Support Care Cancer (2017) 25:3607–3643
DOI 10.1007/s00520-017-3824-3

REVIEW ARTICLE

Risk factors of pain in breast cancer survivors: a systematic review and meta-analysis

Laurence Leysen[1,2] · **David Beckwée**[2,3] · **Jo Nijs**[1,2,4] · **Roselien Pas**[1,2] · **Thomas Bilterys**[2] · **Sofie Vermeir**[2] · **Nele Adriaenssens**[2,5]

Received: 17 May 2017 / Accepted: 3 July 2017 / Published online: 10 August 2017

Abstract
Background Breast cancer remains the number 1 lethal malignancy in women. With rising incidence and decreased mortality, the number of breast cancer survivors has increased. Consequently, sequelae, such as pain, are becoming more important.
Purpose The purpose of this study was to identify risk factors for the development of pain in breast cancer survivors.
Methods PubMed and Web of Science were systematically screened for studies encompassing risk factors for the development of pain in breast cancer survivors. Meta-analyses were carried out for risk factors described in more than one article. Moderator analysis was performed in case of high heterogeneity ($I^2 > 50\%$) across studies.
Results Seventeen studies were found eligible. Meta-analyses were performed for 17 factors. Significant differences for the odds of developing chronic pain were found for BMI (overall OR: 1.34, 95%CI 1.08–1.67, $p = 0.008$), education (overall OR: 1.23, 95%CI 1.07–1.42, $p = 0.005$), lymphedema (overall OR: 2.58, 95%CI 1.93–3.46, $p < 0.00001$), smoking status (overall OR: 0.75, 95%CI 0.62–0.92, $p = 0.005$), axillary lymph node dissection (overall OR: 1.25, 95%CI 1.04–1.52, $p = 0.02$), chemotherapy (overall OR: 1.44, 95%CI 1.24–1.68, $p < 0.00001$), and radiotherapy (overall OR: 1.32, 95%CI 1.17–1.48, $p < 0.00001$). After performing moderator analyses for age, comorbidities, hormone therapy, and breast surgery, hormone therapy became a significant risk factor as well (overall OR: 1.33, 95%CI 1.15–1.54, $p = 0.0001$).
Conclusion BMI > 30, education < 12–13 years, lymphedema, not smoking, axillary lymph node dissection, chemotherapy, hormone therapy, and radiotherapy were significantly associated with higher odds for the development of chronic pain, with lymphedema being the biggest risk factor. Lack of uniformity across the studies in defining pain, follow-up, measurement tools, and cut-off values for the diagnosis of pain was noted, resulting in greater inter-study variability.

Keywords Chronic pain · Pain · Breast cancer survivor · Risk factors

Electronic supplementary material The online version of this article (doi:10.1007/s00520-017-3824-3) contains supplementary material, which is available to authorized users.

✉ Laurence Leysen
laurence.leysen@vub.be

[1] Pain in Motion International Research Group, http://www.paininmotion.be

[2] Department of Physiotherapy, Human Physiology and Anatomy, Faculty of Physical Education and Physiotherapy, Vrije Universiteit Brussel, Building F-Kine, Laarbeeklaan 103, BE-1090 Brussels, Belgium

[3] Department of Rehabilitation Sciences and Physiotherapy, Faculty of Medicine and Health Sciences, University of Antwerp, Wilrijk, Belgium

[4] Department of Oncology, University Hospital Brussels, Brussels, Belgium

[5] Department of Physical Medicine and Physiotherapy, University Hospital Brussels, Brussels, Belgium

Introduction

Breast cancer remains the most lethal malignancy among women worldwide [1]. Over the last decades, the incidence of breast cancer has increased [1, 2]. According to estimates made by the International Agency for Research on Cancer (IARC), 1.67 million new cancer cases were diagnosed in 2012 worldwide [1]. The increasing incidence can partially be explained by improved

detection, population growth, and aging of the population. Furthermore, a decline in mortality has been observed as a result of improved screening strategies and more effective treatment strategies [3]. Due to the combination of the declined mortality rate and the increased incidence, the number of breast cancer survivors has increased [4].

However, an important portion of breast cancer survivors has to deal with complications and sequelae of physical (lymphedema, neuropathy/pain, fatigue, menopausal symptoms, weight gain, etc.) and psychological nature (fear of recurrence, fear of death, change in body image, change in relationship, financial stress, etc.). These complications can arise during the treatment or can persist long after treatment cessation [5]. The development of chronic pain is one of the most frequently seen sequelae in the cancer survivor population [6]. Forsythe et al. reported that about 30% of the breast cancer survivors are confronted with above-average pain 10 years after ending the treatment [7].

The International Association for the Study of Pain (IASP) defined pain as "An unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage" [8]. As the lesion recovers or the threat disappears, the pain sensation should normally decrease. However, when the pain remains persistent after the normal tissue healing process, it can be considered as chronic. To differentiate acute from chronic pain, the cut-off point of less than 1 month can be used, but 6 months is favored for research purposes [8].

So far, chronic pain in breast cancer survivors has been poorly defined in the literature.

In previous studies, there is a lack of uniformity in the applied definitions for chronic pain. Yet, postmastectomy pain syndrome has been defined by the IASP as "Chronic pain commencing immediately or soon after mastectomy or removal of a lump, affecting the anterior thorax, axilla, and/or medial upper arm." [9]. However, this definition may be too limiting, as it only focuses on the operated region and rules out other natures of chronic pain like central sensitization.

The exact etiology underlying the development of pain in cancer survivors remains an enigma. Several researchers attempted to identify risk factors for the development of pain in breast cancer survivors [10, 11], which are not only of a crucial matter for the improvement of the prevention, but also for the implementation of treatment strategies.

To our knowledge, two systematic reviews were previously conducted regarding risk factors for the development of chronic pain in cancer survivors, but neither of them performed a meta-analysis or focused on the post-cancer treatment phase exclusively [10, 11]. In addition to reporting several risk factors for the development of chronic pain after breast surgery, Chang et al. [10] mainly focused reviewing the literature on the use of analgesic techniques for breast cancer surgery. However, eligibility criteria were not presented, making it difficult to assess whether the identified risk factors are applicable to breast cancer survivors specifically.

Andersen et al. identified several risk factors for the development of persistent pain after breast cancer [11], but also included studies on patients with recurrence and/or metastasis. A final reason warranting the need for a systematic review is the lack of reviews on risk factors of pain in cancer survivors since 2011. Given the increasing survival rate and associated interest of researchers, an increase in the number of studies can be expected. Therefore, a systematic review with strict eligibility criteria and exclusion of patients with recurrent cancer or metastasis is emerging.

Objective

The objectives of this review are: (1) to identify risk factors of pain in breast cancer survivors in a systematic, transparent, and reproducible way with strict eligibility criteria and (2) to conduct a meta-analysis.

We expect to find a combination of underlying factors such as cancer-related (tumor size, staging, etc.), treatment-related (chemotherapy, radiotherapy, surgery, etc.), and patient-related (age, body mass index (BMI), comorbidities, etc.) factors that might put breast cancer patients at an increased risk for the development of chronic pain.

Method

A systematic literature review was performed following the PRISMA guidelines [12]. To identify relevant studies regarding pain in cancer survivors, a systematic search of literature was conducted in databases PubMed and Web of Science up to March 2017. Authors were contacted if the full texts of studies could not be retrieved.

Eligibility criteria

In order to be included, studies needed to meet the following criteria:

(1) subjects needed to fulfill our definition of a cancer survivor. According to the definition of the National Cancer Institute's Office of Cancer Survivorship, a cancer survivor is "A patient with a history of cancer that is beyond the acute diagnosis and treatment phase" [13]. We used a dissimilar definition, as the cancer survivors had to be at least 6 months post-treatment (with exception of hormone therapy) and without recurrence or metastasis.
(2) subjects needed to be diagnosed with breast cancer in the past
(3) data to determine risk factors of pain had to be available.

The following exclusion criteria were applied:

(1) study design: case reports, reviews, protocol, commentary, and letters
(2) subjects not fulfilling the cancer survivor definition due to recurrence of cancer or diagnosed metastasis
(3) time since completion of radiotherapy or chemotherapy was less than 6 months
(4) time since surgery was less than 6 months
(5) time since diagnosis was less than 1 year
(6) subjects being diagnosed with other cancers besides breast cancer
(7) pain was not presented as an outcome.

All articles were restricted to recent publications between 1990 and 2017 with a primary emphasis on English abstracts concerning humans.

Search

The primary search was performed in PubMed using MeSH terms and free key words. The search was based on the PECO method in which the population was represented as the cancer survivors, the exposure as risk factors, and the outcome as pain. A similar search was conducted in Web of Science, using free key words.

Study selection

The study selection encompassed two phases. In the first phase, duplicates were removed. Subsequently, all titles and abstracts were screened for eligibility in a blinded standardized manner by three independent researchers (S.V., T.B., and L.L.), using the Rayyan software [14]. Any disagreement between the three reviewers was resolved by consensus. In the second phase, the remaining articles were screened for full textual review by two researchers. In both phases, reasons for exclusion were registered.

Data collection process

A self-created extraction form was used to collect following data: year of publication, study design, sample size of participants, age (year ± SD), follow-up (year ± SD), type of pain, risk factor variable, number of patients with pain exposed to risk factor, number of patients without pain exposed to risk factor, number of patients with pain unexposed to risk factor, number of patients without pain unexposed to risk factor, odds ratio or relative risk, adjusted odds ratio or relative risk, significance, standard error (SE), pain outcome measures, cut-off values, and opioid analgesic use. Three authors extracted the data from included studies. Two authors double-checked the extracted data afterwards.

Four authors were contacted to obtain supplementary data concerning the risk factors BMI, age, and tumor size [7, 15–17]. Both number of patients with pain and the number of patients without pain of each subgroup were requested to make dichotomization possible.

Quality assessment

Three authors assessed the methodological characteristics of the included studies using the Strengthening The Reporting of Observational Studies in Epidemiology (STROBE) checklist.

This checklist contains 22 items, related to the different sections of the articles. Four items are specific for cohort, case-control, or cross-sectional studies; the remaining 18 items are common to all three study designs [18]. When an item was discussed in an article, it received one point. When nothing was mentioned about the item, a score of 0 was given. Disagreements were resolved by consensus.

Summary measures

Odds ratio (OR) with 95% confidence intervals (CIs) was the primary outcome measure. When an article did not mention the needed odds ratio, raw data (number of patients with and without pain of both the exposed and unexposed groups) were used to calculate the odds ratio.

These data were used afterwards to perform a meta-analysis by applying the random effect model [19].

Planned methods of analysis

Heterogeneity was assessed by the I^2 statistics using the method proposed by Higgens et al. [19]. The I^2 statistic represents an estimation of the inter-study variability. The significance of the heterogeneity was determined on the basis of the p - value obtained by the Chi-squared (χ^2) test. Given the limited number of included studies for several risk factors, a p - value of 0.10 was used as cut-off for statistical significance instead of the more conventional level of 0.05 [20] (Deeks JJ et al. 2008). An I^2 value >50% was classified as an important presence of heterogeneity [19]. In this case, a moderator analysis was carried out, investigating possible underlying true systematic differences that may explain heterogeneity.

Not only the total score on the STROBE checklist, but also the presence of the most important items were taken into account. The study with the respectively highest scores on the items ‘data measurement’, ‘bias’, ‘outcome data’, ‘limitations’, ‘generalizability’ of the STROBE checklist were considered as best evidence. Studies that did not attain the average score of the STROBE checklist and scored a minimum of 2 out of 5 on the best evidence items were excluded from the meta-analyses.

The data acquired from the studies needed to be comparable to perform a meta-analysis. Therefore, several transformations were conducted: age was dichotomized as >50–55/<50–55 years [15, 21–23], alcohol use as yes/no [21], BMI as

>30/<30 [7, 21, 22, 24, 25], chemotherapy as yes/no [21], radiotherapy as yes/no [26], hormone therapy as yes/no [21], education as >12–13/<12–13 years [21, 22, 25], tumor size as >20 mm/<20 mm [21, 23], cancer stage as stage 1/>stage 1 [21, 23, 25], smoking status as ex-or no-smoker/smoker [25], and cohabitation status as single/cohabiting [15, 22, 25].

Instead of using the given adjusted OR (<46 years) of the risk factor age by Bredal et al., which was not based on similar groups (>50–55/<50–55) as with other authors, the age groups with and without pain in this study were dichotomized and afterwards used for calculation of a comparable OR [15].

In the study of Johannsen et al., the 7–9-year post-surgery OR was preferred over the 15 months equivalent for the meta-analysis, as the 7–9-year post-surgery OR is a better approximation of the follow-up of the other studies [21].

All meta-analyses were conducted with the RevMan software (Review manager 5.3).

Results

Study selection

The initial search of data yielded a total of 934 articles on PubMed and 864 on Web of Science. After removing duplicates, 1431 articles remained. These studies were screened on title and abstract. Based on the prespecified exclusion criteria, 1357 articles were excluded.

The remaining 74 articles were screened for eligibility by full textual review. Fifty-seven of the 74 articles were excluded due to not fulfilling the cancer survivor definition (n = 32) or providing insufficient data (n = 25). Therefore, 17 articles were included in our synthesis. Figure 1 presents the flowchart of the study selection process.

Study characteristics

The 17 included studies consisted of five cohort [7, 16, 21, 23, 27] and 12 cross-sectional studies [15, 17, 22, 24–26, 28–33]. In all studies, the breast cancer survivors were at least 6 months post-treatment. The sample size of the studies ranged from 85 to 2160. Four studies were performed in the USA [7, 30, 32, 34], three in Denmark [21, 22, 24], two in Sweden [26, 33], two in Turkey [25, 29], two in Australia [16, 35], one in the Netherlands [27], one in Belgium [17], one in Spain [23], and one in Norway [15].

Across those studies, several pain measurement tools were used with varying cut-off values. For the assessment of pain, 11 articles used a study specific questionnaire [17, 21–26, 30, 32, 33, 35], and four other studies relied on a valid measurement tool [7, 15, 16, 34]. Two studies did not provide a proper description of the measurement tools used to diagnose pain [27, 29]. The studies and their characteristics are listed in Tables 1, 2, and 3.

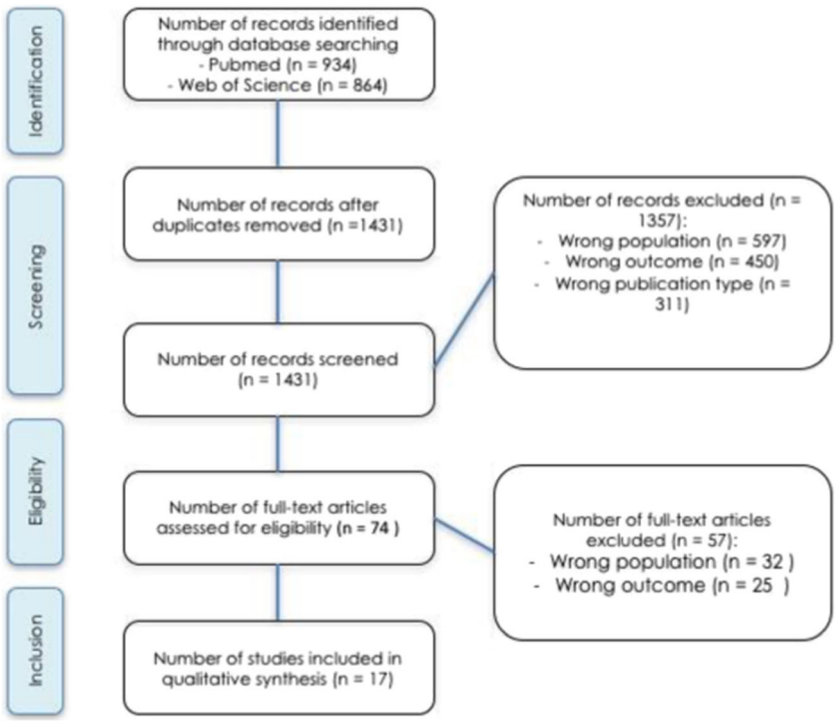

Fig. 1 Flowchart of the study selection process

Table 1 Patient-related determinants for the development of chronic pain in breast cancer survivors

Study	Design	Sample size (N)	Age (mean ± SD) unless otherwise stated	Follow-up (mean ± SD)	Pain outcome	Cut-off	Analgesic use (% of patients)	Type of pain	Risk factor category	PE (n)	(Adjusted) OR or RR (95 CI%)
Patient-related determinants											
Age											
Alkan et al. (2016) Turkey	CS	614	54.4 ± 10.1y	NM	Study specific questionnaire	NM	72%	PMPS	< 65y (Ref) > 65y	515 99	**OR: 0.59 [0.37-0.92]**[MA*]
Andersen Juhl et al. (2016) Denmark	CS	261	63.6 ± 11.3y	NM	Study specific questionnaire	Dichotomous	NM	Pain in the area of the missing breast, axilla, side of the thorax, mastectomy scar or arm	< 60y (Ref) ≥ 60y	169 92	OR: 1.50 [0.89-2.52][MA]
Bantema et al. (2012) The Netherlands	C	940	58.7 ± 10.2y at start of RT	Median: 30 m (Range: 6-54 m)	NM	NM	NM	Chest wall pain	≤ 50y (Ref) > 50y	214 726	**OR: 0.41 [0.23-0.72]**[MA**]
Bredal et al. (2014) Norway	CS	834	56 ± 7.8y	NM (Range: 2-6y since treatment)	NPRS	NPRS: ≥1	30.8%	Chronic pain	25- 55y (Ref) 56 - 65y Multivariate Logistic regression model Age (>46y)	305 529 **OR$_{Adj}$[f]: 0.95 [0.93-0.98]**[***]
Johannsen et al. (2015) Denmark	C	1905	Median: 56.5y at 15m post-operative	7.1 ± 0.7y since surgery 15.2 ± 0.8m since surgery	Study specific questionnaire	≥3 on 6-point Likert scale	34.5%	Pain at the arm / shoulder of the operated side and the surgical area	< 50y (Ref) ≥ 50y 60-71y (Ref) 50-59y 40-49y <40y	479 1426 666 760 400 79	**OR$_{7-9y}$: 0.65 [0.51-0.83]**[MA***] **OR$_{15m}$: 1.65 [1.31-2.07]**[***] **OR$_{15m}$: 1.68 [1.28-2.19]**[***] **OR$_{15m}$: 2.09 [1.30-3.38]**[***]
Moloney et al. (2016) Australia	C	121	54 ± 11.4y	21m since surgery	Pain item of the QLQ-C30	Dichotomous	NM	Pain	< 60y (Ref) > 60y	NM NM	OR: 1.60 [0.70-3.66][MA]
Peuckmann et al. (2009) Denmark	CS	1316	Numbers per age group: < 49y: 455 50-59y: 454 60-69y: 445 > 70y: 429	NM Time since surgery: 5-10y: 1127 > 10 y: 656	Study specific questionnaire	Dichotomous	12%	Chronic pain ≥6 m	40-49y (Ref) 50-70y	317 944	OR: 0.94 [0.71-1.24][MA]
Romero et al. (2016) Spain	C	1057	Number per age group: 50-54y: 310 55-59y: 283 60-64y: 278 65-70y: 186	Median: 8.7y (range 7.2–10.6 y)	Clinical record review	Pain ≥ 3m since surgery	NM	Persistent pain in the operated breast area, axilla, shoulder or arm	50-54y (Ref) ≥ 55y	310 747	OR: 0.93 [0.61-1.41][MA]
Alcohol use											
Alkan et al. (2016) Turkey	CS	614	54.4 ± 10.1y	NM	Study specific questionnaire	NM	72%	PMPS	No (Ref) Yes	586 26	OR: 0.59 [0.27-1.30][MA]

Table 1 (continued)

Study	Design	Sample size (N)	Age (mean ± SD) unless otherwise stated	Follow-up (mean ± SD)	Pain outcome	Cut-off	Analgesic use (% of patients)	Type of pain	Risk factor category	PE (n)	(Adjusted) OR or RR (95 CI%)
Johannsen et al. (2015) Denmark	C	1905	Median: 56.5y at 15m post-operative	7.1 ± 0.7y since surgery 15.2 ± 0.8 m since surgery	Study specific questionnaire	≥3 on 6-point Likert scale	34.5%	Pain at the arm / shoulder of the operated side and the surgical area	No (Ref) Yes	410 1491	 $OR_{7\text{-}9y}$: 1.23 [0.95-1.60]^{MA}
BMI											
Alkan et al. (2016) Turkey	CS	614	54.4 ± 10.1y	NM	Study specific questionnaire	NM	72%	PMPS	< 30 (Ref) > 30	375 238	 OR: 0.96 [0.69-1.32]^{MA}
Andersen Juhl et al. (2016) Denmark	CS	261	63.6 ± 11.3y	NM	Study specific questionnaire	Dichotomous	NM	Pain in the area of the missing breast, axilla, side of the thorax, mastectomy scar or arm	< 30 ≥ 30	213 45	 OR: 1.88 [0.99-3.60]^{MA}
Bredal et al. (2014) Norway	CS	834	56 ± 7.8y	NM (Range: 2-6y since treatment)	NPRS	NPRS: ≥1	30.8%	Chronic pain	BMI		OR: 1.02 [0.99-1.06]
Forsythe et al. (2013) USA	C	522	65.1 ± 9.2y	NM 10y since diagnosis	SF-36 bodily pain item	SF-36 bodily pain scores ≥1/2 SD worse than age-specific population norms	NM	Above-average pain	Normal weight (Ref) > 30 < 25 (Ref) 25-30	220 174 220 167	 **OR: 1.81 [1.12-2.93]**^{MA*} OR: 1.36 [0.83-2.34]
Johannsen et al. (2015) Denmark	C	1905	Median: 56.5y at 15m post-operative	7.1 ± 0.7y since surgery 15.2 ± 0.8 m since surgery	Study specific questionnaire	≥3 on 6-point Likert scale	34.5%	Pain at the arm / shoulder of the operated side and the surgical area	<30 (Ref) >30 Normal weight (Ref) Underweight Overweight Obese Severely obese	1663 209 1071 34 558 160 49	 **$OR_{7\text{-}9y}$: 1.44 [1.04-2.01]**^{MA*} OR_{15m}: 1.39 [0.69-2.81] $OR_{Adj\ 15m}^{a}$: 1.41 [0.70-2.87] OR_{15m}: 1.12 [0.90-1.40] $OR_{Adj\ 15m}^{a}$: 1.15 [0.92-1.44] **OR_{15m}: 1.75 [1.25-2.45]*** **$OR_{Adj\ 15m}^{a}$: 1.80 [1.28-2.54]*** OR_{15m}: 0.99 [0.53-1.84] $OR_{Adj\ 15m}^{a}$: 1.02 [0.54-1.90]
Moloney et al. (2016) Australia	C	121	54 ± 11.4y	21m since surgery	Pain item of the QLQ-C30	Dichotomous	NM	Pain	25 (Ref) >25	NM NM	 OR: 1.62 [0.80-3.28]^{MA}
Peuckmann et al. (2009) Denmark	CS	1316	Numbers per age group: < 49y: 455 50-59y: 454 60-69y: 445	NM Time since surgery: 5-10y: 1127	Study specific questionnaire	Dichotomous	12%	Chronic pain ≥6 m	25-30 (Ref) > 30	1098 133	 OR: 1.18 [0.8-1.7]^{MA}

Table 1 (continued)

Study	Design	Sample size (N)	Age (mean ± SD) unless otherwise stated	Follow-up (mean ± SD)	Pain outcome	Cut-off	Analgesic use (% of patients)	Type of pain	Risk factor category	PE (n)	(Adjusted) OR or RR (95 CI%)
			> 70y: 429	> 10 y: 656							
Children											
Alkan et al. (2016) Turkey	CS	614	54.4 ± 10.1y	NM	Study specific questionnaire	NM	72%	PMPS	No children (Ref) Children	67 534	 OR: 0.85 [0.51-1.43][MA]
Johannsen et al. (2015) Denmark	C	1905	Median: 56.5y at 15m post-operative	7.1 ± 0.7y since surgery 15.2 ± 0.8 m since surgery	Study specific questionnaire	≥3 on 6-point Likert scale	34.5%	Pain at the arm / shoulder of the operated side and the surgical area	No children (Ref) Children	208 1697	 $OR_{7\text{-}9y}$: 0.95 [0.67-1.35][MA] OR_{15m}: 1.00 [0.74-1.36] $OR_{Adj}{}^{a}{}_{15m}$:1.08 [0.79-1.47] $OR_{Adj}{}^{b}{}_{7\text{-}9y}$: 0.97 [0.66-1.43]
Comorbidities											
Alkan et al. (2016) Turkey	CS	614	54.4 ± 10.1y	NM	Study specific questionnaire	NM	72%	PMPS	No (Ref) Yes	586 26	 OR: 0.90 [0.65-1.25][MA]
Bredal et al. (2014) Norway	CS	834	56 ± 7.8y	NM (Range: 2-6y since treatment)	NPRS	NPRS: ≥1	30.8%	Chronic pain	No (Ref) Yes	NM NM	 **OR: 2.37 [1.72-3.27][MA]***
Johannsen et al. (2015) Denmark	C	1905	Median: 56.5y at 15m post-operative	7.1 ± 0.7y since surgery 15.2 ± 0.8 m since surgery	Study specific questionnaire	≥3 on 6-point Likert scale	34.5%	Pain at the arm / shoulder of the operated side and the surgical area	No (Ref) Yes	1736 163	 **$OR_{7\text{-}9y}$: 1.86 [1.48-2.34][MA]*** **OR_{15m}: 1.41 [1.01-1.96]*** **$OR_{Adj}{}^{a}{}_{15m}$: 1.54 [1.1-2.15]****
Education											
Alkan et al. (2016) Turkey	CS	614	54.4 ± 10.1y	NM	Study specific questionnaire	NM	72%	PMPS	< Year 13 (Ref) ≥ Year 13	495 119	 OR: 0.99 [0.66-1.48][MA]
Bell et al. (2014) Australia	CS	540	Median: 54y	5.7y since diagnosis	Study specific questionnaire	Dichotomous	NM	Breast pain at 5 - 6.7y since diagnosis	< Year12 (Ref) > Year 12	268 262	 OR: 1.02 [0.67-1.56][MA]
Bredal et al. (2014) Norway	CS	834	56 ± 7.8y	NM (Range: 2-6y since treatment)	NPRS	NPRS: ≥1	30.8%	Chronic pain	< 12y (Ref) > 12y	469 365	 OR: 1.28 [0.96-1.69][MA]
Johannsen et al. (2015) Denmark	C	1905	Median: 56.5y at 15m post-operative	7.1 ± 0.7y since surgery 15.2 ± 0.8 m since surgery	Study specific questionnaire	≥3 on 6-point Likert scale	34.5%	Pain at the arm / shoulder of the operated side and the surgical area	> Year 13 (Ref) ≤ Year 13	582 1304	 **$OR_{7\text{-}9y}$: 1.48 [1.15-1.92][MA]****

Table 1 (continued)

Study	Design	Sample size (N)	Age (mean ± SD) unless otherwise stated	Follow-up (mean ± SD)	Pain outcome	Cut-off	Analgesic use (% of patients)	Type of pain	Risk factor category	PE (n)	(Adjusted) OR or RR (95 CI%)
									Tertiary master degree (Ref)	97	
									Tertiary < master degree (14–17 years)	485	OR_{15m}: 1.28 [0.78-2.12] $OR_{7\text{-}9y}$: 1.82 [0.91-3.65] $OR_{Adj\ 15m}^{a}$: 1.34 [0.81-2.21] $OR_{Adj\ 7\text{-}9y}^{b}$: 1.68 [0.80-3.52]
									Upper secondary (11-13years)	766	**OR_{15m}: 1.65 [1.01-2.67]*** **$OR_{7\text{-}9y}$: 2.54 [1.29-4.99]**** **$OR_{Adj\ 15m}^{a}$: 1.79 [1.10-2.92]*** $OR_{Adj\ 7\text{-}9y}^{b}$: 2.14 [1.04-4.39]
									Lower secondary (8-10years)	254	**OR_{15m}: 1.76 [1.04-2.98]*** **$OR_{7\text{-}9y}$: 3.12 [1.53-6.35]**** **$OR_{Adj\ 15m}^{a}$: 1.85 [1.09-3.14]*** $OR_{Adj\ 7\text{-}9y}^{b}$: 2.50 [1.17-5.34]
									Lower secondary general (7years)	284	OR_{15m}: 1.26 [0.74-2.13] $OR_{7\text{-}9y}$: 1.86 [0.90-3.83] $OR_{Adj\ 15m}^{a}$: 1.68 [0.97-2.89] $OR_{Adj\ 7\text{-}9y}^{b}$: 1.94 [0.88-4.25]
Peuckmann et al. (2009) Denmark	CS	1316	Numbers per age group: < 49y: 455 50-59y: 454 60-69y: 445 > 70y: 429	NM Time since surgery: 5-10y: 1127 > 10 y: 656	Study specific questionnaire	Dichotomous	12%	Chronic pain ≥6 m	< 13y (Ref)	451	
									≥ 13y	645	OR: 0.81 [0.62-1.06]**MA**
Lymphedema											
Bell et al. (2014) Australia	CS	540	Median: 54y	5.7y since diagnosis	Study specific questionnaire	Dichotomous	NM	Breast pain at 5 - 6.7y since diagnosis	No (Ref)	397	
									Yes	132	**OR: 2.54 [1.39-4.64]**MA**
	CS	834	56 ± 7.8y	NM	NPRS	NPRS: ≥1	30.8%	Chronic pain	No (Ref) Yes	677 157	

Table 1 (continued)

Study	Design	Sample size (N)	Age (mean ± SD) unless otherwise stated	Follow-up (mean ± SD)	Pain outcome	Cut-off	Analgesic use (% of patients)	Type of pain	Risk factor category	PE (n)	(Adjusted) OR or RR (95 CI%)
Bredal et al. (2014) Norway				(Range: 2-6y since treatment)							**OR: 2.83 [1.98-4.05]**[MA***]
Gulluoglu et al. (2006) Turkey	CS	85	57,6y ± NM (Range: 28-85y)	≥ 6m since treatment	NM	NM	NM	Chronic pain at ipsilateral breast, chest wall or axilla	No (Ref) Yes	60 25	 OR: 1.42 [0,56-3.61][MA]
Relationship status											
Alkan et al. (2016) Turkey	CS	614	54.4 ± 10.1y	NM	Study specific questionnaire	NM	72%	PMPS	Cohabiting (Ref) Single	464 150	 OR: 0.85 [0.58-1.23][MA]
Bell et al. (2014) Australia	CS	540	Median: 54y	5.7y since diagnosis	Study specific questionnaire	Dichotomous	NM	Breast pain at 5 - 6.7y since diagnosis	Cohabiting (Ref) Single	443 87	 OR: 0.81 [0.47-1.4][MA]
Bredal et al. (2014) Norway	CS	834	56 ± 7.8y	NM (Range: 2-6y since treatment)	NPRS	NPRS: ≥1	30.8%	Chronic pain	Cohabiting (Ref) Single	592 242	 OR: 0.99 [0.73-1.34][MA]
Johannsen et al. (2015) Denmark	C	1905	Median: 56.5y at 15m post-operative	7.1 ± 0.7y since surgery 15.2 ± 0.8 m since surgery	Study specific questionnaire	≥3 on 6-point Likert scale	34.5%	Pain at the arm / shoulder of the operated side and the surgical area	Cohabiting (Ref) Single	1485 420	 $OR_{7\text{-}9y}$: 3.00 [2.27-3.98][MA] OR_{15m}: 1.07 [0.85-1.34] $OR_{Adj\ 15m}$[a]: 1.08 [0.86-1.36]
Peuckmann et al. (2009) Denmark	CS	1316	Numbers per age group: < 49y: 455 50-59y: 454 60-69y: 445 > 70y: 429	NM Time since surgery: 5-10y: 1127 > 10 y: 656	Study specific questionnaire	Dichotomous	12%	Chronic pain ≥6 m	Cohabiting (Ref) Single	844 396	 **OR: 1.34 [1.04-1.74]**[MA*]
Smoking status											
Alkan et al. (2016) Turkey	CS	614	54.4 ± 10.1y	NM	Study specific questionnaire	NM	72%	PMPS	Ex- or No-smoker (Ref) Smoker	546 66	 OR: 0.80 [0.48-1.34][MA]
Johannsen et al. (2015) Denmark	C	1905	Median: 56.5y at 15m post-operative	7.1 ± 0.7y since surgery 15.2 ± 0.8m since surgery	Study specific questionnaire	≥3 on 6-point Likert scale	34.5%	Pain at the arm / shoulder of the operated side and the surgical area	Ex- or No-smoker (Ref) Smoker	1364 509	 **$OR_{7\text{-}9y}$: 0.75 [0.6-0.92]**[MA**]
Others											
Alkan et al. (2016) Turkey	CS	614	54.4 ± 10.1y	NM	Study specific questionnaire	NM	72%	PMPS	Total monthly income: - > 1000 Turkish lira (Ref) - < 1000 Turkish lira Posttraumatic stress disorder: - No (Ref)	 536 76 164	 **OR: 1.89 [1.08-3.38]**[*]

Table 1 (continued)

Study	Design	Sample size (N)	Age (mean ± SD) unless otherwise stated	Follow-up (mean ± SD)	Pain outcome	Cut-off	Analgesic use (% of patients)	Type of pain	Risk factor category	PE (n)	(Adjusted) OR or RR (95 CI%)
									- Yes	433	**OR: 3.14 [2.05-4.81]*****
									Psychiatric support:		
									- No (Ref)	410	
									- Yes	204	OR: 1.31 [0.89-1.91]
									Regular use of analgetics:		
									- No (Ref)	168	
									- Yes	443	OR: 1.45 [0.96-2.17]
									Social support:		
									- High (Ref)	NM	
									- Low	NM	OR: 1.08 [0.73-1.61]
Bell et al. (2014) Australia	CS	540	Median: 54y	5.7y since diagnosis	Study specific questionnaire	Dichotomous	NM	Breast pain at 5 - 6.7y since diagnosis	- Severity of initial pain (FQ5):		
									A little disabling (Ref)	375	
									> a little disabling	155	**OR: 2.16 [1.26-3.70]****
									- Quality of original symptoms (FQ5):		
									Other (Ref)	86	
									Aching	263	**OR: 1.92 [1.24-2.98]****
									Shooting Pain	199	OR: 1.15 [0.74-1.80]
									Tingling	108	OR: 1.32 [0.75-2.30]
									Numbness	306	**OR: 1.63 [1.06-2.50]****
									Burning	62	OR: 0.84 [0.44-1.59]
									Phantom pain	43	OR: 1.59 [0.65-3.88]
Bredal et al. (2014) Norway	CS	834	56 ± 7.8y	NM (Range: 2-6y since treatment)	NPRS	NPRS: ≥1	30.8%	Chronic pain	- Anxiety		**OR: 2.88 [2.10-3.94]*****
									- Depression		**OR: 3.74 [2.42-5.40]*****
									Multivariate Logistic Regression Model		
									- Anxiety		**OR_{Adj}[f]: 1.83 [1.26-2.66]****
									- Depression		
Calhoun et al. (2015) USA	CS	761	63,6 ± 10.5y	7y since diagnosis (Range 1 - 43y)	Study specific questionnaire	Dichotomous	NM	Headache, joint, bone, or muscle pain during the past 4w	Race:		
									-White (Ref)	651	
									-Black	106	OR: 1,31 [0.86-1.99]
Crandall et al. (2004) USA	CS	476	50y ± NM	6y since diagnosis (Range: 2-11 y)	Breast Cancer Prevention Trial Symptom Checklist 5-point Likert scale ranging from 0 (Not at all) to 4 (Extremely)	The presence of a symptom was defined by a score of ≥1	NM	Joint pain	Menopausal status:		
									-premenopausal (Ref)	64	
									-perimenopausal	76	OR_{Adj}[d]: 0.73 [0.33-1.65]
									Peri + Tx trans:		OR_{Adj}[d]: 1,49 [0.61-3.66]
											OR_{Adj}[e]: 1.33 [0.53-3.35]

Table 1 (continued)

Study	Design	Sample size (N)	Age (mean ± SD) unless otherwise stated	Follow-up (mean ± SD)	Pain outcome	Cut-off	Analgesic use (% of patients)	Type of pain	Risk factor category	PE (n)	(Adjusted) OR or RR (95 CI%)
									Peri no Tx trans:		OR_{Adj}[d]: 0,45 [0.17-1.21] OR_{Adj}[e]: 0.44 [0.16-1.19]
									-postmenopausal	336	OR_{Adj}[d]: 1.04 [0.46-2.31]
									Post + Tx trans:		OR_{Adj}[d]: 1,28 [0.58-2.82] OR_{Adj}[e]:1.34 [0.60-3.00]
									Post no Tx trans:		OR_{Adj}[d]: 1,18 [0.52-2.68] OR_{Adj}[e]:1.24 [0.54-2.83]
Forsythe et al. (2013) USA	C	522	65.1 ± 9.2y	NM 10y since diagnosis	SF-36 bodily pain item	SF-36 bodily pain scores ≥1/2 SD worse than age-specific population norms	NM	Above-average pain	*Individual model*	*10 year analyses*	
									- Physical activity No activity (Ref)	242	
									Activity not meeting guidelines	188	OR: 0.94 [0.59-1.48]
									Meeting guidelines	121	**OR: 0.41 [0.22-0.75]**[**]
									- Television Time		
									Low (<2.5h/day) (Ref)	302	
									High(≥2.5h/day)	259	OR: 1.15 [0.76-1.72]
									Combined model		
									- BMI		
									Normal weight (Ref)		
									Overweight		OR: 1.42 [0.84-2.41]
									Obese		OR: 1.69 [0.99-2.88]
									- Physical activity		
									No activity (Ref)		
									Activity not meeting guidelines		OR: 0.99 [0.61-1.59]
									Meeting guidelines		**OR: 0.46 [0.24-0.86]**[*]
									- Television Time		
									Low (<2.5h/day) (Ref)		
									High(≥2.5h/day)	*Pain change analyses*	OR: 1.00 [0.65-1.56]
									Individual model -		
									- Changes in BMI	267	
									Maintained BMI 5%(Ref)		
									BMI increased >5%	98	**OR: 1.93 [1.17-3.17]**[*]

Table 1 (continued)

Study	Design	Sample size (N)	Age (mean ± SD) unless otherwise stated	Follow-up (mean ± SD)	Pain outcome	Cut-off	Analgesic use (% of patients)	Type of pain	Risk factor category	PE (n)	(Adjusted) OR or RR (95 CI%)
									BMI decreased >5%	137	OR: 1.01 [0.64-1.61]
									- Physical activity		
									Always inactive (Ref)	273	
									Active to inactive	110	OR: 0.90 [0.54-1.48]
									Inactive to active	26	OR: 0.36 [0.10-1.28]
									Always active	82	**OR: 0.38 [0.19-0.78]****
									- TV time		
									Maintained low TV time (Ref)	201	
									Decreased TV time	70	OR: 1.11 [0.58-2.11]
									Increased TV time	69	OR: 0.95 [0.48-1.88]
									Maintained high TV time	160	OR: 1.30 [0.79-2.14]
									Combined model - -		
									-Changes in BMI		
									Maintained BMI 5%(Ref)		
									BMI increased >5%		**OR:1.76 [1.03, 3.01]***
									BMI decreased > 5%		OR:0.89 [0.52, 1.53]
									- Physical activity		
									Always inactive (Ref)		
									Active to inactive		OR: 0.77 [0.45-1.34]
									Inactive to active		OR: 0.36 [0.10-1.28]
									Always active		**OR: 0.40 [0.20-0.84)***
									- TV time		
									Maintained low TV time (Ref)		
									Decreased TV time		OR: 1.09 [0.55-2.16]
									Increased TV time		OR: 0.84 [0.41-1.71]
									Maintained high TV time		OR: 1.15 [0.68-1.94]
Johannsen et al. (2015) Denmark	C	1905	Median: 56.5y at 15m post-operative	7.1 ± 0.7y since surger 15.2 ± 0.8 m since surgery	Study specific questionnaire	≥3 on 6-point Likert scale	34.5%	Pain at the arm / shoulder of the operated side and the surgical area	- Occupational status		
									Manager or Employee-medium or upper level (Ref)	574	
									Employee basic Level, in education or others	774	**OR_{15m}: 1.34 [1.06-1.69]*** **$OR_{7\text{-}9y}$: 1.36 [1.04-1.78]*** **$OR_{Adj}{}^{a}{}_{15m}$: 1.39 [1.10-1.75]***** $OR_{Adj}{}^{b}{}_{7\text{-}9y}$: 1.21 [0.90-1.63]
									Unemployed, recipient of temporary allow-ance-, cash- or pre-retirement benefits etc.	339	OR_{15m}: 1.03 [0.76-1.38] $OR_{7\text{-}9y}$: 0.95 [0.67-1.35] **$OR_{Adj}{}^{a}{}_{15m}$: 1.41 [1.02-1.94]***** $OR_{Adj}{}^{b}{}_{7\text{-}9y}$: 1.08 [0.72-1.63]

Table 1 (continued)

Study	Design	Sample size (N)	Age (mean ± SD) unless otherwise stated	Follow-up (mean ± SD)	Pain outcome	Cut-off	Analgesic use (% of patients)	Type of pain	Risk factor category	PE (n)	(Adjusted) OR or RR (95 CI%)
									Old age pension	81	OR_{15m}: 0.85 [0.50-1.44] $OR_{7\text{-}9y}$: 0.79 [0.41-1.50] $OR_{Adj}{}^{a}{}_{15m}$: 1.53 [0.86-2.73] $OR_{Adj}{}^{b}{}_{7\text{-}9y}$: 1.23 [0.58-2.64]
									Recipients of early retirement pension, rehabilitation- or sickness benefits	133	**OR_{15m}: 1.65 [1.12-2.44]*** $OR_{7\text{-}9y}$: 1.55 [1.00-2.42] **$OR_{Adj}{}^{a}{}_{15m}$: 2.14 [1.43-3.22]***** $OR_{Adj}{}^{b}{}_{7\text{-}9y}$: 1.32 [0.79-2.21]
									- Personal income (US$)		
									>55.000 (Ref)	373	
									>40.000 and ≤55.000	532	OR_{15m}: 1.03 [0.77-1.38] $OR_{7\text{-}9y}$: 1.09 [0.78-1.52] $OR_{Adj}{}^{a}{}_{15m}$: 1.03 [0.77-1.38] $OR_{Adj}{}^{b}{}_{7\text{-}9y}$: 1.02 [0.71-1.48]
									>30.000 and ≤40.000	398	OR_{15m}: 1.31 [0.97-1.77] $OR_{7\text{-}9y}$: 1.38 [0.97-1.95] **$OR_{Adj}{}^{a}{}_{15m}$: 1.38 [1.01-1.87]**** $OR_{Adj}{}^{b}{}_{7\text{-}9y}$: 1.23 [0.84-1.80]
									>20.000 and ≤30.000	358	OR_{15m}: 1.24 [0.91-1.69] $OR_{7\text{-}9y}$: 0.94 [0.65-1.37] **$OR_{Adj}{}^{a}{}_{15m}$: 1.55 [1.12-2.14]**** $OR_{Adj}{}^{b}{}_{7\text{-}9y}$: 0.89 [0.58-1.35]
									>20.000	240	OR_{15m}: 1.23 [0.87-1.73] $OR_{7\text{-}9y}$: 1.17 [0.78-1.75] **$OR_{Adj}{}^{a}{}_{15m}$: 1.65 [1.15-2.38]**** $OR_{Adj}{}^{b}{}_{7\text{-}9y}$: 1.19 [0.75-1.90]

Table 1 (continued)

Study	Design	Sample size (N)	Age (mean ± SD) unless otherwise stated	Follow-up (mean ± SD)	Pain outcome	Cut-off	Analgesic use (% of patients)	Type of pain	Risk factor category	PE (n)	(Adjusted) OR or RR (95 CI%)
									- Houshold net wealth per person (US $)		
									≥120.000 (Ref)	399	
									≥55.000 and <120.000	438	OR_{15m}: 1.27 [0.94-1.72] $OR_{7\text{-}9y}$: 0.91 [0.64-1.29] $OR_{Adj}{}^{a}{}_{15m}$: 1.23 [0.91-1.66] $OR_{Adj}{}^{b}{}_{7\text{-}9y}$: 0.76 [0.52-1.11]
									≥20.000 and <55.000	372	OR_{15m}: 1.19 [0.87-1.63] $OR_{7\text{-}9y}$: 0.99 [0.69-1.41] $OR_{Adj}{}^{a}$: 1.09 [0.80-1.50] $OR_{Adj}{}^{b}{}_{7\text{-}9y}$: 0.83 [0.56-1.25]
									≥0 and <20.000	333	**OR_{15m}: 1.38 [1.01-1.90]***** $OR_{7\text{-}9y}$: 0.95 [0.66-1.39] $OR_{Adj}{}^{a}$: 1.24 [0.90-1.72] $OR_{Adj}{}^{b}{}_{7\text{-}9y}$: 0.68 [0.45-1.04]
									<0	359	**OR_{15m}: 2.05 [1.51-2.79]***** **$OR_{7\text{-}9y}$: 1.73 [1.24-2.43]**** **$OR_{Adj}{}^{a}{}_{15m}$: 1.76 [1.28-2.41]*** $OR_{Adj}{}^{b}{}_{7\text{-}9y}$: 1.05 [0.71-1.57]
									- Ethnicity		
									Immigrant or descendant (Ref)	49	
									Non-immigrant or non-descendant	1853	OR_{15m}: 1.51 [0.78-2.92] $OR_{7\text{-}9y}$: 2.29 [0.90-5.82] $OR_{Adj}{}^{a}{}_{15m}$: 1.47 [0.76-2.86] $OR_{Adj}{}^{b}{}_{7\text{-}9y}$: 2.08 [0.78-5.55]

Table 1 (continued)

Study	Design	Sample size (N)	Age (mean ± SD) unless otherwise stated	Follow-up (mean ± SD)	Pain outcome	Cut-off	Analgesic use (% of patients)	Type of pain	Risk factor category	PE (n)	(Adjusted) OR or RR (95 CI%)
									- PASE components Walking	1696	OR_{15m}: 0.99 [0.97-1.01] $OR_{7\text{-}9y}$: 1.02 [1.00-1.05] $OR_{Adj}{}^{a}{}_{15m}$: 1.00 [0.98-1.02] **$OR_{Adj}{}^{b}{}_{7\text{-}9y}$: 1.03 [1.01-1.06]***
									Mild exercise	337	OR_{15m}: 1.00 [0.94-1.05] $OR_{7\text{-}9y}$: 1.03 [0.97-1.09] $OR_{Adj}{}^{a}{}_{15m}$: 1.00 [0.94-1.05] $OR_{Adj}{}^{b}{}_{7\text{-}9y}$: 1.04 [0.97-1.12]
									Moderate exercise	905	**OR_{15m}: 0.94 [0.91-0.98]**** $OR_{7\text{-}9y}$: 1.00 [0.97-1.04] $OR_{Adj}{}^{a}{}_{15m}$: **0.94 [0.91-0.98]**** $OR_{Adj}{}^{b}{}_{7\text{-}9y}$: 1.04 [1.00-1.08]
									Strenuous exercise	643	**OR_{15m}: 0.88 [0.82-0.94]***** $OR_{7\text{-}9y}$: 0.99 [0.93-1.058] **$OR_{Adj}{}^{a}{}_{15m}$: 0.88 [0.82-0.94]***** $OR_{Adj}{}^{b}{}_{7\text{-}9y}$: 1.04 [0.98-1.04]
									Weight training	330	OR_{15m}: 0.96 [0.89-1.03] $OR_{7\text{-}9y}$: 1.06 [0.99-1.13] $OR_{Adj}{}^{a}{}_{15m}$: 0.96 [0.90-1.03] $OR_{Adj}{}^{b}{}_{7\text{-}9y}$: **1.10 [1.03-1.19]****
									Physical workload	731	OR_{15m}: 0.97 [0.93-1.02] $OR_{7\text{-}9y}$: 1.04 [1.00-1.09] **$OR_{Adj}{}^{a}{}_{15m}$: 0.94 [0.90-0.99]**** $OR_{Adj}{}^{b}{}_{7\text{-}9y}$: 1.05 [1.00-1.11]

Table 1 (continued)

Study	Design	Sample size (N)	Age (mean ± SD) unless otherwise stated	Follow-up (mean ± SD)	Pain outcome	Cut-off	Analgesic use (% of patients)	Type of pain	Risk factor category	PE (n)	(Adjusted) OR or RR (95 CI%)
									- SF-36 PF 100(best) (Ref)	488	
									> 90 and <100	409	**OR_{15m}: 1.71 [1.20-2.43]***** **$OR_{7\text{-}9y}$: 2.49 [1.64-3.78]***** **$OR_{Adj}{}^{a}{}_{15m}$:1.73 [1.21-2.47]***** **$OR_{Adj}{}^{b}{}_{7\text{-}9y}$: 2.00 [1.29-3.11]****
									> 80 and ≤90	448	**OR_{15m}: 4.02 [2.91-5.55]***** **$OR_{7\text{-}9y}$: 3.63 [2.44-5.39]***** **$OR_{Adj}{}^{a}{}_{15m}$:4.29 [3.09-5.95]***** **$OR_{Adj}{}^{b}{}_{7\text{-}9y}$: 2.08 [1.36-3.19]****
									> 70 and ≤80	267	**OR_{15m}: 7.51 [5.26-10.7]***** **$OR_{7\text{-}9y}$: 5.63 [3.70-8.56]***** **$OR_{Adj}{}^{a}{}_{15m}$:7.79 [5.44-11.17]***** **$OR_{Adj}{}^{b}{}_{7\text{-}9y}$: 2.40 [1.52-3.79]****
									≥ 0 and ≤70 (worst)	274	**OR_{15m}: 8.48 [5.95-12.08]***** **$OR_{7\text{-}9y}$: 5.33 [3.51-8.09]***** **$OR_{Adj}{}^{a}{}_{15m}$:9.87 [6.87-14.19]***** **$OR_{Adj}{}^{b}{}_{7\text{-}9y}$: 2.00 [1.25-3.20]****
Moloney et al. (2016) Australia	C	121	54 ± 11.4y	21m since surgery	Pain item of the QLQ-C30	Dichotomous	NM	Pain	Physical function	NM	OR: 1.4 [0.5-4.1]
									Insomnia	NM	OR: 1.8 [0.8-4.1]
									Baseline pain	NM	OR: 1.7 [0.6-4.4]
									Emotional function	NM	**OR: 0.4 [0.2-0.9]***
									Arm symptoms	NM	**OR: 10.0 [1.2-81.5]***
									Breast symptoms	NM	OR: 1.4 [0.6-3.2]
Peuckmann et al. (2009) Denmark	CS	1316	Numbers per age group: < 49y: 455 50-59y: 454 60-69y: 445 > 70y: 429	NM Time since surgery: 5-10y: 1127 > 10 y: 656	Study specific questionnaire	Dichotomous	12%	Chronic pain ≥6 m	- Time since surgery		
									> 10y (Ref)	453	
									5-10y	808	**OR: 1.35 [1.01-1.81]***
									- Medication		
									Analgesics (opiods)	17	**$RR_{Adj}{}^{a}$: 2.36 [1.56-3.57]***
									Analgesics (non-opioids)	123	**$RR_{Adj}{}^{a}$:1.46 [1.33-1.60]***

Table 1 (continued)

Study	Design	Sample size (N)	Age (mean ± SD) unless otherwise stated	Follow-up (mean ± SD)	Pain outcome	Cut-off	Analgesic use (% of patients)	Type of pain	Risk factor category	PE (n)	(Adjusted) OR or RR (95 CI%)
									Sedatives/ anxiolytics/ antidepressants	45	**RR_{Adj}[a]:1.67 [1.33-2.10]***
Romero et al. (2016) Spain	C	1057	Number per age group: 50-54y: 310 55-59y: 283 60-64y: 278 65-70y: 186	Median: 8.7y (range 7.2–10.6 y)	Clinical record review	Pain ≥ 3m since surgery	NM	Persistent pain in the operated breast area, axilla, shoulder or arm	Charlson index:		
									- 0 (Ref)	776	
									- 1	182	**OR_{adj}[h]: 2.8 [1.4-5.4]****
									- ≥ 2	99	**OR_{adj}[h]: 4.5 [2.1-9.5]*****
Steyaert et al. (2016) Belgium	CS	128	56.5 ± 12.4y	80 ± 18.5m since surgery	Study specific questionnaire	Dichotomous	28.6%	Pain at time of questioning	Height:		OR: 1.12 [0.94-1.33]
									Weight:		OR: 0.97 [0.82-1.16]
									Recall of preoperative pain:		**OR_{adj}[i]: 1.27 [1.09-1.48]****

Abbreviations:

AI, Aromatase inhibitors; BMI, Body Mass Index; CI, Confidence interval; C, Cohort; CS, Cross-sectional; NM, Not mentioned; NPRS, Numeric Pain Rating Scale; OR, Odds ratio; PE, Patients exposed to variable; Ref, Reference; RR, Relative Risk; SD, Standard deviation; TAM, Tamoxifen; DBCG, Danish Breast Cancer Cooperative Group; FQ1, Follow-up questionnaires after 12 months; FQ5, Follow-up questionnaire after 5 years; LRRT, Locoregional radiotherapy to the axillary level; PASE, Physical Activity Scale for the Elderly; PF, Physical function; Tx trans, Menopause status transition in association with treatment for breast cancer; no Tx trans, Menopause transition did not occur in proximity to treatment for breast cancer; VCR, Victorian Cancer Registry; NSAID, nonsteroidal anti-inflammatory drugs; PACU, postanesthesia care unit

*: Odds ratio included in meta-analysis

a: Adjusted for age

b: Adjusted for age and pain at 15 months

c: When appropriate, the relative risks is adjusted for age at follow-up, educational level, time since randomisation, body mass index at follow-up, body mass index during treatment, smoking habits and tumour size, using the SAS procedure GENMOD (SAS version 9.2; SAS Institute Inc., Cary, NC) with binomial distribution and logarithmic link function.

d: Adjusted for age, years since diagnosis, BMI, self-rated health, mood, smoking, alcohol intake, type of breast cancer surgery, type of breast cancer treatment, and whether the participant experienced a transition in relation to treatment for breast cancer.

e: Adjusted for age, years since diagnosis, BMI, self-rated health, mood, smoking, alcohol intake, type of breast cancer surgery, type of breast cancer treatment, restless sleep, current tamoxifen, and whether the participant experienced a transition in relation to treatment for breast cancer.

f: An analysis was performed in which chemotherapy and LRRT were entered as categorical variables in the regression and controlling for age, anxiety, depression, and previous pain.

g: Adjusted for edema

h: Adjusted for detection method, age, Charlson index, histological type, phenotype, axillary treatment, neoadjuvant treatment and chemotherapy after surgery

7-9y: Follow-up of 7-9 years

15m: Follow-up of 15 months

Table 2 Treatment-related determinants for the development of chronic pain in breast cancer survivors

Study	Design	Sample size (N)	Age (mean ± SD) unless otherwise stated	Follow-up (mean ± SD)	Pain outcome	Cut-off	Analgesic use (% of patients)	Type of pain	Risk factor category	PE (n)	(Adjusted) OR or RR (95 CI%)
Treatment-related determinants											
Axillary surgery: Axillary lymph node dissection VS Sentinel lymph node biopsy											
Anderson Juhl et al. (2016)	CS	261	63.6 ± 11.3	NM	Study specific question-naire	Dichotomous	NM	Pain in the area of the missing breast, axilla, side of the thorax, mastectomy scar or arm	Sentinel lymph node biopsy (Ref)	102	
									Axillary lymph node dissection	157	OR: 1.46 [0.74-2.88]^{MA}
Bredal et al. (2014) Norway	CS	834	56 ± 7.8y	NM	NPRS	NPRS: ≥1	30.8%	Chronic pain	Sentinel lymph node biopsy (Ref)	393	
				(Range: 2-6y since treatment)					Axillary lymph node dissection	275	OR: 1.18 [0.86-1.60]^{MA}
Gulluoglu et al. (2006) Turkey	CS	85	57,6y ± NM (Range: 28-85y)	≥ 6m since treatment	NM	NM	NM	Chronic pain at ipsilateral breast, chest wall or axilla	No axillary dissection (Ref)	11	
									Axillary lymph node dissection	74	OR: 1.57 [0.42-5.82]^{MA}
Johannsen et al. (2015) Denmark	C	1905	Median: 56.5y at 15m post-operative	7.1 ± 0.7y since surgery	Study specific question-naire	≥3 on 6-point Likert scale	34.5%	Pain at the arm / shoulder of the operated side and the surgical area	Sentinel lymph node biopsy (Ref)	1332	
				15.2 ± 0.8m since surgery					Axillary lymph node dissection	437	$OR_{7\text{-}9y}$: 4.10 [2.77-6.05]^{MA} **OR_{15m}: 1.93 [1.42-2.61]***** **$OR_{Adj\ 15m}^{a}$: 2.05 [1.59-2.64]*****
Moloney et al. (2016) Australia	C	121	54 ± 11.4y	21m since surgery	Pain item of the QLQ-C30	Dichotomous	NM	Pain	Sentinel lymph node biopsy (Ref)	50	
									Axillary lymph node dissection	71	OR: 0.70 [0.40-1.22]^{MA}
Romero et al. (2016) Spain	C	1057	Number per age group: 50-54y: 310 55-59y: 283 60-64y: 278 65-70y: 186	Median: 8.7y (range 7.2–10.6 y)	Clinical record review	Pain ≥ 3m since surgery	NM	Persistent pain in the operated breast area, axilla, shoulder or arm	Sentinel lymph node biopsy (Ref)	268	
									Axillary lymph node dissection	726	**OR: 2.00 [1.00-4.00]^{MA*}**
Breast surgery: Mastectomy VS Breast conserving surgery											
Alkan et al. (2016) Turkey	CS	614	54.4 ± 10.1y	NM	Study specific question-naire	NM	72%	PMPS	Breast conserving surgery (Ref)	212	
									Mastectomy	397	**OR: 0.69 [0.50-0.97]^{MA*}**

Table 2 (continued)

Study	Design	Sample size (N)	Age (mean ± SD) unless otherwise stated	Follow-up (mean ± SD)	Pain outcome	Cut-off	Analgesic use (% of patients)	Type of pain	Risk factor category	PE (n)	(Adjusted) OR or RR (95 CI%)
Bell et al. (2014) Australia	CS	540	Median: 54y	5.7y since diagnosis	Study specific question-naire	Dichotomous	NM	Breast pain at 5 - 6.7y since diagnosis	Breast conserving surgery (Ref)	377	
									Mastectomy	151	OR: 1.20 [0.74-1.95]^{MA}
Bredal et al. (2014) Norway	CS	834	56 ± 7.8y	NM (Range: 2-6y since treatment)	NPRS	NPRS: ≥1	30.8%	Chronic pain	Breast conserving surgery (Ref)	503	
									Mastectomy	331	OR: 1.01 [0.76-1.34]^{MA}
Gulluoglu et al. (2006) Turkey	CS	85	57,6y ± NM (Range: 28-85y)	≥ 6m since treatment	NM	NM	NM	Chronic pain at ipsilateral breast, chest wall or axilla	Breast conserving surgery (Ref)	22	
									Mastectomy	63	OR: 0.38 [0.14 -1.03]^{MA}
Johannsen et al. (2015) Denmark	C	1905	Median: 56.5 at 15 month post op	7.1 ± 0.7 years since surgery 15.2 ± 0.8 months since surgery	Study specific question-naire	≥3 on 6-point Likert scale	34,5%	Pain at the arm / shoulder of the operated side and the surgical area	Lumpectomy (Ref)	940	
									Mastectomy	965	OR: 1.21 [0.96-1.51]^{MA} OR_{15m}: 0.86 [0.71-1.04] $OR_{Adj\ 15m}^{a}$: 0.85 [0.70-1.03]
Moloney et al. (2016) Australia	C	121	54 ± 11.4y	21m since surgery	Pain item of the QLQ-C30	Dichotomous	NM	Pain	Breast conserving surgery (Ref)	64	
									Mastectomy	57	OR: 1.10 [0.50-2.42]^{MA}
Peuckmann et al. (2009) Denmark	CS	1316	Numbers per age group: < 49y: 455 50-59y: 454 60-69y: 445 > 70y: 429	NM Time since surgery: 5-10y: 1127 > 10 y: 656	Study specific question-naire	Dichotomous	12%	Chronic pain ≥6 m	Lumpectomy (Ref)	403	
									Mastectomy	858	**OR: 0.72 [0.56-0.93]^{MA*}**
Romero et al. (2016) Spain	C	1057	Number per age group: 50-54y: 310 55-59y: 283 60-64y: 278 65-70y: 186	Median: 8.7y (range 7.2–10.6 y)	Clinical record review	Pain ≥ 3m since surgery	NM	Persistent pain in the operated breast area, axilla, shoulder or arm	Breast conserving surgery (Ref)	829	
									Mastectomy	226	OR: 1.10 [0.69-1.73]^{MA}
Chemotherapy											
Anderson Juhl et al. (2016)	CS	261	63.6 ± 11.3	NM	Study specific question-naire	Dichotomous	NM	Pain in the area of the missing breast, axilla, side of the thorax, mastectomy scar or arm	No (Ref)	165	
									Yes	96	OR: 1.65 [0.98-2.78]^{MA}
Bell et al. (2014) Australia	CS	540	Median: 54y	5.7y since diagnosis	Study specific	Dichotomous	NM	Breast pain at 5 - 6.7y since diagnosis	No (Ref)	227	
									Yes	303	**OR: 1.74 [1.13-2.67]^{MA*}**

Table 2 (continued)

Study	Design	Sample size (N)	Age (mean ± SD) unless otherwise stated	Follow-up (mean ± SD)	Pain outcome	Cut-off	Analgesic use (% of patients)	Type of pain	Risk factor category	PE (n)	(Adjusted) OR or RR (95 CI%)
					question-naire						
Bredal et al. (2014) Norway	CS	834	56 ± 7.8y	NM (Range: 2-6y since treatment)	NPRS	NPRS: ≥1	30.8%	Chronic pain	No (Ref) Yes	390 444	**OR: 1.88 [1.42-2.49]**[MA]***
Gulluoglu et al. (2006) Turkey	CS	85	57,6y ± NM (Range: 28-85y)	≥ 6m since treatment	NM	NM	NM	Chronic pain at the ipsilateral breast, chest wall or axilla	No (Ref) Yes	36 49	OR: 1.64 [0.68-3.92][MA]
Johannsen et al. (2015) Denmark	C	1905	Median: 56.5y at 15m post-operative	7.1 ± 0.7y since surgery 15.2 ± 0.8m since surgery	Study specific question-naire	≥3 on 6-point Likert scale	34.5%	Pain at the arm / shoulder of the operated side and the surgical area	No (Ref) Yes Pre-menopausal No (Ref) Yes Post-menopausal No (Ref) Yes	781 1078 134 623 944 158	**$OR_{7\text{-}9y}$: 0.52 [0.41-0.65]**[MA]*** OR_{15m}: 1.26 [0.85-1.88] $OR_{7\text{-}9y}$: 1.05 [0.68-1.64] $OR_{Adj}{}^{a}{}_{15m}$: 1.22 [0.82-1.83] $OR_{Adj}{}^{b}{}_{7\text{-}9y}$: 0.91 [0.55-1.49] OR_{15m}: 0.83 [0.57-1.21] $OR_{7\text{-}9y}$: 0.66 [0.41-1.08] $OR_{Adj}{}^{a}{}_{15m}$: 0.79 [0.54-1.17] $OR_{Adj}{}^{b}{}_{7\text{-}9y}$: 0.66 [0.39-1.12]
Romero et al. (2016) Spain	C	1057	Number per age group: 50-54y: 310 55-59y: 283 60-64y: 278 65-70y: 186	Median: 8.7y (range 7.2–10.6 y)	Clinical record review	Pain ≥ 3m since surgery	NM	Persistent pain in the operated breast area, axilla, shoulder or arm	No (Ref) Yes	513 505	$OR_{Adj}{}^{h}$: 1.40 [0.70-2.80][MA]
Steyaert et al. (2016) Belgium	CS	128	56.5 ± 12.4y	80 ± 18.5m since surgery	Study specific question-naire	Dichotomous	28.6%	Pain at time of questioning	No (Ref) Yes	45 83	**OR: 1.29 [1.09-1.53]**[MA]**
Hormone Therapy											
Anderson Juhl et al. (2016)	CS	261	63.6 ± 11.3	NM	Study specific question-naire	Dichotomous	NM	Pain in the area of the missing breast, axilla, side of the thorax, mastectomy scar or arm	No (Ref) Yes	47 182	OR: 0.92 [0.48-1.77][MA]
	CS	540	Median: 54y	5.7y since diagnosis	Study specific	Dichotomous	NM	Breast pain at 5 - 6.7y since diagnosis	No (Ref) Yes	357 173	

Table 2 (continued)

Study	Design	Sample size (N)	Age (mean ± SD) unless otherwise stated	Follow-up (mean ± SD)	Pain outcome	Cut-off	Analgesic use (% of patients)	Type of pain	Risk factor category	PE (n)	(Adjusted) OR or RR (95 CI%)
Bell et al. (2014) Australia					question-naire						OR: 1.29 [0.81-2.06]^{MA}
Bredal et al. (2014) Norway	CS	834	56 ± 7.8y	NM (Range: 2-6y since treatment)	NPRS	NPRS: ≥1	30.8%	Chronic pain	No (Ref)	362	
									Yes	472	**OR: 1.32 [1.00-1.75]^{MA*}**
									Tamoxifen	208	OR: 1.03 [0.99-1.72]
									AI	60	OR: 0.91 [0.68-1.23]
									Tamoxifen + AI	203	OR: 0.93 [0.67-1.28]
Gulluoglu et al. (2006) Turkey	CS	85	57,6y ± NM (Range: 28-85y)	≥ 6m since treatment	NM	NM	NM	Chronic pain at ipsilateral breast, chest wall or axilla	No (Ref)	23	
									Yes	62	OR: 0.89 [0.34-2.34]^{MA}
Johannsen et al. (2015) Denmark	C	1905	Median: 56.5y at 15m post-operative	7.1 ± 0.7y since surgery 15.2 ± 0.8 m since surgery	Study specific question-naire	≥3 on 6-point Likert scale	34.5%	Pain at the arm / shoulder of the operated side and the surgical area	No (Ref)	641	
									Yes	1218	**$OR_{7\text{-}9y}$: 1.29 [1.01-1.64]^{MA*}**
									Pre-menopausal		
									No (Ref)	247	
									In treatment	510	OR_{15m}: 1.24 [0.90-1.70] $OR_{7\text{-}9y}$: 0.91 [0.64-1.29] $OR_{Adj\ 15m}^{a}$: 1.23 [0.90-1.69] $OR_{Adj\ 7\text{-}9y}^{b}$: 0.82 [0.55-1.22]
									Post-menopausal		
									No (Ref)	394	
									In treatment	708	**OR_{15m}: 1.49 [1.13-1.97]** $OR_{7\text{-}9y}$: 1.71 [1.21-2.41]** $OR_{Adj\ 15m}^{a}$: 1.51 [1.14-2.00]** $OR_{Adj\ 7\text{-}9y}^{b}$: 1.62 [1.11-2.35]***
Romero et al. (2016) Spain	C	1057	Number per age group: 50-54y: 310 55-59y: 283 60-64y: 278 65-70y: 186	Median: 8.7y (range 7.2–10.6 y)	Clinical record review	Pain ≥ 3m since surgery	NM	Persistent pain in the operated breast area, axilla, shoulder or arm	No (Ref)	219	
									Yes	800	OR: 0.80 [0.51-1.25]^{MA}
Steyaert et al. (2016) Belgium	CS	128	56.5 ± 12.4y	80 ± 18.5m since surgery	Study specific question-naire	Dichotomous	28.6%	Pain at time of questioning	No (Ref)	22	
									Yes	106	OR: 0.98 [0.83-1.16]^{MA**}

Table 2 (continued)

Study	Design	Sample size (N)	Age (mean ± SD) unless otherwise stated	Follow-up (mean ± SD)	Pain outcome	Cut-off	Analgesic use (% of patients)	Type of pain	Risk factor category	PE (n)	(Adjusted) OR or RR (95 CI%)
Van Londen et al. (2014) USA	CS	1013	53 ± 10y	5.4 ± 5.2y since diagnosis	Livestrong survey	Dichotomous	NM	Pain	No (Ref)	387	
Radiotherapy									Yes	626	**OR: 1.55 [1.18-2.04]^{MA**}**
Alkan et al. (2016) Turkey	CS	614	54.4 ± 10.1y	NM	Study specific questionnaire	NM	72%	PMPS	No (Ref)	197	
									Yes	416	OR: 1.33 [0.95-1.86]^{MA}
Andersen Juhl et al. (2016) Denmark	CS	261	63.6 ± 11.3y	NM	Study specific questionnaire	Dichotomous	NM	Pain in the area of the missing breast, axilla, side of the thorax, mastectomy scar or arm	No (Ref)	149	
									Yes	112	OR: 1.21 [0.87-1.68]^{MA}
Bell et al. (2014) Australia	CS	540	Median: 54y	5.7y since diagnosis	Study specific questionnaire	Dichotomous	NM	Breast pain at 5 - 6.7y since diagnosis	No (Ref)	117	
									Yes	413	OR: 0.91 [0.54-1.53]^{MA}
Bredal et al. (2014) Norway	CS	834	56 ± 7.8y	NM (Range: 2-6y since treatment)	NPRS	NPRS: ≥1	30.8%	Chronic pain	No (Ref)	204	
									Yes	630	OR: 1.27 [0.92-1.77]^{MA}
									Locoregional radiotherapy of axilla	444	**OR: 1.69 [1.22-2.34]****
Gulluoglu et al. (2006) Turkey	CS	85	57,6y ± NM (Range: 28-85y)	≥ 6m since treatment	NM	NM	NM	Chronic pain at ipsilateral breast, chest wall or axilla	No (Ref)	39	
									Yes	46	**OR: 2.60 [1.07-6.30]^{MA*}**
Johannsen et al. (2015) Denmark	C	1905	Median: 56.5y at 15m post-operative	7.1 ± 0.7y since surgery 15.2 ± 0.8m since surgery	Study specific questionnaire	≥3 on 6-point Likert scale	34.5%	Pain at the arm / shoulder of the operated side and the surgical area	No (Ref)	394	
									Yes	1511	$OR_{7\text{-}9y}$: 1.05 [0.77-1.43]^{MA}
									No (Ref)	394	
									Yes	1511	OR_{15m}: 1.25 [0.98-1.59] $OR_{Adj\ 15m}^{a}$: 1.22 [0.96-1.56]
Lundstedt et al. (2010) Sweden	CS	365	66.6y ± NM	13.8y since treatment (Range: 10-17y since treatment)	7-point Likert scale	Pain by pressuring or touching was defined by a score of ≥5 Severe pain or discomfort was defined by answering "moderate" or "to much"	NM	Occasionally breast pain the previous 6m	No (Ref)	193	
									Yes	171	**OR: 2,25 [1.39-3.62]^{MA***}**
Lundstedt et al.(2015) Sweden	CS	701	Intervention group: 58,3 ± 9.1y (Range: 33-76y) Control group: 54,7 ± 8,6y (Range: 35-76y)	Intervention group: 5,2 ± 1,4y since treatment (Range: 3-8y) Control group: 5,2 ± 1,3y since treatment (Range: 3-8y)	Study specific questionnaire	Paresthesia was defined by answering "Yes, at least every week"	NM	-Paresthesia	No (Ref)	505	
									Yes	191	**OR: 1.60 [1.03-2.47]^{MA*}**
								-Breast pain ≥1/week the previous 6m	No (Ref)	193	
									Yes	171	**RR_{Adj}^{c}: 15.1 [2.03-112]*****

Table 2 (continued)

Study	Design	Sample size (N)	Age (mean ± SD) unless otherwise stated	Follow-up (mean ± SD)	Pain outcome	Cut-off	Analgesic use (% of patients)	Type of pain	Risk factor category	PE (n)	(Adjusted) OR or RR (95 CI%)
								-Breast pain when pressuring the breast the previous 6m	No (Ref) Yes	193 171	**RR_{Adj}[c]: 5.09 [1.80-14.4]**[***]
								-Breast pain when touching the breast the previous 6m	No (Ref) Yes	193 171	**RR_{Adj}[c]: 3.10 [1.04-9.24]**[*]
								-Severe breast pain the previous 6m	No (Ref) Yes	193 171	RR_{Adj}[c]: 7.05 [0.89-55.8]
								- Pain in the skin on the breast, on occasion	No (Ref) Yes	193 171	**RR_{Adj}[c]: 1.86 [1.14-3.04]**[*]
								- Pain in the skin on the breast ≥1/week	No (Ref) Yes	193 171	RR_{Adj}[c]: 2.07 [0.54-7.86]
								- Pain in the skin when pressuring the breast the previous 6m	No (Ref) Yes	193 171	**RR_{Adj}[c]: 2.67 [1.09-6.58]**[*]
								- Pain in the skin when touching the breast the previous 6m	No (Ref) Yes	193 171	RR_{Adj}[c]: 8.02 [1.03-62.6]
								- Severe pain or discomfort in the skin on the breast the previous 6 m	No (Ref) Yes	193 171	RR_{Adj}[c]: 4.34 [0.51-36.7]
Peuckmann et al. (2009) Denmark	CS	1316	Numbers per age group: < 49y: 455 50-59y: 454 60-69y: 445 > 70y: 429	NM Time since surgery: 5-10y: 1127 > 10 y: 656	Study specific question-naire	Dichotomous	12%	Chronic pain ≥6 m	No (Ref) Yes	779 482	**OR: 1.43 [1.07-1.91]**[MA*]
Romero et al. (2016) Spain	C	1057	Number per age group: 50-54y: 310 55-59y: 283 60-64y: 278 65-70y: 186	Median: 8.7y (range 7.2–10.6 y)	Clinical record review	Pain ≥ 3m since surgery	NM	Persistent pain in the operated breast area, axilla, shoulder or arm	No (Ref) Yes	155 843	OR: 1.24 [0.70-2.20][MA]
Steyaert et al. (2016) Belgium	CS	128	56.5 ± 12.4y	80 ± 18.5m since surgery	Study specific question-naire	Dichotomous	28.6%	Pain at time of questioning	No (Ref) Yes	51 77	**OR: 1.27 [1.07-1.50]**[MA**]
Others											
Alkan et al. (2016) Turkey	CS	614	54.4 ± 10.1y	NM	Study specific question-naire	NM	72%	PMPS	Interval after surgery: - > 46 months (Ref) - < 46 months	 NM NM	 **OR: 1.71 [1.18-2.49]**[**]

Table 2 (continued)

Study	Design	Sample size (N)	Age (mean ± SD) unless otherwise stated	Follow-up (mean ± SD)	Pain outcome	Cut-off	Analgesic use (% of patients)	Type of pain	Risk factor category	PE (n)	(Adjusted) OR or RR (95 CI%)
									Taxane in adjuvant therapy:		
									- No (Ref)	23	
									- Yes	340	OR: 1.19 [0.79-1.81]
									Reoperation:		
									- No (Ref)	557	
									- Yes	57	OR: 1.57 [0.85-2.89]
Andersen Juhl et al. (2016) Denmark	CS	261	63.6 ± 11.3y	NM	Study specific question-naire	Dichotomous	NM	Pain in the area of the missing breast, axilla, side of the thorax, mastectomy scar or arm	Dominant hand same as side of surgery:		
									- No (Ref)	120	
									- Yes	141	OR: 0.67 [0.41-1.11]
Bantema et al. (2012) The Netherlan-ds	C	940	58.7 ± 10.2y at start of RT	Median: 30 m (Range: 6-54 m)	NM	NM	NM	Chest wall pain	- Boost dosage RT		
									Low (64.4 Gy)(Ref)	705	
									High (67.2 Gy)	235	**OR: 2.06[1,16-3,67]***
Bell et al. (2014) Australia	CS	540	Median: 54y	5.7y since diagnosis	Study specific question-naire	Dichotomous	NM	Breast pain at 5 - 6.7y since diagnosis	- Number of nodes removed (VCR)		
									≤ 5 (Ref)	160	
									> 5	365	OR: 1.10 [0.69-1.74]
									- Endocriene therapy at FQ5		
									None/Tamoxi-fen (Ref)	411	
									AI	119	OR: 1.31 [0.77-2.24]
									- Any surgery from FQ1-FQ5		
									No (Ref)	485	
									Yes	45	OR: 1.69 [0.70-4.10]
Bredal et al. (2014) Norway	CS	834	56 ± 7.8y	NM (Range: 2-6y since treatment)	NPRS	NPRS: ≥1	30.8%	Chronic pain	*Multivariate Logistic Regression Model*		
									- Chemotherapy and LRRT		**OR_{Adj}[f]: 1.69 [1.07-2.67]***

Table 2 (continued)

Study	Design	Sample size (N)	Age (mean ± SD) unless otherwise stated	Follow-up (mean ± SD)	Pain outcome	Cut-off	Analgesic use (% of patients)	Type of pain	Risk factor category	PE (n)	(Adjusted) OR or RR (95 CI%)
									No chemotherapy or LRRT (Ref)		
									Chemotherapy without LRRT		OR_{Adj}[f]: 1.10 [0.75-1.61]
									LRRT without chemotherapy		OR_{Adj}[f]: 1.43 [0.69-2.96]
Gulluoglu et al. (2006) Turkey	CS	85	57,6y ± NM (Range: 28-85y)	≥ 6m since treatment	NM	NM	NM	Chronic pain at ipsilateral breast, chest wall or axilla	- Breast Reconstruction		
									No (ref)	79	
									Yes	6	OR:1.19 [0.23-6.29]
									- Complications		
									No (Ref)	58	
									Yes	27	OR: 2.21 [0.87-5.61]
Johannsen et al. (2015) Denmark	C	1905	Median: 56.5y at 15m post-operative	7.1 ± 0.7y since surgery 15.2 ± 0.8 m since surgery	Study specific question-naire	≥3 on 6-point Likert scale	34.5%	Pain at the arm / shoulder of the operated side and the surgical area	- DBCG protocol		
									Pre-menopausal		
									A (Ref)	134	
									B	510	OR_{15m}: 1.30 [0.87-1.95] OR_{7-9y}: 1.01 [0.64-1.59] OR_{Adj}[a] $_{15m}$: 1.26 [0.84-1.89] OR_{Adj}[b] $_{7-9y}$: 0.87 [0.52-1.44]
									D	113	OR_{15m}: 1.12 [0.66-1.90] OR_{7-9y}: 1.26 [0.71-2.24] OR_{Adj}[a] $_{15m}$: 1.05 [0.61-1.81] OR_{Adj}[b] $_{7-9y}$: 1.12 [0.58-2.17]
									Post-menopausal		
									A (Ref)	236	
									C	708	**OR_{15m}: 1.60 [1.14-2.25]**[*] **OR_{7-9y}: 1.72 [1.13-2.61]**[**] **OR_{Adj}[a] $_{15m}$: 1.59 [1.13-2.24]**[*] OR_{Adj}[b] $_{7-9y}$: **1.58 [1.00-2.49]**[*]
									E	158	OR_{15m}: 1.19 [0.75-1.90] OR_{7-9y}: 1.01 [0.56-1.84]

Table 2 (continued)

Study	Design	Sample size (N)	Age (mean ± SD) unless otherwise stated	Follow-up (mean ± SD)	Pain outcome	Cut-off	Analgesic use (% of patients)	Type of pain	Risk factor category	PE (n)	(Adjusted) OR or RR (95 CI%)
											OR_{Adj} [a] $_{15m}$: 1.13 [0.71-1.81] OR_{Adj} [b] $_{7\text{-}9y}$: 0.95 [0.50-1.81]
Lundstedt et al.(2015) Sweden	CS	701	Intervention group: 58,3 ± 9.1y (Range: 33-76y) Control group: 54,7 ± 8,6y (Range: 35-76y)	Intervention group: 5,2 ± 1,4y since treatment (Range: 3-8y) Control group: 5,2 ± 1,3y since treatment (Range: 3-8y)	Study specific question-naire	Paresthesia was defined by answering "Yes, at least every week"	NM	Paresthesia in the previous 6 months	- Irradiated volume with ≥40 Gy (cm^3)		
									None (Ref)	505	
									≥13.5	65	**RR: 1.83 [1.13-2.95]*** **RR_{Adj} [g]: 1.64 [1.12-2.41]***
									11.4-13.4	65	RR: 1.60 [0.96-2.67] RR_{Adj} [g]: 1.09 [0.69-1.72]
									≤11.3	61	RR: 0.97 [0.49-1.93] RR_{Adj} [g]: 1.16 [0.62-2.14]
									- Highest Dose (Gy)		
									None (Ref)	505	
									≥55.0	12	RR: 1.86 [0.68-5.07] RR_{Adj} [g]: 1.54 [0.70-3.40]
									50.1-54.9	97	RR: 1.38 [0.86-2.21] RR_{Adj} [g]: 1.21 [0.80-1.83]
									≤50.0	82	RR: 1.54 [0.96-2.48] RR_{Adj} [g]: 1.33 [0.88-2.00]
Romero et al. (2016) Spain	C	1057	Number per age group: 50-54y: 310 55-59y: 283 60-64y: 278 65-70y: 186	Median: 8.7y (range 7.2–10.6 y)	Clinical record review	Pain ≥ 3m since surgery	NM	Persistent pain in the operated breast area, axilla, shoulder or arm	Detection method:		
									- Screening (Ref)	732	
									- Interval	325	OR_{adj} [h]: 0.8 [0.4-1.4]
									Neoadjuvant treatment:		
									- No (Ref)	948	
									- Yes	109	OR_{adj} [h]: 0.4 [0.1-1.3]
Steyaert et al. (2016) Belgium	CS	128	56.5 ± 12.4y	80 ± 18.5m since surgery	Study specific question-naire	Dichotomous	28.6%	Pain at time of questioning	Lymph node involvement:		
									- No (Ref)		
									- Yes		**OR: 1.2 [1.01-1.43]***
									Duration of surgery		
									- (Ref)		
									-		OR: 1.03 [0.86-1.22]

Table 2 (continued)

Study	Design	Sample size (N)	Age (mean ± SD) unless otherwise stated	Follow-up (mean ± SD)	Pain outcome	Cut-off	Analgesic use (% of patients)	Type of pain	Risk factor category	PE (n)	(Adjusted) OR or RR (95 CI%)
									Perioperative anesthesthetic-s and analgetics:		
									- Sufentanil:		OR: 0.89 [0.75-1.06]
									- Clonidine		OR: 1.13 [0.95-1.34]
									- Ketamine		OR: 1.16 [0.98-1.38]
									- $MgSO_4$		OR: 0.97 [0.82-1.16]
									- NSAID		OR: 1.08 [0.91-1.28]
									- Halogenated agent		**OR: 0.81 [0.70-0.95]***
									- Nitrous oxide		OR: 1.16 [0.42-3.25]
									- Need for piritramide in PACU		**OR: 1.24 [1.05-1.47]***

Abbreviations:

AI, Aromatase inhibitors; BMI, Body Mass Index; CI, Confidence interval; C, Cohort; CS, Cross-sectional; NM, Not mentioned; NPRS, Numeric Pain Rating Scale; OR, Odds ratio; PE, Patients exposed to variable; Ref, Reference; RR, Relative Risk; SD, Standard deviation; TAM, Tamoxifen; DBCG, Danish Breast Cancer Cooperative Group; FQ1, Follow-up questionnaires after 12 months; FQ5, Follow-up questionnaire after 5 years; LRRT, Locoregional radiotherapy to the axillary level; PASE, Physical Activity Scale for the Elderly; PF, Physical function; Tx trans, Menopause status transition in association with treatment for breast cancer; no Tx trans, Menopause transition did not occur in proximity to treatment for breast cancer; VCR, Victorian Cancer Registry; NSAID, nonsteroidal anti-inflammatory drugs; PACU, postanesthesia care unit

*: Odds ratio included in meta-analysis

a: Adjusted for age

b: Adjusted for age and pain at 15 months

c: When appropriate, the relative risks is adjusted for age at follow-up, educational level, time since randomisation, body mass index at follow-up, body mass index during treatment, smoking habits and tumour size, using the SAS procedure GENMOD (SAS version 9.2; SAS Institute Inc., Cary, NC) with binomial distribution and logarithmic link function.

d: Adjusted for age, years since diagnosis, BMI, self-rated health, mood, smoking, alcohol intake, type of breast cancer surgery, type of breast cancer treatment, and whether the participant experienced a transition in relation to treatment for breast cancer.

e: Adjusted for age, years since diagnosis, BMI, self-rated health, mood, smoking, alcohol intake, type of breast cancer surgery, type of breast cancer treatment, restless sleep, current tamoxifen, and whether the participant experienced a transition in relation to treatment for breast cancer.

f: An analysis was performed in which chemotherapy and LRRT were entered as categorical variables in the regression and controlling for age, anxiety, depression, and previous pain.

g: Adjusted for edema

h: Adjusted for detection method, age, Charlson index, histological type, phenotype, axillary treatment, neoadjuvant treatment and chemotherapy after surgery

7-9y: Follow-up of 7-9 years

15m: Follow-up of 15 months

Table 3 Cancer-related determinants for the development of chronic pain in breast cancer survivors

Study	Design	Sample size (N)	Age (mean ± SD) unless otherwise stated	Follow-up (mean ± SD)	Pain outcome	Cut-off	Analgesic use (% of patients)	Type of pain	Risk factor category	PE (n)	(Adjusted) OR or RR (95 CI%)
Cancer-related determinants											
Cancer stage											
Alkan et al. (2016) Turkey	CS	614	54.4 ± 10.1y	NM	Study specific questionnaire	NM	72%	PMPS	Stage 1 (Ref)	131	
									> Stage 1	466	OR: 1.12 [0.75-1.67]^{M}
Bell et al. (2014) Australia	CS	540	Median: 54y	5.7y since diagnosis	Study specific questionnaire	Dichotomous	NM	Breast pain at 5 - 6.7y since diagnosis	Stage 1 (Ref)	255	
									> Stage 1	264	**OR: 1.66 [1.07-2.58]**^{MA*}
Johannsen et al. (2015) Denmark	C	1905	Median: 56.5y at 15m post-operative	7.1 ± 0.7y since surgery 15.2 ± 0.8 m since surgery	Study specific questionnaire	≥3 on 6-point Likert scale	34.5%	Pain at the arm / shoulder of the operated side and the surgical area	Stage 1 (Ref)	513	
									> Stage 1	1023	$OR_{7\text{-}9y}$: 0.98 [0.78-1.23]^{MA}
Romero et al. (2016) Spain	C	1057	Number per age group: 50-54y: 310 55-59y: 283 60-64y: 278 65-70y: 186	Median: 8.7y (range 7.2–10.6 y)	Clinical record review	Pain ≥ 3m since surgery	NM	Persistent pain in the operated breast area, axilla, shoulder or arm	Stage 1 (Ref)	228	
									> Stage 1	618	OR: 0.70 [0.41-1.19]^{MA}
Hormone receptor status											
Bell et al. (2014) Australia	CS	540	Median: 54y	5.7y since diagnosis	Study specific questionnaire	Dichotomous	NM	Breast pain at 5 - 6.7y since diagnosis	Negative (Ref)	76	
									Positive	437	OR: 1.00 [0.54-1.85]^{MA}
Johannsen et al. (2015) Denmark	C	1905	Median: 56.5y at 15m post-operative	7.1 ± 0.7y since surgery 15.2 ± 0.8m since surgery	Study specific questionnaire	≥3 on 6-point Likert scale	34.5%	Pain at the arm / shoulder of the operated side and the surgical area	Negative (Ref)	299	
									Positive	1595	$OR_{7\text{-}9y}$: 1.14 [0.8-1.61]^{MA} OR_{15m}: 1.09 [0.84-1.43] $OR_{Adj\ 15m}^{a}$: 1.13 [0.86-1.47]
Tumor size > 20mm											
Andersen Juhl et al. (2016) Denmark	CS	261	63.6 ± 11.3y	NM	Study specific questionnaire	Dichotomous	NM	Pain in the area of the missing breast, axilla, side of the thorax, mastectomy scar or arm	≤ 20 mm (Ref)	120	
									>20 mm	141	OR: 1.35 [0.82-2.22]^{MA}
Bell et al. (2014) Australia	CS	540	Median: 54y	5.7y since diagnosis	Study specific questionnaire	Dichotomous	NM	Breast pain at 5 - 6.7y since diagnosis	≤ 20 mm (Ref)	365	
									>20 mm	165	OR: 0.90 [0.57-1.41]^{MA}
Johannsen et al. (2015) Denmark	C	1905	Median: 56.5y at 15m post-operative	7.1 ± 0.7y since surgery 15.2 ± 0.8 m since surgery	Study specific questionnaire	≥3 on 6-point Likert scale	34.5%	Pain at the arm / shoulder of the operated side and the surgical area	≤ 20 mm (Ref)	1252	
									>20 mm	647	$OR_{7\text{-}9y}$: 1.17 [0.92-1.47]^{MA}
									≤ 20 mm (Ref)	1252	
									>20 mm ≤ 50 mm	610	OR_{15m}: 1.07 [0.87-1.31]

Table 3 (continued)

Study	Design	Sample size (N)	Age (mean ± SD) unless otherwise stated	Follow-up (mean ± SD)	Pain outcome	Cut-off	Analgesic use (% of patients)	Type of pain	Risk factor category	PE (n)	(Adjusted) OR or RR (95 CI%)
											$OR_{7\text{-}9y}$:1.19 [0.94-1.51] $OR_{Adj}{}^{a}{}_{15m}$: 1.07 [0.87-1.31] $OR_{Adj}{}^{b}{}_{7\text{-}9y}$: 1.17 [0.90-1.52]
									>50 mm	37	OR_{15m}: 0.89 [0.43-1.82] $OR_{7\text{-}9y}$: 0.80 [0.33-1.93] $OR_{Adj}{}^{a}{}_{15m}$: 0.87 [0.42-1.78] $OR_{Adj}{}^{b}{}_{7\text{-}9y}$: 0.63 [0.24-1.65
Romero et al. (2016) Spain	C	1057	Number per age group: 50-54y: 310 55-59y: 283 60-64y: 278 65-70y: 186	Median: 8.7y (range 7.2–10.6 y)	Clinical record review	Pain ≥ 3m since surgery	NM	Persistent pain in the operated breast area, axilla, shoulder or arm	≤ 20 mm (Ref)	628	
									>20 mm	308	OR: 1.02 [0.59-1.75][MA]
Others											
Andersen Juhl et al. (2016) Denmark	CS	261	63.6 ± 11.3y	NM	Study specific question-naire	Dichotomous	NM	Pain in the area of the missing breast, axilla, side of the thorax, mastectomy scar or arm	Location of tumor: - All other locations (Ref)	198	
									- Upper lateral quadrant	63	OR: 0.99 [0.55-1.77]
									Tumor side: - Left (Ref)	117	
									- Right	143	OR: 0.88 [0.53-1.45]
Johannsen et al. (2015) Denmark	C	1905	Median: 56.5y at 15m post-operative	7.1 ± 0.7y since surgery 15.2 ± 0.8 m since surgery	Study specific question-naire	≥3 on 6-point Likert scale	34.5%	Pain at the arm / shoulder of the operated side and the surgical area	- Lymph node status		
									negative (Ref)	1011	
									positive	894	**OR_{15m}: 1.42 [1.17-1.72]**[***] **$OR_{7\text{-}9y}$: 1.46 [1.16-1.82]**[***] **$OR_{Adj}{}^{a}{}_{15m}$: 1.40 [1.15-1.70]**[**] $OR_{Adj}{}^{b}{}_{7\text{-}9y}$: 1.28 [1.00-1.64]

Table 3 (continued)

Study	Design	Sample size (N)	Age (mean ± SD) unless otherwise stated	Follow-up (mean ± SD)	Pain outcome	Cut-off	Analgesic use (% of patients)	Type of pain	Risk factor category	PE (n)	(Adjusted) OR or RR (95 CI%)
Romero et al. (2016) Spain	C	1057	Number per age group: 50-54y: 310 55-59y: 283 60-64y: 278 65-70y: 186	Median: 8.7y (range 7.2–10.6 y)	Clinical record review	Pain ≥ 3m since surgery	NM	Persistent pain in the operated breast area, axilla, shoulder or arm	Histological type: - In situ (Ref) - Ductal - Lobular - Other Phenotype: - Luminal A (Ref) - Luminal B - Her2 - Triple negative	 93 773 99 85 407 210 67 85	 OR_{adj}^{h}: 0.5 [0.1-4.2] OR_{adj}^{h}: 1.1 [0.5-2.7] OR_{adj}^{h}: 0.6 [0.2-2.1] OR_{adj}^{h}: 0.6 [0.3-1.3] OR_{adj}^{h}: 0.8 [0.3-2.3] OR_{adj}^{h}: 1.1 [0.5-2.6]

Abbreviations:

AI, Aromatase inhibitors; BMI, Body Mass Index; CI, Confidence interval; C, Cohort; CS, Cross-sectional; NM, Not mentioned; NPRS, Numeric Pain Rating Scale; OR, Odds ratio; PE, Patients exposed to variable; Ref, Reference; RR, Relative Risk; SD, Standard deviation; TAM, Tamoxifen; DBCG, Danish Breast Cancer Cooperative Group; FQ1, Follow-up questionnaires after 12 months; FQ5, Follow-up questionnaire after 5 years; LRRT, Locoregional radiotherapy to the axillary level; PASE, Physical Activity Scale for the Elderly; PF, Physical function; Tx trans, Menopause status transition in association with treatment for breast cancer; no Tx trans, Menopause transition did not occur in proximity to treatment for breast cancer; VCR, Victorian Cancer Registry; NSAID, nonsteroidal anti-inflammatory drugs; PACU, postanesthesia care unit

*: Odds ratio included in meta-analysis

a: Adjusted for age

b: Adjusted for age and pain at 15 months

c: When appropriate, the relative risks is adjusted for age at follow-up, educational level, time since randomisation, body mass index at follow-up, body mass index during treatment, smoking habits and tumour size, using the SAS procedure GENMOD (SAS version 9.2; SAS Institute Inc., Cary, NC) with binomial distribution and logarithmic link function.

d: Adjusted for age, years since diagnosis, BMI, self-rated health, mood, smoking, alcohol intake, type of breast cancer surgery, type of breast cancer treatment, and whether the participant experienced a transition in relation to treatment for breast cancer.

e: Adjusted for age, years since diagnosis, BMI, self-rated health, mood, smoking, alcohol intake, type of breast cancer surgery, type of breast cancer treatment, restless sleep, current tamoxifen, and whether the participant experienced a transition in relation to treatment for breast cancer.

f: An analysis was performed in which chemotherapy and LRRT were entered as categorical variables in the regression and controlling for age, anxiety, depression, and previous pain.

g: Adjusted for edema

h: Adjusted for detection method, age, Charlson index, histological type, phenotype, axillary treatment, neoadjuvant treatment and chemotherapy after surgery

7-9y: Follow-up of 7-9 years

15m: Follow-up of 15 months

Quality assessment

The results of the individual studies on the STROBE checklist are presented in Fig. 2, with scores ranging from 12 to 20 out of 22 points. The mean score on the STROBE checklist was 16.18 ± 2.33, indicative for a moderate quality. The main weaknesses were lack of correct information on 'title and abstract', 'objectives', 'study design', 'statistical methods', 'funding', and scarce efforts to address potential sources of bias.

Risk factors for the development of chronic pain in cancer survivors

Looking at the included studies, over 70 risk factors were examined for the development of chronic pain in cancer survivors.

The risk factors presented in two or more studies are as follows: age [15, 16, 21–25, 27], alcohol use [21, 25], BMI [7, 16, 21, 22, 24–26, 33], children [21, 25], comorbidities [15, 21, 25], education [15, 21, 22, 25, 35], lymphedema [15, 29, 35], relationship status [15, 21, 22, 25, 35], smoking status [21, 25], axillary surgery [15, 16, 21, 23, 24, 29], breast surgery [15, 16, 21–23, 25, 29, 35], chemotherapy [15, 17, 21–24, 29, 35], hormone therapy [15, 21, 29, 32, 35], radiotherapy [15, 17, 21–26, 29, 33, 35], cancer stage [21, 23, 25, 28], hormone receptor status [21, 35], and tumor size [17, 21, 23, 24, 35].

Meta-analyses were carried out for the risk factors described in more than one article (Appendix A).

Patient-related risk factors

Age Steyaert et al. [17] did not provide sufficient data and was subsequently removed. The meta-analysis demonstrated a significant difference for the chance of developing chronic pain in breast cancer survivors between the >50–55-year group and the <50–55-year group. Data from eight studies [15, 16, 21–25, 27] (n = 7048) were combined, showing that the odds for developing chronic pain in subjects with an age >50–55 were lower than those with an age <50–55 (overall OR: 0.76, 95% CI 0.57–1.01, p = 0.06); however, these results were found to be not significant.

A moderator analysis was carried out since the heterogeneity across the studies was high (I^2 = 76%, p = 0.0001). After withdrawing the weakest methodological studies [17, 22, 23, 25], the heterogeneity increased a bit (I^2 = 82%, p = 0.001) and the overall odds ratio for the development of chronic pain for breast cancer survivors older than 50–55 years, in comparison with younger breast cancer survivors, lowered to 0.65 (overall OR: 0.65, 95% CI 0.42–1.01, p = 0.05). The results of all moderator analyses can be found in Table 4.

Alcohol use Alcohol use was studied in two articles (n = 2519) [21, 25]. A significant lower chance to develop chronic pain was found in patients consuming alcohol

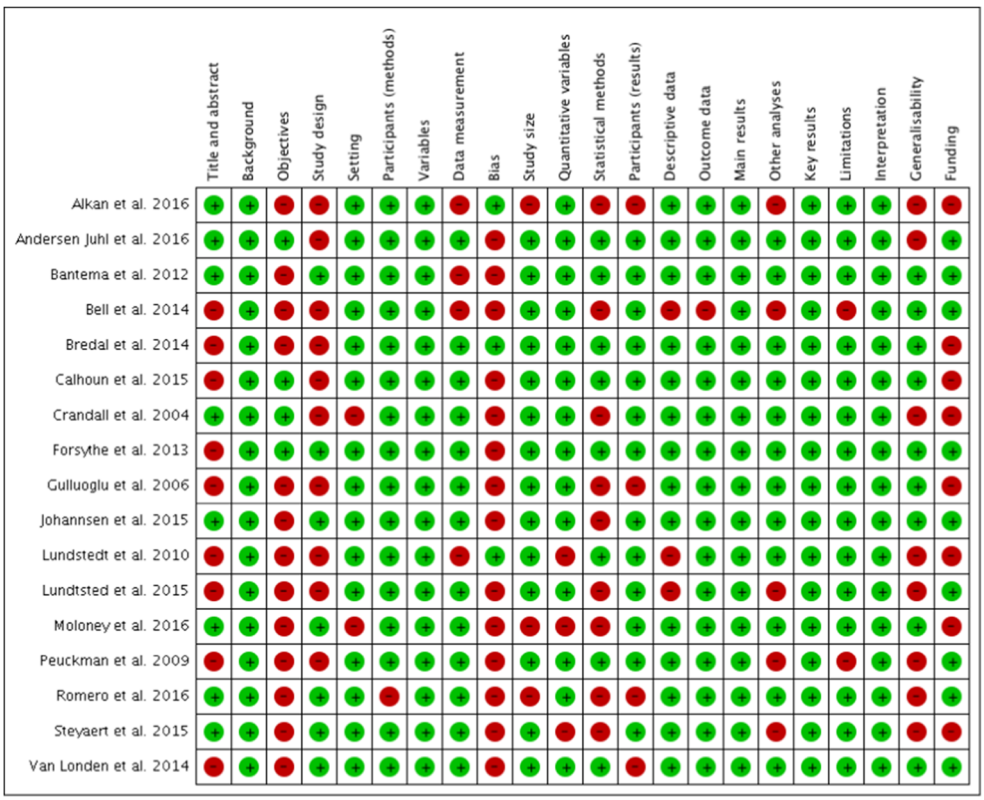

Fig. 2 Quality assessment by the STROBE checklist

Table 4 Moderator analyses for risk factors demonstrating high heterogeneity

Determinant	Pooled estimate [95% confidence Interval]	I2	p value Chi^2
Patient-related			
Age < 50–55	0.65 [0.42–1.01]	82%	0.001
Having ≥1 comorbidities	1.23 [0.33–4.56]	95%	<0.00001
Treatment-related			
Breast conserving surgery	1.03 [0.78–1.36]	44%	0.15
Hormone therapy	1.33 [1.15–1.54]	0%	0.54

compared to those not consuming alcohol (overall OR: 0.94, 95% CI 0.47–1.89, $p = 0.86$). A high heterogeneity was found ($I^2 = 67\%$, $p = 0.08$) but given the fact that this risk factor was only discussed in two articles, no moderator analysis could be performed.

BMI Bredal et al. [15] and Forsythe et al. [7] did not provide the required data. The groups, on which the given OR in Bredal et al. was based, were not clearly presented. Consequently, Bredal et al. was excluded from the meta-analysis [15]. The original OR of Forsythe et al., based on the obese and normal weighted cancer survivors without taking overweight participants into account, was used in the meta-analysis instead of a newly formed OR based on all participants [7]. This limitation was taken into account for possible moderator analysis.

A significant dissimilarity of the odds for the development of chronic pain in breast cancer survivors is presented in the meta-analysis between the two BMI groups (>30 and <30).

The odds for the development of chronic pain are 1.33 times higher in people with a BMI > 30 compared to those with a BMI < 30, according to the data from the 6 combined studies ($n = 5573$) (overall OR: 1.34, 95% CI 1.08–1.67, $p = 0.008$) [7, 16, 21, 22, 24, 25]. No significant heterogeneity (I^2) was found ($I^2 = 33\%$, $p = 0.19$).

Children The risk factor 'children' was discussed in two studies ($n = 2519$) [21, 25]. The meta-analysis delivered no difference between the risk for developing chronic pain after having children or not (overall OR 0.92, 95% CI 0.69–1.23, $p = 0.56$). A low heterogeneity was found ($I^2 = 0\%$, $p = 0.74$).

Comorbidities Comorbidities were approached in three articles ($n = 3353$) [15, 21, 25]. No significant intergroup difference was observed (overall OR: 1.11, 95% CI 0.50–2.44, $p = 0.80$). Furthermore, a significant heterogeneity was found ($I^2 = 93\%$, $p < 0.00001$), which could possibly be explained by the discrepancy in the applied definitions for comorbidities. Bredal et al. defined comorbidities as previous pain, whereas Johannsen et al. and Alkan et al. did not provide a proper definition for comorbidities, possibly resulting in the inclusion of non-pain-related disorders [15, 21, 25].

A moderator analysis was performed with the removal of Alkan et al. [25]. No improvement in heterogeneity was found ($I^2 = 95\%$, $p < 0.00001$), nor did the analysis have an influence on the odds ratio (overall OR: 1.23, 95% CI 0.33–4.56, $p = 0.76$).

Education Five articles reported on education ($n = 5209$) [15, 21, 22, 25, 35]. A significant higher chance to develop chronic pain was found in subjects with a lower education (<12 or 13 years) (overall OR: 1.23, 95% CI 1.07–1.42, $p = 0.005$). A low heterogeneity was found ($I^2 = 10\%$, $p = 0.35$).

Lymphedema Lymphedema was studied in three articles ($n = 1459$) [15, 29, 35]. The meta-analysis found that the odds of developing chronic pain were 2.58 times higher in the group with lymphedema (overall OR: 2.58, 95% CI 1.93–3.46, $p < 0.00001$). No significant heterogeneity was observed ($I^2 = 0\%$, $p = 0.40$).

Relationship status Five articles ($n = 5209$) declared the relationship status as risk factor [15, 21, 22, 25, 35]. The meta-analysis did not lead to a significant difference between groups (overall OR: 1.05, 95% CI 0.88–1.26, $p = 0.56$). A modest heterogeneity was observed ($I^2 = 31\%$, $p = 0.21$).

Smoking status A significant dissimilarity of the odds for the development of chronic pain in breast cancer survivors is presented in the meta-analysis between the smoking and ex-/no-smoking group. Smokers have a smaller chance to develop chronic pain in comparison to the ex- or no-smoking group (overall OR: 0.75, 95% CI 0.62–0.92, $p = 0.005$). No heterogeneity was observed ($I^2 = 0\%$, $p = 0.80$).

Others Several other patient-related risk factors were only studied once, such as the following: monthly income [25], posttraumatic stress disorder [25], psychiatric support [25], regular use of analgetics [25], social support [25], severity of initial pain [35], quality of original symptoms [35], anxiety [15], depression [15], race [30], menopausal status [34], physical activity [7], television time [7], occupational status [21], personal income [21], household net wealth per person [21], ethnicity [21], Physical Activity Scale for the Elderly (PASE) components [21], SF-36 Physical Function, physical function [16], insomnia [16], baseline pain [16], emotional function [16], arm symptoms [16], breast symptoms [16], time since surgery [22], medication use [22], Charlson index [23], height [17], weight [17], and recall of preoperative pain [17]. The data regarding these risk factors are further specified in Table 1.

Treatment-related risk factors

Axillary surgery: axillary lymph node dissection versus sentinel lymph node biopsy This risk factor was examined in six articles ($n = 4263$) [15, 16, 21, 23, 24, 29]. In this meta-analysis, a significant difference between axillary dissection and sentinel dissection was found. Patients who underwent axillary dissection had a 1.25 greater chance to develop chronic pain (overall OR: 1.25, 95% CI 1.04–1.52, $p = 0.02$) compared to those who underwent a sentinel dissection. I^2 was 27% ($p = 0.23$), indicative for moderate heterogeneity.

Breast surgery: mastectomy versus breast conserving surgery The risk factor 'breast surgery' was discussed in eight articles ($n = 6472$) [15, 16, 21–23, 25, 29, 35]. The meta-analysis delivered no significant difference between the risk for developing chronic pain after mastectomy compared to breast conserving surgery (overall OR 0.92, 95% CI 0.75–1.14, $p = 0.47$). An important heterogeneity was found ($I^2 = 59\%$, $p = 0.02$). After performing a moderator analysis with withdrawal of the methodological weakest studies [22, 23, 25, 28], the heterogeneity decreased ($I^2 = 44\%$, $p = 0.15$) and the odds ratio increased (overall OR: 1.03, 95% CI 0.78–1.36, $p = 0.83$).

Chemotherapy Seven studies ($n = 4810$) encompassed this category [15, 17, 21, 23, 24, 29, 35]. Overall, a significant difference in odds for the development of chronic pain was found between subjects treated with and without chemotherapy. The odds in subjects who received chemotherapy were 1.44 times higher compared to those who did not receive chemotherapy (overall OR: 1.44, 95% CI 1.23–1.69, $p < 0.00001$). A slight heterogeneity was observed ($I^2 = 33\%$, $p = 0.18$).

Hormone therapy Hormone therapy was studied in eight articles ($n = 5823$) [15, 17, 21, 23, 24, 29, 32, 35].

The meta-analysis demonstrated a non-significant difference between participants subjected to and not subjected to hormone therapy (overall OR: 1.16, 95% CI 0.99–1.37, $p = 0.07$).

Since a significant heterogeneity was detected ($I^2 = 47\%$, $p = 0.07$), a moderator analysis was performed. After removal of the weakest methodological studies [17, 23, 28], the results became homogenous ($I^2 = 0\%$, $p = 0.54$). Survivors exposed to hormone therapy were 1.33 times more likely to develop chronic pain (overall OR: 1.33, 95% CI 1.15–1.54, $p = 0.0001$).

Radiotherapy Data from 11 articles ($n = 7806$) were combined for the meta-analysis of radiotherapy as risk factor to develop chronic pain [15, 17, 21–26, 29, 33, 35]. A significant increased chance of developing chronic pain was found in patients exposed to radiotherapy compared to the unexposed patients (overall OR: 1.32, 95% CI 1.17–1.48, $p < 0.00001$). A slight heterogeneity was found ($I^2 = 22\%$, $p = 0.24$).

Others The other treatment-related risk factors that were only mentioned by one study are as follows: interval after surgery [25], taxane in adjuvant therapy [25], reoperation [25], dominant hand as side of surgery [24], boost dosage radiotherapy [27], number of lymph nodes removed [35], endocrine therapy at FQ5 [35], any surgery from FQ1-FQ5 [35], chemotherapy and locoregional radiotherapy [15], breast reconstruction [29], complications [29], Danish Breast Cancer Cooperative Group (DBCG) protocol [21], irradiated volume with ≥40 Gy (cm^3) [33], highest dose (Gy) [26], detection method [23], neoadjuvant treatment [36], lymph node involvement [17], duration of surgery [17], and perioperative anesthesthetics and analgetics [17].

Specific details concerning these risk factors are outlined in Table 2.

Cancer-related risk factors

Cancer stage The cancer stages were discussed in four articles ($n = 4116$) [21, 23, 25, 28].

No significant intergroup difference was observed for patient diagnosed with a stage 1 or stage >1 cancer (overall OR: 1.07, 95% CI 0.80–1.44, $p = 0.64$).

A significant heterogeneity was found ($I^2 = 56\%$, $p < 0.08$). However, no moderator analysis could be performed since 3 out of the 4 included studies had to be removed [23, 25, 28], based on the prespecified criteria, leaving us with only 1 study in the meta-analysis.

Hormone receptor status Two studies reported on hormone receptor status ($n = 2445$) [21, 35]. The meta-analysis of these results demonstrated no significant difference in the risk for development of chronic pain (overall OR: 1.10, 95% CI 0.81–1.50, $p = 0.53$) and no heterogeneity could be observed ($I^2 = 0\%$, $p = 0.72$).

Tumor size >20 mm Steyaert et al. [17] did not provide sufficient data and was subsequently removed. The tumor size was examined in four articles ($n = 3891$) [21, 23, 24, 35]. The meta-analysis revealed no significant difference (overall OR: 1.12, 95% CI 0.94–1.35, $p = 0.20$). Furthermore, no heterogeneity was observed ($I^2 = 0\%$, $p = 0.65$).

Others The remaining cancer-related risk factors, only discussed in one study, encompass the following: location of the tumor [24], tumor side [24], lymph node status [21], histological type [23], and phenotype [36].

A detailed overview of these risk factors can be found in Table 3.

Discussion

The purpose of this systematic review and meta-analysis was to identify factors that contribute to the development of chronic pain in breast cancer survivors. Seventeen different studies were included which together provided over 70 different risk factors. For 17 risk factors, it was possible to carry out a meta-analysis. Seven out of the 17 examined factors (BMI > 30, education <12–13 years, lymphedema, no- or ex-smoker, axillary lymph node dissection, chemotherapy, and radiotherapy) demonstrated to be significantly associated with an elevated chance for the development of chronic pain in breast cancer survivors, with lymphedema being the strongest risk factor. The remaining ten risk factors (age < 50-55, alcohol use, children, comorbidities, relation status, breast surgery, hormone therapy, cancer stage, hormone receptor status, and tumor size) are not related to the development of chronic pain in breast cancer survivors. After applying moderator analyses for the meta-analyses with a high grade of heterogeneity (age, comorbidities, hormone therapy, breast surgery), hormone therapy became a significant risk factor for the development of chronic pain in breast cancer survivors as well.

In the past, two systematic reviews concerning risk factors for the development of chronic pain were conducted [10, 11]. Chang et al. reported age younger than 65 years, type of surgery (breast-conserving surgery, breast reconstruction, axillary dissection), higher post-operative pain scores, and radiotherapy to be risk factors for the development of chronic pain following breast surgery [10]. The findings for age and radiotherapy were comparable to the results of this review. However, it should be taken into consideration that Chang et al. primarily focused on patients after breast surgery, making a true comparison with the present findings difficult [10]. The second review failed in the detection of significant risk factors due to the unclear definitions of pain, treatment, and outcome measures and methodological weakness of the found articles [11]. This study proclaimed that data collection needs to be performed in a more systematical way [11].

Whether lymphedema leads to the development of chronic pain in breast cancer survivors or not has been a point of discussion. However, the present study demonstrated that lymphedema is the strongest risk factor for the development of chronic pain in breast cancer survivors. Results from previous studies deliver indirect evidence for the relation between lymphedema and pain in gynecological cancer survivors, in which a reduction of the lymphedema was correlated with a decrease in pain after applying complex decongestive physiotherapy [37]. Furthermore, one should be aware of the fact that breast cancer-related lymphedema might cause many inconveniences in the upper extremity, such as a poor range of motion, stiffness, weakness, numbness, a general poor upper body function, and pain [38]. Jeong et al. stated that the rotator cuff tendinitis is a frequently seen complication in patients with lymphedema. A total of 53.3% of the patients with lymphedema were diagnosed with a supraspinatus tear (75% showed a partial thickness tear and 25% a full thickness tear), 53.3% with an adhesive capsulitis, 13.3% with a tenosynovitis, 13.3% with an acromioclavicular arthritis, and 13.3% with a subdeltoid bursitis [38]. All these definitive structural abnormalities in patients with lymphedema might in turn lead to the development of pain [38].

The presence of obesity has been postulated as another associated factor in the development of chronic pain, which was demonstrated to be significant in this study [39, 40]. Taylor R. Jr. et al. suggested that obesity could possibly lead to the development of pain due to mechanical stress and metabolic disruptions [39]. Furthermore, they stated that emotional factors such as stress, anxiety, and depression could arise from the significant obesity and pain burdens on the individual, the healthcare system, and society as a whole, which in turn lead to further healthcare utilization and burden [39]. According to Okifuji A. et al., there are several potential contributors linking obesity to pain such as the following: mechanical and structural changes due to the increased loading (e.g., altered body mechanics and postures), chemical mediators (e.g., proinflammatory cytokines causing a low-grade chronic inflammatory state), depression, disturbed sleep, and an inactive lifestyle [40]. The presence of both pain and obesity often lead to a vicious cycle of pain–inactivity–obesity.

After axillary dissection, axillary web syndrome (AWS) might occur. AWS is characterized by the formation of multiple chords that span from the axilla to the medial arm in a web-like matter. AWS can trigger a painful sensation when performing movements in which abduction of the shoulder is involved [41, 42]. Postoperative pain is commonly seen in breast cancer survivors and is mostly caused by changes in the peripheral and central nervous system (CNS). Due to the local tissue injury of the surgery, an increased sensitivity of the nociceptors to stimuli (primary hyperalgesia) and a spontaneous firing of these nociceptors will be observed. Secondary hyperalgesia may occur after a disproportional pain experience due to the central neural plasticity. Secondary hyperalgesia is thought to be the basis for chronic post-surgical pain [43, 44].

Chemotherapy and/or adjuvant radiotherapy are frequently administered after breast cancer surgery. It is well known that both have the ability to cause neurotoxity and neuropathic pain [45, 46]. Chemotherapy can cause damage to the nerves and induce peripheral neuropathy; however, the exact pathophysiologic mechanism underlying the nerve injury in chemotherapy-induced peripheral neuropathy (CIPN) is still not completely understood. CIPN appears to be agent-specific and is thought to be caused by drug-induced damage to components of the peripheral nervous system (PNS). As a consequence of the structural damage to the PNS, the somatosensory processing in the central and peripheral nervous systems

is abnormal and results in allodynia, hyperalgesia, and pain. Pain processing abnormalities seem to play an important role in the development of chronic painful conditions [47, 48].

Despite the benefits of adjuvant radiotherapy in reducing tumor burden, it might induce late effects. As it causes a high toxicity to the skin and vital organs, it might subsequently lead to the development of significant chronic pain. Delayed painful brachial and lumbosacral plexopathies, osteoradionecrosis and fractures, pelvic pain, and in some cases secondary malignancies have been reported after radiotherapy [49–51].

About 75% of the postmenopausal patients are diagnosed with a hormone receptor-positive breast cancer for which endocrine treatment is prescribed [53]. Despite the fact that they improve the disease-free survival by 10–40%, about 46% will develop aromatase inhibitor-induced arthralgia (AIA), an adverse event not only leading to a decrease in health-related quality of life but also in treatment compliance [54–60]. The exact mechanism underlying the development of the AIA remains an enigma. Hershman et al. suggests that this phenomenon is the result of estrogen deprivation and shares components with auto-immune diseases [61]. Another study suggests that aromatase inhibitors might selectively target the transient receptor potential ankyrin 1 (TRPA1) channel [62]. The stimulation of TRPA1 through the aromatase inhibitors is associated with the release of pro-inflammatory neuropeptides from sensory nerve endings, which mediate neurogenic inflammatory responses in the innervated peripheral tissue [62].

Overall, there is not only a lack of uniformity in the definition of pain, but also in the use of measurement tools and applied cut-off values for the diagnosis of pain. These dissimilarities might possibly explain the observed differences between the studies.

Furthermore, it should be noted that the current literature regarding risk factors for the development of chronic pain in breast cancer survivors has a primary focus set on treatment-related, cancer-related, and demographic factors. There is a need to shift the research focus away from the biomedical point of view onto the broader biopsychosocial dimension, as it is demonstrated that psychosocial factors play an important role in other chronic pain conditions [63–64]. Turk et al., for example, described that avoiding activities due to fear of pain plays a relevant part in the persistency and aggravation of pain [63]. According to Boersma et al., fear acts as a risk factor for the development or persistence of chronic pain [64]. Additionally, psychological factors like anxiety, depression, stress, and catastrophizing are proven to strongly correlate with chronic post-surgical pain [64].

The present study has several strengths, including the compliance with the PRISMA guidelines [12] for rigorous performance and reporting of systematic literature reviews and meta-analyses, the use of multiple, blinded researchers to perform the literature searches as well as data processing and quality assessments. Also, this is the first meta-analysis of all available studies exploring possible risk factors for the development of chronic pain in breast cancer survivors. Of course, some limitations to our study should be acknowledged.

First, in order to perform the meta-analyses, the ORs of the different studies needed to be comparable with each other. Therefore, dichotomization of data was needed, which is inextricably linked to a loss of information. For instance, Johannsen et al. compared the normal weight group with four other BMI groups. The results showed that the 'obese group' had a higher chance for the development of chronic pain, which could not be observed for the 'severely obese group'. This kind of information could not be retrieved from our meta-analyses.

Second, using the STROBE involves some restrictions since it is constructed to provide guidance on how to report observational studies properly. It is not meant as a methodological guideline or assessment tool, in which all items can be assigned with equal weights, as some items are more meaningful than others. Therefore, the use of overall scores is, from an objective point of view, inappropriate and makes the interpretation of the results harder. However, this limitation was countered by taking into account the five most important STROBE-items for the moderator analysis.

As this review encompasses only a limited number of studies and the strength of those studies is merely mediocre, the strength of the evidence is not sufficient to draw firm conclusions regarding the risk factors for the development of chronic pain. Future research should focus on providing a proper definition for pain in breast cancer survivors. Furthermore, a consensus should be drawn about globally accepted measurement tools with clear cut-off values for the diagnosis of chronic pain in this population. This would bring more clarity and uniformity across studies examining pain. Proper knowledge about risk factors is of imperative need to not only screen patients that are at a higher risk for the development of pain but also to preventively target those factors in order to avoid acute pain from becoming chronic.

Compliance with ethical standards

Funding Jo Nijs is holder of a Chair funded by the Berekuyl Academy, the Netherlands. Roselien Pas is a PhD student funded by the Berekuyl Acadely Chair.

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

References

1. Ferlay J et al (2015) Cancer incidence and mortality worldwide: Sources, methods and major patterns in GLOBOCAN 2012. Int J Cancer 136(5):E359–E386

2. Ferlay J et al (2010) Estimates of worldwide burden of cancer in 2008: GLOBOCAN 2008. Int J Cancer 127(12):2893–2917
3. Katanoda K, Matsuda T (2014) Five-year relative survival rate of breast cancer in the USA, Europe and Japan. Jpn J Clin Oncol 44(6):611
4. Organization, W.H., World cancer report 2014. 2014, Lyonn, France: International Agency for Research on Cancer.
5. Befort CA, Klemp J (2011) Sequelae of breast cancer and the influence of menopausal status at diagnosis among rural breast cancer survivors. J Women's Health 20(9):1307–1313
6. Glare PA et al (2014) Pain in cancer survivors. J Clin Oncol 32(16): 1739–1747
7. Forsythe LP et al (2013) Pain in long-term breast cancer survivors: The role of body mass index, physical activity, and sedentary behavior. Breast Cancer Res Treat 137(2):617–630
8. Pain, I.A.f.t.S.o. *Pain, IASP Taxonomy*. 2014 2014–10-06 [cited 2016 2016–03-26]; Available from: http://www.iasp-pain.org/Taxonomy - Pain.
9. Merskey, H. and N. Bogduk, Eds. *Classification of chronic pain: descriptions of chronic pain syndromes and definitions of pain terms.* Second edition ed. 1994, IASP Press: Seattle
10. Chang SH, Metha V, Langford R (2009) *Acute and chronic pain following breast surgery.* Acute Pain 11(1):1–14
11. Andersen KG, Kehlet H (2011) Persistent pain after breast cancer treatment: A critical review of risk factors and strategies for prevention. J Pain 12(7):725–746
12. Liberati A et al (2009) The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: Explanation and elaboration. J Clin Epidemiol 62(10):e1–34
13. NCI, O.o.C.S., *About Cancer Survivorship Research: Survivorship Definitions*.. 2012, Washington, DC
14. Elmagarmid, A., et al., *Rayyan: a systematic reviews web app for exploring and filtering searches for eligible studies for Cochrane Reviews.*, in *Evidence-Informed Public Health: Opportunities and Challenges. Abstracts of the 22nd Cochrane Colloquium*. 2014, John Wiley & sons: Hyderabad, India
15. Bredal IS et al (2014) Chronic pain in breast cancer survivors: Comparison of psychosocial, surgical, and medical characteristics between survivors with and without pain. J Pain Symptom Manag 48(5):852–862
16. Moloney N et al (2016) Prevalence and risk factors associated with pain 21 months following surgery for breast cancer. Support Care Cancer 24(11):4533–4539
17. Steyaert A 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
18. von Elm E et al (2014) *The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement: guidelines for reporting observational studies*. Int J Surg (London, England) **12**(12):1495–1499
19. Higgins JP et al (2003) Measuring inconsistency in meta-analyses. BMJ 327(7414):557–560
20. Higgins, J.P.T. and S. Green, *Cochrane Handbook for Systematic Reviews of Interventions. Version 5.0.1 [updated September 2008]*. Chapter 9: Analysing data and undertaking meta-analyses., ed. J.J. Deeks, J.P.T. Higgins, and D.G. Altman. 2008: The Cochrane Collaboration.
21. Johannsen M et al (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(3): 645–658
22. Peuckmann V et al (2009) Chronic pain and other sequelae in long-term breast cancer survivors: Nationwide survey in Denmark. Eur J Pain 13(5):478–485
23. Romero A et al (2016) Prevalence of persistent pain after breast cancer treatment by detection mode among participants in population-based screening programs. BMC Cancer 16
24. Andersen Juhl A, Christiansen P, Damsgaard TE (2016) Persistent pain after breast cancer treatment: A questionnaire-based study on the prevalence, associated treatment variables, and pain type. J Breast Cancer 19(4):447–454
25. Alkan A 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(9): 3747–3755
26. Lundstedt D et al (2015) Radiation therapy to the plexus brachialis in breast cancer patients: Analysis of paresthesia in relation to dose and volume. Int J Radiat Oncol Biol Phys 92(2):277–283
27. Bantema-Joppe EJ et al (2012) Simultaneous integrated boost irradiation after breast-conserving surgery: Physician-rated toxicity and cosmetic outcome at 30 months' follow-up. Int J Radiat Oncol Biol Phys 83(4):e471–e477
28. Bell RJ et al (2014) Persistent breast pain 5 years after treatment of invasive breast cancer is largely unexplained by factors associated with treatment. J Cancer Surviv 8(1):1–8
29. Gulluoglu BM et al (2006) Factors related to post-treatment chronic pain in breast cancer survivors: The interference of pain with life functions. Int J Fertil Womens Med 51(2):75–82
30. Calhoun C, Helzlsouer KJ, Gallicchio L (2015) Racial differences in depressive symptoms and self-rated health among breast cancer survivors on aromatase inhibitor therapy. J Psychosoc Oncol 33(3): 263–277
31. Crandall C et al (2004) Association of breast cancer and its therapy with menopause-related symptoms. Menopause- J North Am Menopause Soc 11(5):519–530
32. van Londen GJ et al (2014) Associations between adjuvant endocrine therapy and onset of physical and emotional concerns among breast cancer survivors. Support Care Cancer 22(4):937–945
33. Lundstedt D et al (2010) Symptoms 10-17 years after breast cancer radiotherapy data from the randomised SWEBCG91-RT trial. Radiother Oncol 97(2):281–287
34. Crandall C et al (2004) Association of breast cancer and its therapy with menopause-related symptoms. Menopause 11(5):519–530
35. Bell RJ et al (2014) Persistent breast pain 5 years after treatment of invasive breast cancer is largely unexplained by factors associated with treatment. Journal of Cancer Survivorship 8(1):1–8
36. Berrios-Rivera R, Rivero-Vergine A, Romero I (2008) The pediatric cancer hospitalization experience: Reality co-constructed. J Pediatr Oncol Nurs 25(6):340–353
37. Kim SJ, Park YD (2008) Effects of complex decongestive physiotherapy on the oedema and the quality of life of lower unilateral lymphoedema following treatment for gynecological cancer. Eur J Cancer Care (Engl) 17(5):463–468
38. Jeong HJ et al (2011) Causes of shoulder pain in women with breast cancer-related lymphedema: A pilot study. Yonsei Med J 52(4): 661–667
39. Taylor RJ et al (2014) Pain and obesity in the older adult. Curr Pharm Des 20(38):6037–6041
40. Okifuji A, Hare BD (2015) The association between chronic pain and obesity. J Pain Res 14(8):399–408
41. Piper, M., et al (2016), Axillary Web Syndrome*: Current Understanding and New Directions for Treatment.* Ann Plast Surg
42. Yeung WM, McPhail SM, Kuys SS (2015) A systematic review of axillary web syndrome (AWS). J Cancer Surviv 9(4):576–598
43. Cregg R, Anwar S, Farquhar-Smith P (2013) Persistent postsurgical pain. Curr Opin Support Palliat Care 7(2):144–152
44. Shipton EA (2011) The transition from acute to chronic post surgical pain. Anaesth Intensive Care 39(5):824–836

45. Delanian S, Lefaix JL, Pradat PF (2012) Radiation-induced neuropathy in cancer survivors. Radiother Oncol 105(3):273–282
46. Grisold W, Cavaletti G, Windebank AJ (2012) Peripheral neuropathies from chemotherapeutics and targeted agents: Diagnosis, treatment, and prevention. Neuro-Oncology 14:45–54
47. Bhagra A, Rao RD (2007) Chemotherapy-induced neuropathy. Curr Oncol Rep 9(4):290–299
48. Boland EG et al (2014) Central pain processing in chronic chemotherapy-induced peripheral neuropathy: A functional magnetic resonance imaging study. PLoS One 9(5):e96474
49. Lee E et al (2016) Characterization of risk factors for adjuvant radiotherapy-associated pain in a tri-racial/ethnic breast cancer population. Pain 157(5):1122–1131
50. Burton AW et al (2007) Chronic pain in the cancer survivor: A new frontier. Pain Med 8(2):189–198
51. Levy MH, Chwistek M, Mehta RS (2008) Management of chronic pain in cancer survivors. Cancer J 14(6):401–9
52 Altundag K, Ibrahim NK (2006) Aromatase inhibitors in breast cancer: An overview. Oncologist 11(6):553–562
53 Mao JJ et al (2009) Patterns and risk factors associated with aromatase inhibitor-related arthralgia among breast cancer survivors. Cancer 115(16):3631–3639
54 Beckwee, D., et al. (2017) Prevalence of aromatase inhibitor-induced arthralgia in breast cancer: A systematic review and meta-analysis. Support Care Cancer
55 Howell A et al (2005) Results of the ATAC (Arimidex, tamoxifen, alone or in combination) trial after completion of 5 years' adjuvant treatment for breast cancer. Lancet 365(9453):60–62
56 Goss PE et al (2003) A randomized trial of letrozole in postmenopausal women after five years of tamoxifen therapy for early-stage breast cancer. N Engl J Med 349(19):1793–1802
57 Jakesz R et al (2005) Switching of postmenopausal women with endocrine-responsive early breast cancer to anastrozole after 2 years' adjuvant tamoxifen: Combined results of ABCSG trial 8 and ARNO 95 trial. Lancet 366(9484):455–462
58 Burstein HJ (2007) Aromatase inhibitor-associated arthralgia syndrome. Breast 16(3):223–234
59 Peppone LJ et al (2015) The effect of YOCAS(c)((R)) yoga for musculoskeletal symptoms among breast cancer survivors on hormonal therapy. Breast Cancer Res Treat 150(3):597–604
60 Hershman DL, Loprinzi C, Schneider BP (2015) Symptoms: Aromatase inhibitor induced Arthralgias. Adv Exp Med Biol 862: 89–100
61 Fusi C et al (2014) Steroidal and non-steroidal third-generation aromatase inhibitors induce pain-like symptoms via TRPA1. Nat Commun 5:5736
62 Turk DC, Wilson HD (2010) Fear of pain as a prognostic factor in chronic pain: Conceptual models, assessment, and treatment implications. Curr Pain Headache Rep 14(2):88–95
63 Boersma K, Linton SJ (2005) Screening to identify patients at risk: Profiles of psychological risk factors for early intervention. Clin J Pain 21(1):38–43
64 Rashiq S, Dick BD (2014) Post-surgical pain syndromes: A review for the non-pain specialist. Can J Anesth 61(2):123–130