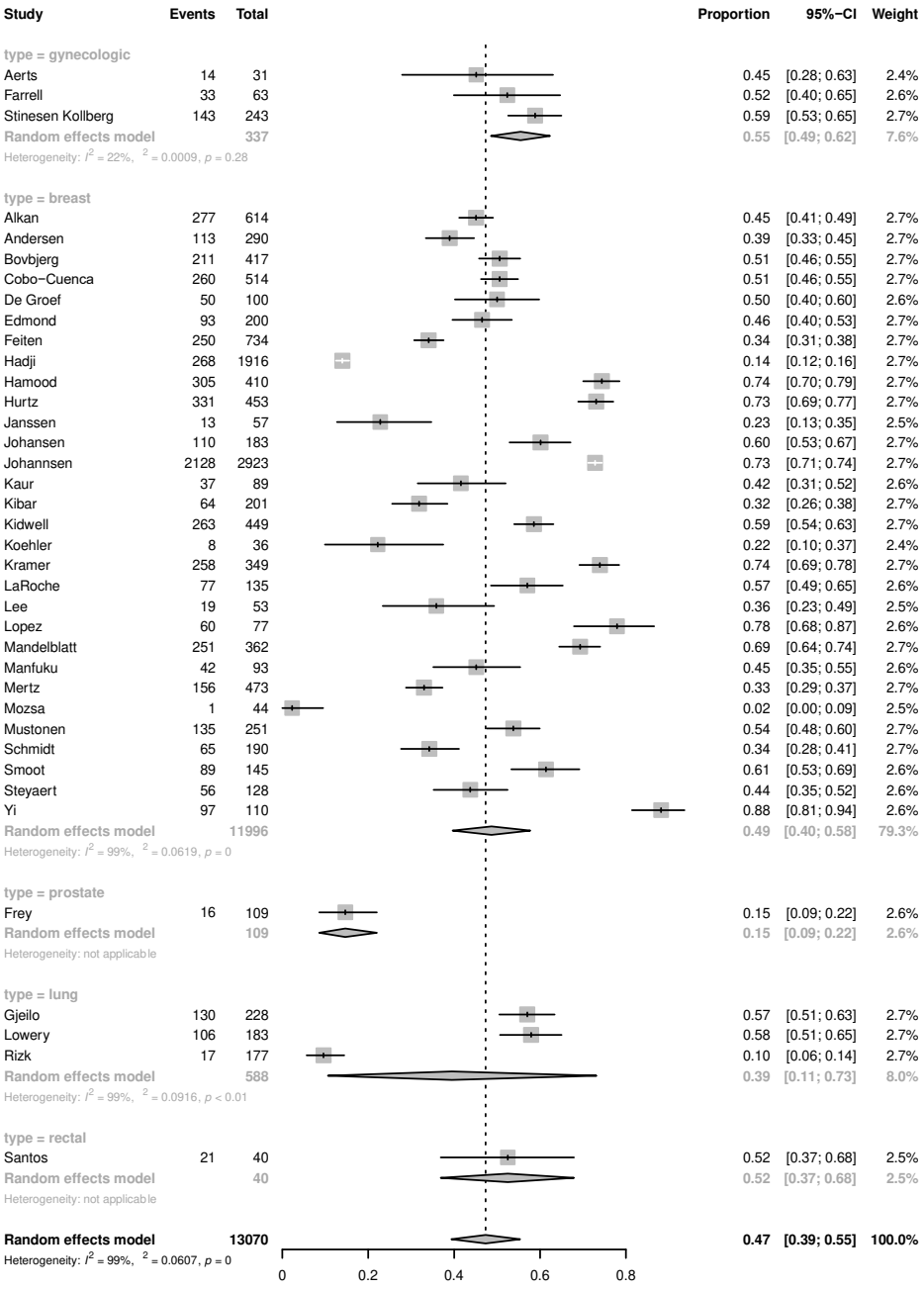

Figure 3: forest plot of the highest reported pain prevalence rates, subgrouped by cancer type

The meta-regression analyses for the variable cancer type, treatment location, pain measurement and follow-up time showed no significant influence (p = 0.6209, p = 0.8999, p = 0.3305 and p = 0.8823 respectively) on the high amount of heterogeneity (I^2=98.99%) (Table 2).

Covariate	**ß (95% CI)**	***P-value***	***R^2***
Cancer type		0.5267	
Breast (n = 30)	0.7710 (0.6912 - 0.8508)	< 0.0001	
Gynecological (n = 3)	0.0381 (-0.2324 - 0.3087)	0.7824	0%
Lung (n = 3)	-0.0911 (-0.3548 - 0.1726)	0.4985	
Prostate (n = 1)	-0.3689 (-0.8158 - 0.0780)	0.1057	
Rectal (n = 1)	0.0388 (-0.4245 - 0.5021)	0.8696	
Treatment strategy		0.6503	
Localized	0.7151 (0.5168 - 0.9134)	< 0.0001	0%
Localized and systemic	0.0491 (-0.1633 - 0.2616)	0.6503	
Pain measurement		0.5437	
Combination	0.7175 (0.5350 - 0.9001)	<0.0001	
Not specified	0.0631 (-0.2472 - 0.3734)	0.6903	
Not-pain specific	-0.0408 (-0.2631 - 0.1815)	0.7193	0%
NRS/VAS	0.0819 (-0.1884 - 0.3521)	0.5526	
Pain specific	0.0951 (-0.1347 - 0.3248	0.4173	
Study specific	0.2320 (-0.1257 - 0.5896)	0.2036	
Follow-up time		0.7153	
>3 months	0.6931 (0.4934 - 0.8928)	< 0.0001	
>6 months	0.1446 (-0.1168 - 0.4059)	0.2783	
>12 months	0.0985 (-0.1651 - 0.3620)	0.4640	0%
>24 months	-0.0196 (-0.2646 - 0.3039)	0.8924	
>36 months	0.1570 (-0.1242 -0.4381)	0.2738	
>48 months	-0.0435 (-0.3254 - 0.2385)	0.7626	
>60 months	-0.0216 (-0.2789 - 0.3222)	0.8878	

Table 2: Meta-regression outcome. NRS/VAS=Numeric Rating Scale/Visual Analog Scale

Narrative review

Pain characteristics and measurements

Different **types of pain** were used to summarize or to assess pain symptoms. In breast cancer survivors the most used and best defined pain types were *shoulder pain* (n=2), *arthralgia* (n=4) and *arm-shoulder pain* (n=3). [39, 40, 53, 56–60] *Post-mastectomy pain syndrome* or *breast pain* was used by seven studies but each study termed it differently (e.g. *post-mastectomy pain syndrome, chronic postmastectomy pain, persistent breast pain*).[30, 31, 33, 43, 46, 49, 68] Six studies did not specify which type of pain the authors assessed, or failed to describe it.[41, 44, 47, 52, 62, 66]

Regarding the assessment of **pain mechanisms** (*nociceptive, neuropathic, nociplastic or mixed pain*), only three studies assessed for neuropathic pain using the Douleur Neuropathique en 4 Questions (DN4), the Neuropathic Pain Symptom Inventory (NPSI) and ID Pain Questionnaire.[46, 60, 68] Mustonen and colleagues assessed neuropathic pain clinically in breast cancer survivors through a subjective examination and a somatosensory testing protocol as proposed by Finnerup et al.[64, 69] Andersen et al. also assessed sensory dysfunction using quantitative sensory testing in breast cancer

survivors but ascribing neuropathic pain was not in the scope of their study.[49] No other studies utilized the different pain mechanisms as a descriptor for the pain assessed.

Although all studies used questionnaires to assess pain but numerous different types of pain measurement tools were used doing so. The most frequently used questionnaires were the BPI (n=9)[31, 33, 41, 42, 47, 52, 60, 64, 65] VAS (n=8)[37, 40, 44, 50, 59–61, 68], followed by the pain subscale of the European Organization for Research and Treatment for Cancer Quality of Life Questionnaire (EORTC-QLQ-C30) (n=3)[43, 44, 66] (Appendix 3). Three studies did not specify which type of questionnaire they used [30, 34, 62], and two studies used a self-developed study specific questionnaire to assess pain [38, 57]. Six studies used a combination of different questionnaires which most of the time consisted of a VAS in combination with a general health or disability questionnaire [37, 44–46, 59].

Sixteen studies did not report pain severity, or merely reported the presence of pain without quantifying its severity.[30, 34–36, 38, 41, 42, 45, 48, 53, 57, 60, 62, 65] The remaining 22 studies reported the average pain, pain severity ranging from mild to severe pain, or moderate to severe pain.[30, 34–36, 38, 41, 42, 45, 48, 53, 57, 58, 60–62, 65] Mild pain is pain defined as 1-4 on a NRS scale from 0 to 10, whereas moderate pain ranges from 5-6 on the NRS and severe pain ranges from 7 to 10 on the NRS.[9]

Discussion

Main findings

The purpose of this systematic review was to summarize pain prevalence rates after curative treatment for different solid cancer types. If available, prevalence rates of different pain mechanisms, pain characteristics and assessment methods for pain were presented. Based on a meta-analysis, **47%** (95% CI 39 - 55%) of cancer survivors experience pain after finishing cancer treatment. The meta-analysis showed a high heterogeneity (I^2=98.99%) for the included studies and none of the selected covariates seemed to have a significant influence on the heterogeneity of the meta-analysis.

Looking at the different cancer types separately, we could conclude that pain is present in 49% (95% CI 40 - 58%) of breast cancer survivors, in 39% (95% CI 11 - 73%) of lung cancer survivors and in 55% (95% CI 49 - 62%) of gynecological cancer survivors. Due to the lack of studies we are not able to draw conclusions on the presence of pain for the survivors of rectal and prostate cancer. We hypothesized that different cancer types would present different pain prevalence rates. However, it seems that breast and lung cancer survivors seem to have similar rates of pain whereas survivors of gynecological

cancer tend to show higher pain prevalence rates. This comparison needs to be viewed with caution since only three studies on gynecological cancer were included in our review.[38, 48, 51]

With this review we also aimed to present prevalence rates of the different pain mechanisms. Unfortunately only three studies explicitly assessed neuropathic pain whereas the other included studies did not mention any of the different pain mechanisms described by the IASP.[46, 60, 68] It seems there is a lack of studies investigating the presence of these pain mechanisms in cancer survivor. Our narrative review concluded that in cancer studies different types of pain assessment methods are used, together with different types and definitions of pain. Due to the lack of studies and the heterogeneous pain assessment methods and pain definitions, we are not able to draw conclusions from our narrative review.

This review adds to the growing body of evidence on the presence of pain after curative cancer treatment. It is evident that clinicians should routinely screen for pain during follow-up visits in order to improve pain management and QoL after cancer. We would recommend that future studies either use proposed guidelines [17] and/or other simple, validated and recommended questionnaires to assess pain in cancer survivors.[70] Further research is urgently required to examine the prevalence of different pain mechanisms in cancer survivors and concurrently to investigate more effective interventions for pain after cancer treatment.

Risk of bias

Examining the general risk of bias assessment, we noticed that the majority of studies had difficulties providing proper sampling of participants, sample size calculation or description of the subjects. In addition, we choose to mark all studies as unclear for the question “Was the data analysis conducted with sufficient coverage of the identified sample?”. Assessing coverage bias was complicated due to lack of information in the majority of studies, therefore we marked all studies as unclear. Even though only 33% of the included studies were of moderate risk of bias, future studies on prevalence need to consider these biases.

Strengths and limitations

The first strength of this review is that the authors used the JBI manual for systematic reviews of prevalence and incidence.[71] Two other strengths of this review are the clear-cut eligibility criteria and a quality appraisal of the included studies with an endorsed and frequently used quality appraisal tool.[72] Another strength is the meta-analysis used to estimate the prevalence of pain after curative cancer treatment: a Freeman-Tukey double arcsine transformation was performed to approximate a

normal distribution and to stabilize the variance[25]. The majority of studies included in our review showed a low risk of bias (Figure 2). No studies with a high risk of bias were included (Figure 2).

Limitations to this study are present. The high heterogeneity, in combination with the non-significant findings of the meta-regression complicates interpretation of the pooled prevalence. We excluded a number of studies when data were unclear, missing or when the authors did not respond to our questions (Figure 1). Cancer survivors had to have finished treatment for at least three months which in term creates a selection bias. Concurrently, we did not include cancer patients in an advanced or palliative stage, with metastases or undergoing non-curative treatment. Even though we screened articles written in English, French, German or Dutch, language bias was present as English articles were the majority of articles found and only articles in English were included for review. For the assessment of pain, we only noted the utilized questionnaires as this was the most common practice in studies. However, some studies utilized clinical examination such as somatosensory testing to evaluate pain which we did not include in our data extraction and review. The majority of included papers conducted their research in high income countries, therefore generalizability is limited to these type of countries. Furthermore, it is known that persistent pain prevalence rates continue to increase worldwide.[73] It is not known whether the cancer survivors included in our review were already suffering from non-cancer-related pain (e.g. low back pain), and whether studies made a distinction between the assessment of cancer-related pain and non-cancer-related pain. It is known that 19% of adult Europeans suffer from chronic non-cancer related pain.[74] Therefore, by not making this distinction, pain prevalence rates could be overstated. Six studies, reporting an average of 59.8% pain prevalence rate altogether, failed to specify which type of pain they assessed, therefore scrutiny of these prevalence rates is warranted.[41, 44, 47, 52, 62, 66] Regarding the severity of pain, 17 studies did not report this.[30, 34–36, 38, 41, 42, 45, 48, 53, 57, 58, 60–62, 65] It is therefore difficult to conclude if patients had clinically significant pain, defined as 30/100 on a VAS.[33, 68, 75] If patients scored less than 30/100 and were classified as having pain, this could overestimate pain prevalence rates.
Breast cancer was overly represented (12 to 1 ratio) in this systematic review which in term effects the pooled prevalence and limits generalizability towards other solid cancers. Not all solid cancer types were included in this review, again limiting generalizability (e.g. head and neck, gastro-intestinal cancers). A last limitation is that we did not include gray literature or unpublished articles in our systematic search. This could've excluded more recent findings and/or more negative or inconclusive data.

Conclusion

Evidence with a low risk of bias suggests that 47% of cancer survivors who finished curative treatment at least three months ago experience pain. No conclusions could be made on the influence of cancer type, treatment strategy, pain measurement or follow-up time on this pain prevalence rate. In addition, we could not provide information on the prevalence of the different kind of pain mechanisms in cancer survivors. These results have to be weighed carefully since a high amount of unexplained heterogeneity is present. Generalizability towards other solid cancer types is limited due to disproportionate inclusion of breast cancer studies. Further research is necessary to explore pain prevalence rates, presence of different pain mechanisms and pain severity in not only breast cancer but also in other types of cancer.

References

1. Sung H, Ferlay J, Siegel RL, et al (2021) Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. CA Cancer J Clin 71:209–249. https://doi.org/10.3322/caac.21660

2. Marzorati C, Riva S, Pravettoni G (2017) Who Is a Cancer Survivor? A Systematic Review of Published Definitions. J Cancer Educ Off J Am Assoc Cancer Educ 32:228–237. https://doi.org/10/ghfdsf

3. Richards M, Corner J, Maher J (2011) The National Cancer Survivorship Initiative: new and emerging evidence on the ongoing needs of cancer survivors. Br J Cancer 105:S1–S4. https://doi.org/10/dcwb8r

4. National Coalition for Cancer Survivorship (NCCS) [Internet]. NCCS Our Mission. Available from: https://canceradvocacy.org/about/our-mission/

5. Moser EC, Meunier F (2014) Cancer survivorship: A positive side-effect of more successful cancer treatment. EJC Suppl 12:1–4. https://doi.org/10/ghfdr6

6. Gegechkori N, Haines L, Lin JJ (2017) Long-Term and Latent Side Effects of Specific Cancer Types. Med Clin North Am 101:1053–1073. https://doi.org/10.1016/j.mcna.2017.06.003

7. Jacobs LA, Shulman LN (2017) Follow-up care of cancer survivors: challenges and solutions. Lancet Oncol 18:e19–e29. https://doi.org/10/f9tkmp

8. van den Beuken-van Everdingen MHJ, Hochstenbach LMJ, Joosten EAJ, et al (2016) Update on Prevalence of Pain in Patients With Cancer: Systematic Review and Meta-Analysis. J Pain Symptom Manage 51:1070-1090.e9. https://doi.org/10/f8qsjm

9. Serlin RC, Mendoza TR, Nakamura Y, et al (1995) When is cancer pain mild, moderate or severe? Grading pain severity by its interference with function. Pain 61:277–284. https://doi.org/10.1016/0304-3959(94)00178-H

10. Chimenti RL, Frey-Law LA, Sluka KA (2018) A Mechanism-Based Approach to Physical Therapist Management of Pain. Phys Ther 98:302–314. https://doi.org/10/gdp5wc

11. Nijs J, Apeldoorn A, Hallegraeff H, et al (2015) Low back pain: guidelines for the clinical classification of predominant neuropathic, nociceptive, or central sensitization pain. Pain Physician 18:E333-346

12. Malfait A-M, Schnitzer TJ (2013) Towards a mechanism-based approach to pain management in osteoarthritis. Nat Rev Rheumatol 9:654–664. https://doi.org/10/f5wr6g

13. Merskey H, Bogduk N (1994) Classification of Chronic Pain. 2nd Edition, IASP Task Force on Taxonomy. IASP Press, Seattle

14. Baron R (2006) Mechanisms of disease: neuropathic pain--a clinical perspective. Nat Clin Pract Neurol 2:95–106. https://doi.org/10/bkff9h

15. Backonja M-M (2003) Defining Neuropathic Pain: Anesth Analg 785–790. https://doi.org/10/fd4j9q

16. Kosek E, Cohen M, Baron R, et al (2016) Do we need a third mechanistic descriptor for chronic pain states? Pain 157:1382–1386. https://doi.org/10.1097/j.pain.0000000000000507

17. Nijs J, Leysen L, Adriaenssens N, et al (2016) Pain following cancer treatment: Guidelines for the clinical classification of predominant neuropathic, nociceptive and central sensitization pain. Acta Oncol Stockh Swed 55:659–663. https://doi.org/10/ghfd5v

18. Leysen L, Adriaenssens N, Nijs J, et al (2019) Chronic Pain in Breast Cancer Survivors: Nociceptive, Neuropathic, or Central Sensitization Pain? Pain Pract Off J World Inst Pain 19:183–195. https://doi.org/10/ghfdsc

19. Mustonen L, Aho T, Harno H, Kalso E (2020) Static mechanical allodynia in post-surgical neuropathic pain after breast cancer treatments. Scand J Pain 20:683–691. https://doi.org/10.1515/sjpain-2020-0013

20. Page MJ, McKenzie JE, Bossuyt PM, et al (2021) The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ n71. https://doi.org/10.1136/bmj.n71

21. Grisold W, Cavaletti G, Windebank AJ (2012) Peripheral neuropathies from chemotherapeutics and targeted agents: diagnosis, treatment, and prevention. Neuro-Oncol 14:iv45–iv54. https://doi.org/10.1093/neuonc/nos203

22. Munn Z, Moola S, Lisy K, et al (2015) Methodological guidance for systematic reviews of observational epidemiological studies reporting prevalence and cumulative incidence data. Int J Evid Based Healthc 13:147–153. https://doi.org/10.1097/XEB.0000000000000054

23. Hoy D, Brooks P, Woolf A, et al (2012) Assessing risk of bias in prevalence studies: modification of an existing tool and evidence of interrater agreement. J Clin Epidemiol 65:934–939. https://doi.org/10.1016/j.jclinepi.2011.11.014

24. Higgins J, Thomas J, Chandler J, et al (2021) Cochrane Handbook for Systematic Reviews of Interventions version 6.2 (updated February 2021). Cochrane

25. Lin L, Xu C (2020) Arcsine-based transformations for meta-analysis of proportions: Pros, cons, and alternatives. Health Sci Rep 3:. https://doi.org/10.1002/hsr2.178

26. DerSimonian R, Laird N (1986) Meta-analysis in clinical trials. Control Clin Trials 7:177–188. https://doi.org/10.1016/0197-2456(86)90046-2

27. Wang L, Cohen JC, Devasenapathy N, et al (2020) Prevalence and intensity of persistent post-surgical pain following breast cancer surgery: a systematic review and meta-analysis of observational studies. Br J Anaesth 125:346–357. https://doi.org/10.1016/j.bja.2020.04.088

28. Viechtbauer W (2010) Conducting Meta-Analyses in R with the metafor Package. J Stat Softw 36:. https://doi.org/10.18637/jss.v036.i03

29. R Core Team (2016) R: A Language and Environment for Statistical Computing [Internet]

30. Alkan A, Guc ZG, Senler FC, et al (2016) Breast cancer survivors suffer from persistent postmastectomy pain syndrome and posttraumatic stress disorder (ORTHUS study): a study of the palliative care working committee of the Turkish Oncology Group (TOG). Support Care Cancer 24:3747–3755. https://doi.org/10.1007/s00520-016-3202-6

31. Bovbjerg DH, Keefe FJ, Soo MS, et al (2019) Persistent breast pain in post-surgery breast cancer survivors and women with no history of breast surgery or cancer: associations with pain catastrophizing, perceived breast cancer risk, breast cancer worry, and emotional distress. Acta Oncol 58:763–768. https://doi.org/10.1080/0284186X.2019.1574023

32. Cobo-Cuenca AI, Martín-Espinosa NM, Sampietro-Crespo A, et al (2018) Sexual dysfunction in Spanish women with breast cancer. PLOS ONE 13:e0203151. https://doi.org/10.1371/journal.pone.0203151

33. Edmond SN, Shelby RA, Keefe FJ, et al (2017) Persistent Breast Pain Among Women With Histories of Breast-conserving Surgery for Breast Cancer Compared With Women Without Histories of Breast Surgery or Cancer. Clin J Pain 33:51–56. https://doi.org/10.1097/AJP.0000000000000377

34. Feiten S, Dünnebacke J, Heymanns J, et al (2014) Breast Cancer Morbidity. Dtsch Aerzteblatt Online. https://doi.org/10.3238/arztebl.2014.0537

35. Frey A, Pedersen C, Lindberg H, et al (2017) Prevalence and Predicting Factors for Commonly Neglected Sexual Side Effects to External-Beam Radiation Therapy for Prostate Cancer. J Sex Med 14:558–565. https://doi.org/10.1016/j.jsxm.2017.01.015

36. Hamood R, Hamood H, Merhasin I, Keinan-Boker L (2018) Chronic pain and other symptoms among breast cancer survivors: prevalence, predictors, and effects on quality of life. Breast Cancer Res Treat 167:157–169. https://doi.org/10/gczh67

37. Kibar S, Dalyan Aras M, Ünsal Delialioğlu S (2017) The risk factors and prevalence of upper extremity impairments and an analysis of effects of lymphoedema and other impairments on the quality of life of breast cancer patients. Eur J Cancer Care (Engl) 26:e12433. https://doi.org/10.1111/ecc.12433

38. Stinesen Kollberg K, Waldenström A-C, Bergmark K, et al (2015) Reduced vaginal elasticity, reduced lubrication, and deep and superficial dyspareunia in irradiated gynecological cancer survivors. Acta Oncol 54:772–779. https://doi.org/10.3109/0284186X.2014.1001036

39. Kramer N, Ramjith J, Shamley D (2019) Prevalence of shoulder morbidity after treatment for breast Cancer in South Africa. Support Care Cancer 27:2591–2598. https://doi.org/10.1007/s00520-018-4540-3

40. Lopez C, Charles C, Rouby P, et al (2015) Relations between arthralgia and fear of recurrence: results of a cross-sectional study of breast cancer patients treated with adjuvant aromatase inhibitors therapy. Support Care Cancer 23:3581–3588. https://doi.org/10.1007/s00520-015-2722-9

41. Lowery AE, Krebs P, Coups EJ, et al (2014) Impact of symptom burden in post-surgical non-small cell lung cancer survivors. Support Care Cancer 22:173–180. https://doi.org/10.1007/s00520-013-1968-3

42. Manfuku M, Nishigami T, Mibu A, et al (2019) Comparison of central sensitization-related symptoms and health-related quality of life between breast cancer survivors with and without chronic pain and healthy controls. Breast Cancer 26:758–765. https://doi.org/10.1007/s12282-019-00979-y

43. Mertz BG, Duriaud HM, Kroman N, Andersen KG (2017) Pain, sensory disturbances and psychological distress are common sequelae after treatment of ductal carcinoma *in situ* : a cross-sectional study. Acta Oncol 56:724–729. https://doi.org/10.1080/0284186X.2017.1295167

44. Santos LJF, Garcia JB dos S, Pacheco JS, et al (2014) Quality of life, pain, anxiety and depression in patients surgically treated with cancer of rectum. ABCD Arq Bras Cir Dig São Paulo 27:96–100. https://doi.org/10.1590/S0102-67202014000200003

45. Smoot B, Boyd BS, Byl N, Dodd M (2014) Mechanosensitivity in the upper extremity following breast cancer treatment. J Hand Ther 27:4–11. https://doi.org/10.1016/j.jht.2013.08.021

46. Steyaert A, Forget P, Dubois V, et al (2016) Does the perioperative analgesic/anesthetic regimen influence the prevalence of long-term chronic pain after mastectomy? J Clin Anesth 33:20–25. https://doi.org/10.1016/j.jclinane.2015.07.010

47. Yi M, Hwang E (2018) Pain and Menopause Symptoms of Breast Cancer Patients with Adjuvant Hormonal Therapy in Korea: Secondary Analysis. Asia-Pac J Oncol Nurs 5:262. https://doi.org/10.4103/apjon.apjon_45_17

48. Aerts L, Enzlin P, Verhaeghe J, et al (2014) Long-Term Sexual Functioning in Women After Surgical Treatment of Cervical Cancer Stages IA to IB: A Prospective Controlled Study. Int J Gynecol Cancer 24:1527–1534. https://doi.org/10.1097/IGC.0000000000000236

49. Andersen KG, Duriaud HM, Kehlet H, Aasvang EK (2017) The Relationship Between Sensory Loss and Persistent Pain 1 Year After Breast Cancer Surgery. J Pain 18:1129–1138. https://doi.org/10.1016/j.jpain.2017.05.002

50. De Groef A, Van Kampen M, Tieto E, et al (2016) Arm lymphoedema and upper limb impairments in sentinel node-negative breast cancer patients: A one year follow-up study. The Breast 29:102–108. https://doi.org/10.1016/j.breast.2016.07.021

51. Farrell R, Gebski V, Hacker NF (2014) Quality of Life After Complete Lymphadenectomy for Vulvar Cancer: Do Women Prefer Sentinel Lymph Node Biopsy? Int J Gynecol Cancer 24:813–819. https://doi.org/10.1097/IGC.0000000000000101

52. Gjeilo KH, Oksholm T, Follestad T, et al (2020) Trajectories of Pain in Patients Undergoing Lung Cancer Surgery: A Longitudinal Prospective Study. J Pain Symptom Manage 59:818-828.e1. https://doi.org/10.1016/j.jpainsymman.2019.11.004

53. Hadji P, Jackisch C, Bolten W, et al (2014) COMPliance and Arthralgia in Clinical Therapy: the COMPACT trial, assessing the incidence of arthralgia, and compliance within the first year of adjuvant anastrozole therapy. Ann Oncol 25:372–377. https://doi.org/10.1093/annonc/mdt513

54. Hurtz H-J, Tesch H, Göhler T, et al (2017) Persistent impairments 3 years after (neo)adjuvant chemotherapy for breast cancer: results from the MaTox project. Breast Cancer Res Treat 165:721–731. https://doi.org/10.1007/s10549-017-4365-7

55. Janssen S, Glanzmann C, Lang S, et al (2014) Hypofractionated radiotherapy for breast cancer acceleration of the START A treatment regime: intermediate tolerance and efficacy. Radiat Oncol 9:165. https://doi.org/10.1186/1748-717X-9-165

56. Johansen S, Fosså K, Nesvold IL, et al (2014) Arm and shoulder morbidity following surgery and radiotherapy for breast cancer. Acta Oncol 53:521–529. https://doi.org/10.3109/0284186X.2014.880512

57. Johannsen M, Christensen S, Zachariae R, Jensen A (2015) Socio-demographic, treatment-related, and health behavioral predictors of persistent pain 15 months and 7–9 years after surgery: a nationwide prospective study of women treated for primary breast cancer. Breast Cancer Res Treat 152:645–658. https://doi.org/10.1007/s10549-015-3497-x

58. Kidwell KM, Harte SE, Hayes DF, et al (2014) Patient-reported symptoms and discontinuation of adjuvant aromatase inhibitor therapy: Baseline Symptoms & AI Discontinuation. Cancer 120:2403–2411. https://doi.org/10.1002/cncr.28756

59. Koehler LA, Hunter DW, Blaes AH, Haddad TC (2018) Function, Shoulder Motion, Pain, and Lymphedema in Breast Cancer With and Without Axillary Web Syndrome: An 18-Month Follow-Up. Phys Ther 98:518–527. https://doi.org/10.1093/ptj/pzy010

60. Laroche F, Perrot S, Medkour T, et al (2017) Quality of life and impact of pain in women treated with aromatase inhibitors for breast cancer. A multicenter cohort study. PLOS ONE 12:e0187165. https://doi.org/10.1371/journal.pone.0187165

61. Lee M-J, Beith J, Ward L, Kilbreath S (2014) Lymphedema Following Taxane-Based Chemotherapy in Women with Early Breast Cancer. Lymphat Res Biol 12:282–288. https://doi.org/10.1089/lrb.2014.0030

62. Mandelblatt JS, Zhai W, Ahn J, et al (2020) Symptom burden among older breast cancer survivors: The Thinking and Living With Cancer (TLC) study. Cancer 126:1183–1192. https://doi.org/10.1002/cncr.32663

63. Mózsa E, Mészáros N, Major T, et al (2014) Accelerated partial breast irradiation with external beam three-dimensional conformal radiotherapy: Five-year results of a prospective phase II clinical study. Strahlenther Onkol 190:444–450. https://doi.org/10.1007/s00066-014-0633-1

64. Mustonen L, Aho T, Harno H, et al (2019) What makes surgical nerve injury painful? A 4-year to 9-year follow-up of patients with intercostobrachial nerve resection in women treated for breast cancer. Pain 160:246–256. https://doi.org/10.1097/j.pain.0000000000001398

65. Rizk NP, Ghanie A, Hsu M, et al (2014) A Prospective Trial Comparing Pain and Quality of Life Measures After Anatomic Lung Resection Using Thoracoscopy or Thoracotomy. Ann Thorac Surg 98:1160–1166. https://doi.org/10.1016/j.athoracsur.2014.05.028

66. Schmidt ME, Wiskemann J, Steindorf K (2018) Quality of life, problems, and needs of disease-free breast cancer survivors 5 years after diagnosis. Qual Life Res 27:2077–2086. https://doi.org/10.1007/s11136-018-1866-8

67. United Nations (2021) World economic situation and prospects 2021

68. Kaur N, Kumar A, Saxena AK, et al (2018) Postmastectomy Chronic Pain in Breast Cancer Survivors: an Exploratory Study on Prevalence, Characteristics, Risk Factors, and Impact on Quality of Life. Indian J Surg 80:592–598. https://doi.org/10.1007/s12262-017-1663-6

69. Finnerup NB, Haroutounian S, Kamerman P, et al (2016) Neuropathic pain: an updated grading system for research and clinical practice. Pain 157:1599–1606. https://doi.org/10.1097/j.pain.0000000000000492

70. Minello C, George B, Allano G, et al (2019) Assessing cancer pain—the first step toward improving patients' quality of life. Support Care Cancer 27:3095–3104. https://doi.org/10.1007/s00520-019-04825-x

71. Munn Z, Moola S, Lisy K, et al (2020) Chapter 5: Systematic reviews of prevalence and incidence. In: JBI Manual for Evidence Synthesis. JBI

72. Borges Migliavaca C, Stein C, Colpani V, et al (2020) How are systematic reviews of prevalence conducted? A methodological study. BMC Med Res Methodol 20:96. https://doi.org/10.1186/s12874-020-00975-3

73. Mills SEE, Nicolson KP, Smith BH (2019) Chronic pain: a review of its epidemiology and associated factors in population-based studies. Br J Anaesth 123:e273–e283. https://doi.org/10.1016/j.bja.2019.03.023

74. Breivik H, Collett B, Ventafridda V, et al (2006) Survey of chronic pain in Europe: Prevalence, impact on daily life, and treatment. Eur J Pain 10:287–287. https://doi.org/10.1016/j.ejpain.2005.06.009

75. Belfer I, Schreiber KL, Shaffer JR, et al (2013) Persistent Postmastectomy Pain in Breast Cancer Survivors: Analysis of Clinical, Demographic, and Psychosocial Factors. J Pain 14:1185–1195. https://doi.org/10.1016/j.jpain.2013.05.002

Statements and Declarations

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Author contributions

Vincent Haenen and Margaux Evenepoel were responsible for the study conception and design. Study preparation, data collection and analysis were performed by Vincent Haenen and Margaux Evenepoel. The first version of the manuscript was written by Vincent Haenen and all authors reviewed previous versions. The final manuscript was read and approved by all authors.

Ethics approval

N/A

Consent to participate

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Consent to publish

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