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Breathing Exercises for Pain Management in Cancer Survivors: A Systematic Review

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Abstract

Objective: To explore the efficacy and safety of breathing exercises for pain management in cancer survivors.
Design: A systematic review.

Data sources: Thirteen databases, including PubMed, EMBase, CENTRAL, Medline, CINAHL, JBI, Science Direct, Scopus, SocINDEX, Web of Science, PsycINFO, CNKI, and Wan Fang, were searched from inception to May 24, 2021.

Review/analysis methods: Studies that focused on the efficacy of breathing exercises for pain management in cancer survivors were included. Cochrane tools were used for the quality appraisal of the included studies. Due to the heterogeneity of the studies, descriptive data analysis was used to summarize the results.

Results: A total of 10 studies were included in this systematic review. Slow pursed lip breathing showed benefits for post-surgical pain. Contradictory findings were identified in the Enhanced Recovery After Surgery breathing exercise for post-surgical pain. Slow deep breathing and Hey-Hu regular breathing techniques were effective for pain management in pediatric cancer patients. The Active Cycle of Breathing Technique and five-minute mindful breathing did not have any statistically significant effects on pain relief. Quality of life was measured in three studies, with some improvement. Only one study addressed adverse events and reported that no adverse events associated with the breathing exercises occurred during the study.

Conclusion: This review found some evidence of positive effects of breathing exercises for pain relief in cancer survivors. However, the unsatisfactory methodological quality of the studies prevents its generalizability. More large-scale studies are needed to assess the efficacy and safety of breathing exercises for pain relief in cancer survivors.

Keywords: breathing exercises, pain, cancer survivors

1. Introduction

Pain is a common and distressing symptom among cancer survivors. A cancer survivor, based on the time trajectory, is defined as a person living with cancer or has lived with cancer, which includes both cancer patients receiving active cancer treatment and post-treatment survivorship care (Mayer et al., 2017). Statistics show that pain occurs in 66% of cancer survivors with advanced cancer and over 50% with various types of cancer, and 38% of cancer survivors experience moderate to severe pain (Van Den Beuken-Van et al., 2016). Pain has a profound negative impact on cancer survivors' quality of life as manifested in biopsychosocial aspects (Hjermstad et al., 2016; Li et al., 2018). Pain management can also be a financial burden on the individual and the healthcare system (Henschke et al., 2015).

Pharmacologic interventions are fundamental to pain management in cancer survivors (Fallon et al., 2018; Paice et al., 2016). Based on the World Health Organization's analgesic ladder for cancer pain management, medication is the first choice for cancer-related pain management (Anekar & Cascella, 2021; Carlson, 2016). However, side effects, unintended consequences, and inaccessibility of these medications are barriers to effective pain management in cancer survivors (Anderson, 2019; Ballantyne, 2017; Can et al., 2019; Gupta et al., 2018). Nonpharmacological interventions are an important adjunct to pharmacologic interventions for pain relief, and they can also be utilized as stand-alone therapies. The systematic reviews suggested that nonpharmacological interventions should be considered in symptom management in cancer survivors for their potential benefits (Carlson et al., 2017; Eaton et al., 2017). Given that cancer survivorship requires long-term care for symptom management (Loonen et al., 2018; Vardy et al., 2019), strategies for self-care that can increase one's sense of control over pain are important for cancer survivors to ensure their quality of life (Clinical Oncology Society of Australia, 2016).

Breathing exercise by changing breathing depth and frequency (Brown et al., 2013), as one type of nonpharmacological interventions, has demonstrated the benefit of pain relief in various conditions (Elmetwaly & El Sayed, 2020; Purnamasari et al., 2020; Sasongko et al., 2019). Although clear mechanisms of the breathing exercises for pain reduction have not yet been established, the proposed baroreflex theory posits that breathing manipulation can activate baroreflex, which leads to decreased pain sensitivity (Hassan Jafari et al., 2017). Clinical studies have shown that breathing exercises are effective in chronic pain management (Kezele et al., 2020; Tomas-Carus et al., 2018), labor pain control (Nattah & Abbas, 2016; Parsa et al., 2020; Yuksel et al., 2017), post-surgical pain relief (Vahedian et al., 2021), and procedure-induced pain reduction (Bagheriyan et al., 2011; Bozorg-Nejad et al., 2018). A few small-scale studies have explored the effects of breathing exercises for pain relief among cancer survivors, but with contradictory findings, and the safety of breathing exercises for cancer survivors remains unknown (Bayrak & Can, 2020; Guan et al., 2021; Hejazi et al., 2014; Pourmovahed et al., 2013). Whether breathing exercises are effective and safe for pain relief in cancer survivors requires a systematic review of the current literature to build solid evidence. Therefore, this systematic review was conducted to explore the efficacy and safety of breathing exercises for pain relief in cancer survivors and to identify potential research directions for future studies.

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2. Methods

This systematic review was conducted and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Page et al., 2021), as well as the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins et al., 2011). This systematic review protocol has been submitted to PROSPERO, and is under review.

2.1 Eligibility criteria

2.1.1 Types of studies

Randomized controlled trials (RCTs) and non-randomized controlled trials were the study types of focus.

2.1.2 Types of participants

Studies that included participants with a history of cancer suffering from any kind of pain, without any restriction on types and stages of cancer, age, gender, or ethnicity, were eligible.

2.1.3 Types of interventions

Studies were eligible if they focused on assessing the efficacy of breathing exercises for pain relief in cancer patients. Studies that focused on a combination of outcomes of an intervention consisting of breathing exercises and other activities, such as yoga, tai chi, qigong, or pilates, were excluded because this review focused on the efficacy of breathing exercises only, not a combination of outcomes of multiple interventions.

2.1.4 Types of comparisons

Studies that compared breathing exercises with no specific treatment, treatment as usual, pharmacologic intervention, or other interventions were eligible. Co-interventions were allowed only if the difference between the intervention group and the control group was the practice of the breathing exercise.

2.1.5 Types of outcome measurements

Studies were eligible only when pain was measured in the study, as pain was the primary outcome of this systematic review. The quality of life, adverse events, use of analgesics, use of healthcare services, and costs associated with pain and the breathing exercises were set as the secondary outcomes in this systematic review.

Serious adverse events were defined as death, hospitalization, life-threatening situations, congenital anomaly/birth defect, disability or permanent damage or other events requiring medical or surgical intervention in an emergency situation (such as bronchospasm, blood disorders, and seizures/convulsion); and adverse events apart from these were considered not serious (U.S. Food & Drug Admistration, 2016).

2.2 Search methods

Thirteen databases were searched, including PubMed, EMBase, MEDLINE, JBI, Cumulative Index to Nursing and Allied Health Literature (CINAHL), Scopus, Web of Science, Cochrane Central Register of Controlled Trials (CENTRAL), Science Direct, SocINDEX, PsycINFO, China National Knowledge Infrastructure (CNKI), and Wan Fang, from inception to May 24, 2021. The search languages utilized in the electronic searches were English and Chinese. The literature search was conducted with the following MeSH terms: “breathing exercises,” “respiration,” “pain,” “pain management,” “analgesia,” and “neoplasm*”; and key search terms: “breath*,” “inhal*,” “exhal*,” “tumo*,” “cance*,” “oncolog*,” and “malignant.” Keywords used for the Chinese databases search were “呼吸”, “疼痛”, and “癌症”. The search strategy was adapted for each database accordingly as

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necessary. The reference lists of all selected studies and reviews were further scrutinized for any additional studies. Detailed search strategies for this systematic review are presented in **Appendix 1**.

Two reviewers independently screened the titles and abstracts identified during the literature search, and the potentially eligible articles were read in full to determine inclusion based on the systematic review's eligibility criteria. Any discrepancies between the reviewers about the studies was dealt with by consulting with a third reviewer until a consensus was achieved.

2.3 Data collection and extraction

Two reviewers independently extracted data using a pre-defined data extraction form, which included: (1) first author, study settings, year of publication, study design; (2) participants and clinical characteristics (sample size, age, gender, education level, cancer types, and type of pain); (3) intervention and type of control group (types of breathing exercises, exercise instructor, duration, and frequency); and (4) outcome measures and the therapeutic effects of the breathing exercises on self-reported pain relief, quality of life, use of analgesics, use of healthcare services, costs, and adverse events. Discrepancies were dealt with by consulting with another reviewer until an agreement was reached.

2.4 Methodological appraisal

The risk of bias in individual RCTs was assessed by two reviewers independently based on the Cochrane Collaboration's tool of bias assessment, including "selection bias," "performance bias," "detection bias," "attrition bias," "reporting bias," and "other bias" (Higgins et al., 2011, p. 6). Each domain was scored as (1) "low risk of bias," (2) "unclear," or (3) "high risk of bias" (Higgins et al., 2011, p. 6). For non-randomized controlled studies, the Cochrane ROBINS-I tool for risk of bias was utilized for the quality appraisal (Sterne et al., 2016). Discrepancies were consulted with a third reviewer until an agreement was reached.

2.5 Data analysis

The Review Manager 5.2 was originally planned to be used for meta-analysis. However, due to the clinical heterogeneity of the study designs, populations, cancer types, breathing exercise techniques, and control methods, meta-analysis was not applicable, particularly there were a wide variety of breathing exercise interventions in the included studies. Therefore, descriptive analysis based on the types of breathing exercises and the outcome measurements was applied to synthesize the data.

3. Results

3.1 Study selection

Through electronic and manual searches, 1,496 records were identified as potentially relevant to the review topic. After the removal of 237 duplications, 1,259 records were title- and/or abstract-screened and 1,246 of them were further excluded because they did not meet the inclusion criteria. The number of records sought for retrieval was 13, but one article was not retrievable because it was a conference abstract publication without the authors' contact details available (Bayrak & Can, 2020), and the reviewer contacted the authors' institution but had not received a response before publication. Twelve articles were eligible for full-text assessment. After full-text readings, a further two articles were excluded: one did not measure the effect of pain relief (Hookaew et al., 2016), and the other did not meet the intervention inclusion criteria (Wang, 2020). Finally, 10 studies were included in this systematic review (Gong, 2018; Guan et al., 2021; Hejazi et al., 2014; Le & Tong, 2015; Pourmovahed et al., 2013; Shi et al., 2020a; Shi et al., 2020b; Yang, 2020; Zhou et al., 2016a; Zhou et al., 2016b). The PRISMA flowchart of the study selection is presented in **Figure 1**.

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3.2 Study characteristics

3.2.1 Setting and participant characteristics

The included studies consisted of nine journal articles and one master's thesis, and they were published between 2013 and 2021, with three in English and seven in Chinese. Seven studies were conducted in China (Gong, 2018; Le & Tong, 2015; Shi et al., 2020a; Shi et al., 2020b; Yang, 2020; Zhou et al., 2016a; Zhou et al., 2016b), one in Egypt (Hejazi et al., 2014), one in Iran (Pourmovahed et al., 2013), and one in Malaysia (Guan et al., 2021). Eight RCTs and two quasi-experimental studies included a total of 1,030 participants. The sample sizes were ranged between 60 to 240, with a median size of 103 participants. Most of the participants were recruited from hospitals (Gong, 2018; Guan et al., 2021; Le & Tong, 2015; Pourmovahed et al., 2013; Shi et al., 2020a; Shi et al., 2020b; Yang, 2020; Zhou et al., 2016a; Zhou et al., 2016b), and one study recruited participants from a cancer institute (Hejazi et al., 2014). The types of cancer included lung cancer in two studies (Shi et al., 2020b; Yang, 2020), any type of cancer in two studies (Guan et al., 2021; Hejazi et al., 2014), leukemia in one study (Pourmovahed et al., 2013), esophageal cancer in two studies (Le & Tong, 2015; Shi et al., 2020a), and gynecological malignant tumor in three studies (Gong, 2018; Le & Tong, 2015; Zhou et al., 2016a). The participants included children aged 3 to 15 years old in two studies (Hejazi et al., 2014; Pourmovahed et al., 2013) and adults with a median age of 54.2 years old in seven studies (Gong, 2018; Guan et al., 2021; Le & Tong, 2015; Shi et al., 2020a; Shi et al., 2020b; Yang, 2020; Zhou et al., 2016a). One study did not provide the statistical data of the participants' ages (Zhou et al., 2016b). Apart from the studies involving children, only two studies reported the participants' education level (Le & Tong, 2015; Yang, 2020). Only one study reported the participants' ethnicity (Guan et al., 2021). The total number of female participants accounted for 58.9% of all the participants in the selected studies. The characteristics of the studies included in this systematic review are shown in **Table 1**.

3.2.2 Characteristics of the breathing exercise intervention protocols

Six breathing exercise interventions were reported in the studies, which were the Active Cycle of Breathing Technique (Yang, 2020), the Hey-Hu regular breathing technique (Pourmovahed et al., 2013), mindful breathing (Guan et al., 2021), the Enhanced Recovery After Surgery (ERAS) technique (Shi et al., 2020a; Shi et al., 2020b), slow pursed lip breathing (Gong, 2018; Le & Tong, 2015; Zhou et al., 2016a; Zhou et al., 2016b), and slow deep breathing (Hejazi et al., 2014). Seven RCTs and two quasi-experimental studies used breathing exercise interventions compared with routine care (Gong, 2018; Hejazi et al., 2014; Le & Tong, 2015; Pourmovahed et al., 2013; Shi et al., 2020a; Shi et al., 2020b; Yang, 2020; Zhou et al., 2016a; Zhou et al., 2016b). One study compared five-minute mindful breathing with five-minute talking in a semi-structed interview (Guan et al., 2021). Detailed descriptions of the breathing exercises were reported in each study, except one study failed to report the details of the slow deep breathing protocol (Hejazi et al., 2014). The frequency of the breathing exercises ranged from one-off to 10 to 30 minutes per session, three to five times a day, and the duration varied from five minutes to one month. The instructors of the breathing exercises for the participants were nurses in three studies (Yang, 2020; Zhou et al., 2016a; Zhou et al., 2016b) and psychiatrists in one study (Guan et al., 2021). The other six studies did not provide information about the profession of the instructors (Gong, 2018; Hejazi et al., 2014; Le & Tong, 2015; Pourmovahed et al., 2013; Shi et al., 2020a; Shi et al., 2020b). Details on the breathing exercise intervention protocols are presented in **Table 2**.

3.2.3 Outcome measurement tools

Five studies used the Numeric Rating Scale (NRS) for pain severity assessment, with a scale of 0 to 10, in which 0 indicates no pain and 10 indicates the worst pain (Guan et al., 2021; Le & Tong, 2015;

Shi et al., 2020a; Shi et al., 2020b; Yang, 2020). Two studies used the Visual Analogue Scale (VAS) (Zhou et al., 2016a; Zhou et al., 2016b), and one used the Wong Pain Face Scale (Pourmovahed et al., 2013). Two studies did not provide information on the pain assessment tools utilized for pain assessment (Gong, 2018; Hejazi et al., 2014). Seven studies focused on post-surgical pain, and pain assessments were conducted from post-surgery 12 hours to 96 hours (h) for both the intervention and control groups (Gong, 2018; Le & Tong, 2015; Shi et al., 2020a; Shi et al., 2020b; Yang, 2020; Zhou et al., 2016a; Zhou et al., 2016b); the other three studies focused on general pain and procedure-related pain, and pain assessments were conducted at pre and post the breathing exercise (Guan et al., 2021; Hejazi et al., 2014; Pourmovahed et al., 2013). One study (Yang, 2020) utilized a quality of life measurement tool: the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC QLQ-C30). One study used self-designed measurement tools in their study, but without detailed information reported (Hejazi et al., 2014).

3.2.4 Risk of bias

Eight RCTs were appraised for risk of bias according to the Cochrane Collaboration's tool. The details are shown in **Figure 2**. In regard to selection bias, random sequence generation was adequately reported in seven studies (Gong, 2018; Guan et al., 2021; Le & Tong, 2015; Pourmovahed et al., 2013; Shi et al., 2020a; Shi et al., 2020b; Zhou et al., 2016a), and no RCTs reported allocation concealment. The blinding of participants and personnel was reported in two studies, with a high risk of bias (Guan et al., 2021; Pourmovahed et al., 2013), and all the RCTs failed to provide information on whether intended blinding was conducted for the outcome assessments (Gong, 2018; Guan et al., 2021; Le & Tong, 2015; Pourmovahed et al., 2013; Shi et al., 2020a; Shi et al., 2020b; Zhou et al., 2016a; Zhou et al., 2016b). Nine studies had 100% of the recruited participants complete the study (Gong, 2018; Guan et al., 2021; Hejazi et al., 2014; Le & Tong, 2015; Shi et al., 2020a; Shi et al., 2020b; Yang, 2020; Zhou et al., 2016a; Zhou et al., 2016b), and one RCT with a low attrition rate did not conduct intention-to-treat analysis (Pourmovahed et al., 2013). The risk of reporting bias was low in all the studies except two RCTs (Gong, 2018; Shi et al., 2020b), in which one study did not compare the intervention group with the control group and instead compared pre and post outcomes in the intervention group only (Gong, 2018), and the other only reported the comparison outcomes of the selected groups (Shi et al., 2020b). There was a high risk of bias in both the sample size calculation in all studies and the reporting of adverse events in nine studies (Gong, 2018; Guan et al., 2021; Le & Tong, 2015; Pourmovahed et al., 2013; Shi et al., 2020a; Shi et al., 2020b; Yang, 2020; Zhou et al., 2016a; Zhou et al., 2016b). Two studies failed to report the participants' exclusion criteria (Zhou et al., 2016a; Zhou et al., 2016b) and one did not provide the inclusion criteria (Zhou et al., 2016b). All of the studies conducted baseline assessments and evaluations of the pain relief effects in their reports, and all had a low risk of bias in their methods of data analysis (Gong, 2018; Guan et al., 2021; Hejazi et al., 2014; Le & Tong, 2015; Pourmovahed et al., 2013; Shi et al., 2020a; Shi et al., 2020b; Yang, 2020; Zhou et al., 2016a; Zhou et al., 2016b).

The two quasi-experimental studies were appraised according to the Cochrane ROBINS-I tool for risk of bias (Sterne et al., 2016): one study had a very low risk of bias (Yang, 2020), while the other did not have a comparison group, used only a single group with a pre- and post-test design, and failed to provide details of the intervention and tools used for pain assessment (Hejazi et al., 2014); therefore, the risk of bias for that study was considered high. The details on the appraisals are presented in **Figure 2**.

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3.3 Outcomes

3.3.1 Primary outcome

1) Slow pursed lip breathing: Four RCTs (n=70, n=90, n=80, and n=60, respectively) reported that the slow pursed lip breathing exercises had positive effects on post-surgical pain management compared with routine care (Gong, 2018; Le & Tong, 2015; Zhou et al., 2016a; Zhou et al., 2016b). Slow pursed lip breathing is slow deep breathing with the lips pursed during expiration, and it requires a time ratio of inspiration to expiration at 1:2-3 (Gong, 2018; Le & Tong, 2015; Zhou et al., 2016a; Zhou et al., 2016b). These four RCTs were conducted in hospitals, and the efficacy of pain relief was measured from 12h to 72h post-surgery. Two studies measured pain at time points of post-surgery 12h, 24h, 48h, and 72h, with p=0.002, p=0.002, p=0.001, and p=0.008; and p=0.001, p=0.002, p=0.009, and p=0.004, respectively (Zhou et al., 2016a; Zhou et al., 2016b). One study reported that the intervention group had statistically significant differences in post-surgical pain relief in patients who conducted deep breathing (t=3.982), cough (t=4.219), and off-bed walking (t=4.712) compared with the control group (Le & Tong, 2015), and one study reported pain relief in general at post-surgery (p=0.039) (Gong, 2018).

2) ERAS: Two RCTs (n=160, n=240, respectively) studied the effects of the ERAS breathing exercise for post-surgical pain (Shi et al., 2020a; Shi et al., 2020b). These two studies had a similar design, with four arms that compared full laparoscopic surgery with ERAS breathing exercises and traditional open surgery with routine care. Across-group comparisons were conducted and measurements were taken at post-surgery 24h, 48h, 72h, and 96h. One study had a positive outcome at 72h (p=0.033) and 96h (p=0.032) (Shi et al., 2020a), but the other study did not show any statistically significant differences between the intervention group and the control group at all time points (p>0.05) (Shi et al., 2020b). The main difference between the two studies was that the study that reported positive outcomes had recruited participants with esophageal cancer (n=160) and the other study had recruited participants with lung cancer (n=240).

3) Mindful breathing: One RCT (n=60) reported that there were no statistically significant differences in the outcomes of a five-minute mindful breathing exercise for pain relief in palliative care cancer patients (p>0.05) (Guan et al., 2021). The study compared five minutes of mindful breathing with five minutes of talking in semi-structured interviews at three time point measurements: prior to the intervention (T1), immediately after the intervention (T2), and 5 to10 minutes after the intervention (T3). The study found that there were no statistically significant differences in either the intervention group or the control group at T2 (p=0.46 and p=0.72, respectively) and T3 (p=0.32 and 0.72, respectively) compared with T1.

4) Hey-Hu regular breathing: Hey-Hu regular breathing was conducted in one RCT (n=105), in which the participating children were between 6 and 15 years old with leukemia and were receiving intrathecal injections. Hey-Hu regular breathing instructs participants to “take a deep breath, exhale while whispering hey, then inhale deeply again and exhale while whispering hu (Pourmovahed et al., 2013, p. 565). Hey-Hu regular breathing was demonstrated and practiced with the participants to ensure accuracy, and it was then performed one minute before the intrathecal injection and during the procedure until it was finished. Pain assessments were conducted pre and post the procedure, while the comparison group performed normal breathing. This RCT reported that the Hey-Hu regular breathing exercises had a positive outcome of pain relief among the children receiving intrathecal injections (p=0.01) (Pourmovahed et al., 2013).

5) Slow deep breathing: One quasi-experimental study (n=70) reported that slow deep breathing had a significant effect on relieving pain that was associated with cancer and cancer treatment among

children with different types of cancer (Hejazi et al., 2014). This study did not provide detailed information on the slow deep breathing technique or how it was implemented. The researchers of the study utilized self-designed measurement tools with no detailed information provided in the report. The study authors reported that pain relief was demonstrated by decreased pain severity and the percentage of pain presence, with p=0.001, respectively.

6) Active Cycle of Breathing Technique: One quasi-experimental (n=100) study used the Active Cycle of Breathing Technique, which consists of three to four controlled breaths, three to four thoracic expansion, and two to three forced expiration exercises (Yang, 2020). This breathing exercise is a self-controlled breathing rehabilitation exercise that can quickly clear secretions and increase patients' comfort during recovery after post-lung surgery (Yang, 2020). This study compared the Active Cycle of Breathing Technique with routine care at post-surgical Day1, 2, and 3, in mornings and afternoons, and the author concluded that there were no statistically significant differences in pain relief in the intervention group compared with the control group (t=0.000, p=1.000) (Yang, 2020).

3.3.2 Secondary outcomes

1) Quality of life: Quality of life was measured in three studies (Gong, 2018; Le & Tong, 2015; Yang, 2020). One study utilized the EORTC QLQ-C30 measurement tool and reported that the Active Cycle of Breathing Technique provided some improvement in quality of life in physical and emotional functioning (p<0.05), but no statistically significant differences in social, cognitive, and role functioning (p>0.05) compared with the control group. The other two studies did not provide detailed information on the measurement tools utilized in their studies to measure quality of life, but the statistics reported in both studies was p<0.05 (Gong, 2018; Le & Tong, 2015).

2) Adverse events: Adverse events were addressed in only one study, which reported that no adverse events had occurred during the study (Guan et al., 2021).

The use of analgesics, use of healthcare services, and costs associated with pain and the breathing exercises were not measured in any of the included studies.

4. Discussion

4.1 Summary of evidence

In this systematic review of eight RCTs and two quasi-experimental studies, comparable effects were found for slow pursed lip breathing to routine care for post-surgical pain. Conflicting evidence was found when the ERAS technique was compared with routine care for post-surgical pain. Hey-Hu regular breathing was effective compared with routine care for procedure-induced pain during intrathecal injections. Slow deep breathing was beneficial for cancer- and cancer-treatment-associated pain. Five-minute mindful breathing and the Active Cycle of Breathing Technique were not effective for pain relief in general pain and post-surgical pain, respectively. However, given the limited quantity and quality of the included studies, evidence regarding the effects of the breathing exercises for pain relief in cancer survivors remains inconclusive. Evidence on the safety of the breathing exercises also remains unclear.

4.2 Comparing prior evidence

The findings of this systematic review are partly in line with prior evidence of slow breathing and its benefits in pain relief (Jafari et al., 2020; Hassan; Jafari et al., 2017). In an earlier systematic review, Jafari and colleagues (2017) concluded that based on clinical and experimental studies, slow deep breathing had positive effects on pain relief. Recently, a study conducted by the same researcher confirmed that slow deep breathing was effective for pain relief if the breathing was paced at a slow rhythm with expiration longer than inspiration (Jafari et al., 2020), which is in line with the findings

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of this review that five studies that used slow breathing with a time ratio of inspiration to expiration of 1:2-3 had positive outcomes (Gong, 2018; Le & Tong, 2015; Shi et al., 2020a; Zhou et al., 2016a; Zhou et al., 2016b). Although the exact mechanism is not clear, it is believed that slow deep breathing activates the baroreceptor system, which dampens pain through the cardiovascular and/or central branch of the system (Hassan Jafari et al., 2017). An experimental study (n=16) suggested that deep breathing with relaxation had better results in pain relief compared with attentive deep breathing in which the participants' breathing was guided by a respiratory feedback requiring high concentration and constant attention (Busch et al., 2012). The studies in the present systematic review did not emphasize relaxation while conducting slow deep breathing, but they did report that the participants were instructed to practice the slow breathing exercises in a comfortable and relaxed position (Gong, 2018; Le & Tong, 2015; Zhou et al., 2016b). Although the mechanism of respiratory-induced hypoalgesia is unknown, slow deep breathing for pain reduction is beyond the effect of distraction (Hassan; Jafari et al., 2017).

The duration of the breathing exercises in the present review ranged from a few minutes to one month, and the frequency varied from one-off to 10 to 30 minutes per session, 3 to 5 times a day. Another systematic review of yogic breathing (pranayama) showed that the duration ranged from four days to six months, and the frequency varied from 5 to 60 minutes once or twice daily in most of the studies (Jayawardena et al., 2020). Comparatively, the duration of the breathing exercises in the studies in this systematic review on cancer survivors was relatively short, but more frequent. This suggests that an intervention designed for cancer survivors should consider their physical functioning and exercise tolerance as some cancer survivors may experience severe fatigue (Hinz et al., 2020).

In this systematic review, safety was addressed in only one study, which reported that no adverse events had occurred during the study (Guan et al., 2021), and the other studies did not provide information about adverse events, so it is unknown whether there were no adverse events or they were just not reported. Though breathing exercises are widely utilized in clinical practice such as for hyperventilation syndrome (Jones et al., 2013), asthma (Freitas et al., 2013), and chronic obstructive pulmonary disease (COPD) (Holland et al., 2012), evidence of the side effects of breathing exercises in the literature is sparse, and many studies have failed to report adverse events (Holland et al., 2012). Although the adverse events associated with breathing exercises are not common, dyspnea in patients with COPD and annoyance with mouth-taping among asthmatic adults during breathing exercises have been reported (Lausin & Gouilly, 2009; O'Connor et al., 2012). Moreover, none of the studies included in this systematic review provided information on the interventions' content development process, theoretical framework, or implementation rationale. However, this is fundamental and necessary information in guiding safe breathing exercise practices and should have been included in the reports.

Unidimensional pain assessment tools were used in most of the studies included in this systematic review. Although the NRS and VAS are the most reliable and validated pain intensity assessment tools (Caraceni & Shkodra, 2019; Fallon et al., 2018; Mirabile et al., 2016), considering the nature of the complexity of pain, multidimensional pain assessment tools are encouraged for pain assessment in cancer survivors (Petti et al., 2018), such as the Brief Pain Inventory and the McGill Pain Questionnaire (Kumar, 2011; Main, 2016), but none of these tools were utilized in any of the studies included in this systematic review.

For the secondary outcomes, quality of life was measured in only 3 of the 10 studies in this review, but unmanaged pain can have a significant impact on cancer survivors' quality of life, and thus it

should be assessed. The use of analgesics, use of healthcare services, and costs associated with pain should also be addressed and measured if possible.

4.3 Quality of the evidence

There are some concerns regarding the evidence of the findings from this systematic review. Many factors need to be taken into account regarding the effectiveness of an intervention. In this review, the participants were from different countries with different cultural backgrounds, types of cancer, and cancer treatments, which may have influenced the outcomes of the participants' pain experience in the studies (Can et al., 2019; Caraceni & Shkodra, 2019; Leysen et al., 2017). Due to the high heterogeneity of the participants, breathing techniques, and measurement scales in the studies, the definitive effects of the breathing exercises are inconclusive. The methodological quality of the included studies was unsatisfactory. None of the RCTs provided information on allocation concealment and the blinding of the outcome assessments, and the majority of the studies failed to report sample size calculation and adverse events. None of the studies had adhered to standard reporting guidelines, such as the CONSORT for RCTs and the TREND for non-randomized studies (Haynes et al., 2021; Schulz et al., 2010).

5. Implication for future research and clinical practice

More RCTs on breathing exercises for pain relief in cancer survivors are needed to provide more solid evidence about their effects. Future studies should ensure rigorous methodology in sample size calculation, randomization, and blinding of the participants, personnel, and outcomes assessments to increase their validity. Meanwhile, the theoretical framework, content development process, and implementation rationale of the breathing exercises should be addressed in future studies. Relevant reporting guidelines, such as the CONSORT and the TREND, should be utilized when reporting clinical trial studies' procedures and findings. Moreover, multidimensional pain assessment tools should be considered for pain assessment in cancer survivors, and the reporting of the safety of the breathing exercises should be improved. Additionally, individualized slow breathing techniques need to be considered. Although a fixed respiration rate of 6 to 10 breaths per minute for slow breathing is commonly used (Hassan Jafari et al., 2017; Zaccaro et al., 2018), it may not be well tolerated by some cancer survivors and may need to be adjusted based on each individual's health conditions.

6. Conclusion

This systematic review found some promising but preliminary evidence of breathing exercises for pain management, particularly slow pursed lip breathing for pain relief in cancer survivors. Due to the limited quantity and quality of the included studies, more studies with rigorous methodological designs are needed. Future studies are encouraged to follow study reporting guidelines to improve the reporting quality and the safety assessment of the breathing exercises utilized for pain management in cancer survivors.

7. Potential conflict of interest: None

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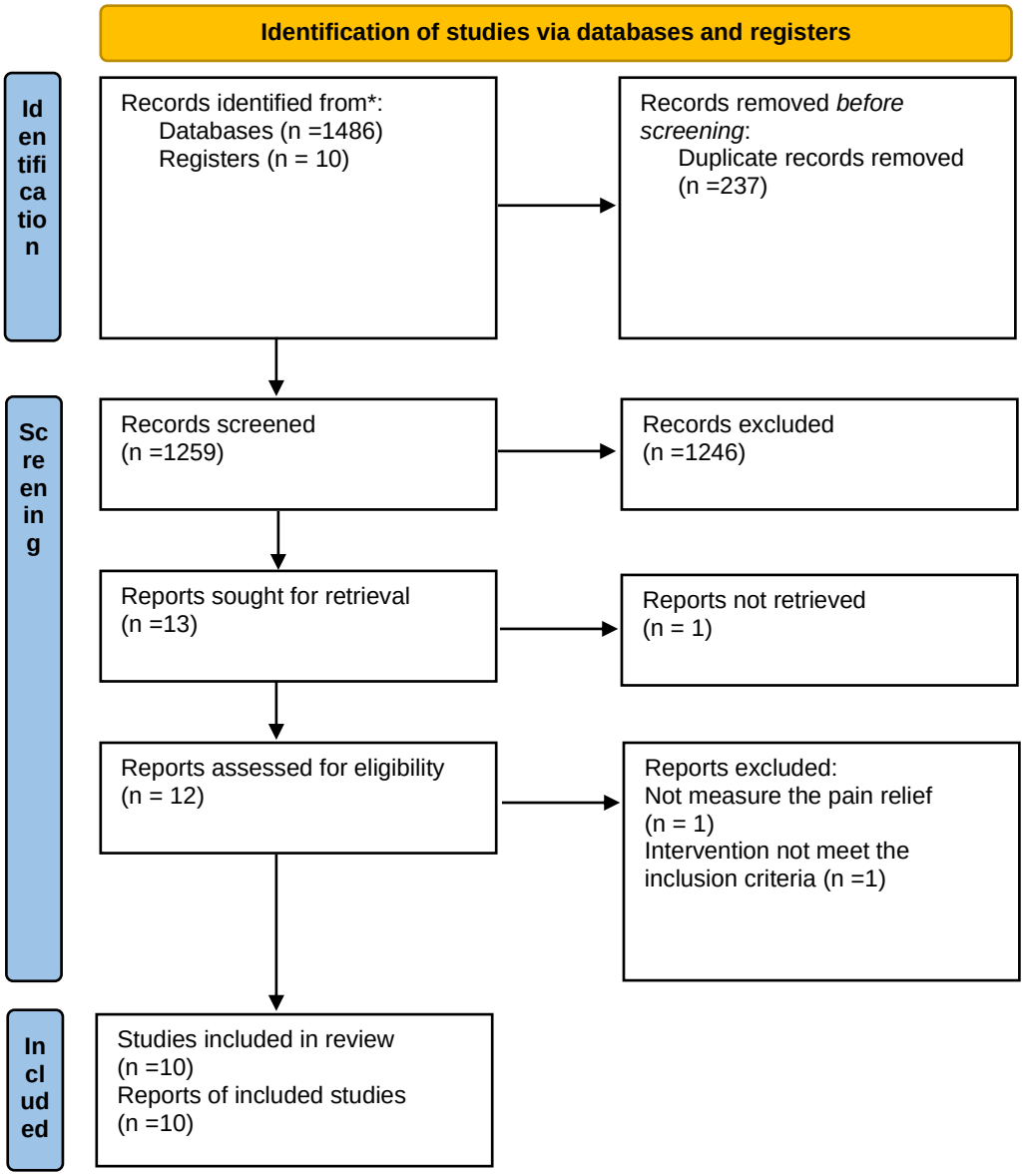
[1]Figure 1. PRISMA flowchart of study selection for the systematic review



[1] From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71

Table 1: Characteristics of included studies

Study and Setting	Type of Cancer	Sample Size	Participants	Type of Pain	Intervention	Control	Outcome Measurements (Pain and *QoL)	Conclusion	Adverse Events
S1: Yang, 2020, quasi-experimental design, hospital, Qingdao, China	Non-small-cell lung cancer	N=100 Intervention=50 Control=50 Completed n=100	≥18 years old, diagnosed with stage I-II non-small-cell lung cancer, Female=46, Male=54	Post-surgical pain	Routine care + Active Cycle of Breathing Technique	Routine care	Pain: *NRS, post-surgical Day 1, 2, and 3, mornings and afternoons; QoL: EORTC QLQ-C30	No statistical significance for pain relief; QoL in physical functioning and emotional functioning improved (p<0.05); no statistical differences in role, social, and cognitive functioning (p>0.05)	Not reported
S2: Hejazi et al., 2014, quasi-experimental design, National Cancer Institute, Egypt	*All, lymphoma, bone tumor, brain tumor	N=70 Completed=70	children >3 years old, with cancer and treated with chemotherapy, Female=33, Male=37	Pain associated with cancer and cancer treatment	Slow deep breathing exercise	N/A	Pain: Self-designed tools, pre and post breathing exercise measurements; QoL: Not reported	Significant differences in pain presence, time of pain, and pain severity in post breathing exercise compared with pre breathing exercise (p=0.001)	Not reported
S3: Pourmovahed	Leukemia	Randomized=105 Completed=100	Children between 6 and	Intrathecal injection	Hey-Hu regular breathing technique	Normal breathing	Pain: Wong Pain Face Scale,	Mean pain score in the	Not reported

et al., 2013, RCT, hospital, Yazd, Iran		Intervention=53 Control=52	15 years old with leukemia, Female=42, Male=58	pain			pre and post the procedure; QoL: Not reported	intervention group was significantly lower than that in the control group (p=0.01)	
S4: Guan et al., 2021, RCT, public hospital, Malaysia	All types of cancer	Randomized=60 Completed=60 Intervention=30 Control=30	≥18 years old, receiving palliative care, with distress score >4 on the distress thermometer, Female=31, Male=29	General pain	Five-minute mindful breathing	Five-minute talking (in a semi-instructed interview)	Pain: NRS, three measurement time points: beginning, immediately after, and 5-10 minutes after the session; QoL: Not reported	No statistical significance for pain relief between the intervention and control groups	No adverse events occurred
S5: Shi et al., 2020a, RCT, Affiliated Hospital of Yangzhou University, China	Esophageal cancer	Randomized=160 Completed=160 A=40 B=40 C=40 D=40	Patients with esophageal cancer, Female=60, Male=100	Post-surgical pain	Group A: Full laparoscopic surgery + ERAS breathing exercise; Group B: Traditional open surgery + ERAS breathing exercise; Group C: Full laparoscopic surgery + routine care; Group D: Traditional open surgery + routine care	Comparison of group A to group C; comparison of group B to group D	Pain: NRS, post-surgery 24h, 48h, 72h, and 96h; QoL: Not reported	Less pain in group A compared with group C at post-surgery 72h (p=0.033) and 96h (p=0.032); less pain in group B compared with group D at post-surgery 96h (p=0.030)	Not reported
S6: Shi et al., 2020b, RCT, Affiliated Hospital of	Lung cancer	Randomized=240 Completed=240 A=60 B=60 C=60	Lung cancer patients underwent endoscopic lung cancer	Post-surgical pain	Group A: Single-hole thoracoscopic surgery + ERAS breathing exercise; Group B:	Comparison of group A to group D; comparison of group B	Pain: NRS, post-surgery 24h, 48h, and 72h; QoL: Not	No statistical differences in pain relief between group A and	Not reported

Yangzhou University and Yancheng First People's Hospital, China		D=60	surgery, Female=98, Male=142		Conventional 3-hole thoracoscopic surgery + ERAS breathing exercise; Group C: Conventional 3-hole thoracoscopic surgery + routine care; Group D: Single-hole thoracoscopic surgery + routine care	to group C	reported	group D; no statistical differences in pain relief between group B and group C (p>0.05)	
S7: Zhou et al., 2016a, RCT, Guangxi National Hospital, China	Gynecological malignant tumor	Randomized=70 Completed=70 Intervention=35 Control=35	Women with gynecological malignant tumor, Female=70, Male=0	Post-surgical pain	Routine care + breathing exercise	Routine care	Pain: *VAS, post-surgery 12h, 24h, 48h, and 72h; QoL: Not reported	Statistical differences at time of pain post-surgery 12h, 24h, 48h, and 72h (p= 0.002, p=0.002, p=0.001, and p=0.008, respectively), and severity of pain mild pain (p=0.03) and severe pain (p=0.02), but no statistical differences in moderate pain (p=0.33) and the worst pain (p=0.31)	Not reported
S8: Gong, 2018, RCT,	Gynecological malignant tumor	Randomized=90 Completed=90 Intervention=45	Women with gynecological malignant	Post-surgical pain	Routine care + breathing exercise	Routine care	Pain: Measurement tool was not	Pain was less in the intervention	Not reported

Xuchang Central Hospital, China		Control=45	tumor, Female=90, Male=0				reported, pre and post breathing exercise; QoL: Tool was not reported	group post breathing exercise compared with baseline (p=0.039); QoL in the intervention group had significant improvement (p<0.05)	
S9: Li & Tong, 2015, RCT, The Second Affiliated Hospital of Harbin Medical University, China	Esophageal cancer	Randomized=80 Completed=80 Intervention=40 Control=40	Patients with esophageal cancer, Female=37, Male=43	Post-surgical pain at breathing, cough, and off-bed walking	Routine care + breathing exercise	Routine care	Pain: NRS, post-surgery (no details on measurement time points); QoL: Tool was not reported	Pain score was significantly lower in the intervention group compared with the control group, comparison of pain in deep breathing (t=3.982), cough (t=4.219), off-bed walking (t=4.712); QoL in the intervention group had significant improvement (p<0.05)	Not reported
S10: Zhou et al., 2016b,	Gynecological malignant	Randomized=60 Completed=60	Women with gynecological	Post-surgical	Routine care + breathing exercise	Routine care	Pain: VAS, post-surgery	Intervention group had	Not reported

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RCT, National Hospital Affiliated with Guangxi Medical University, China	tumor	Intervention=30 Control=30	malignant tumor, Female=60, Male=0	pain		12h, 24h, 48h, and 72h; QoL: Not reported	significant decrease in pain at different time points compared with control group: 12h (p=0.001), 24h (p=0.002), 48h (p=0.009), and 72h (p=0.004)

*All=Acute Lymphoblastic Leukemia

*QoL=Quality of Life

*NRS=Numeric Rating Scale, 0-10 (1-3 mild, 4-6 moderate, 7-9 severe, 10 the worst pain)

*VAS=Visual Analogue Scale

Figure 2: Quality appraisal of included studies.

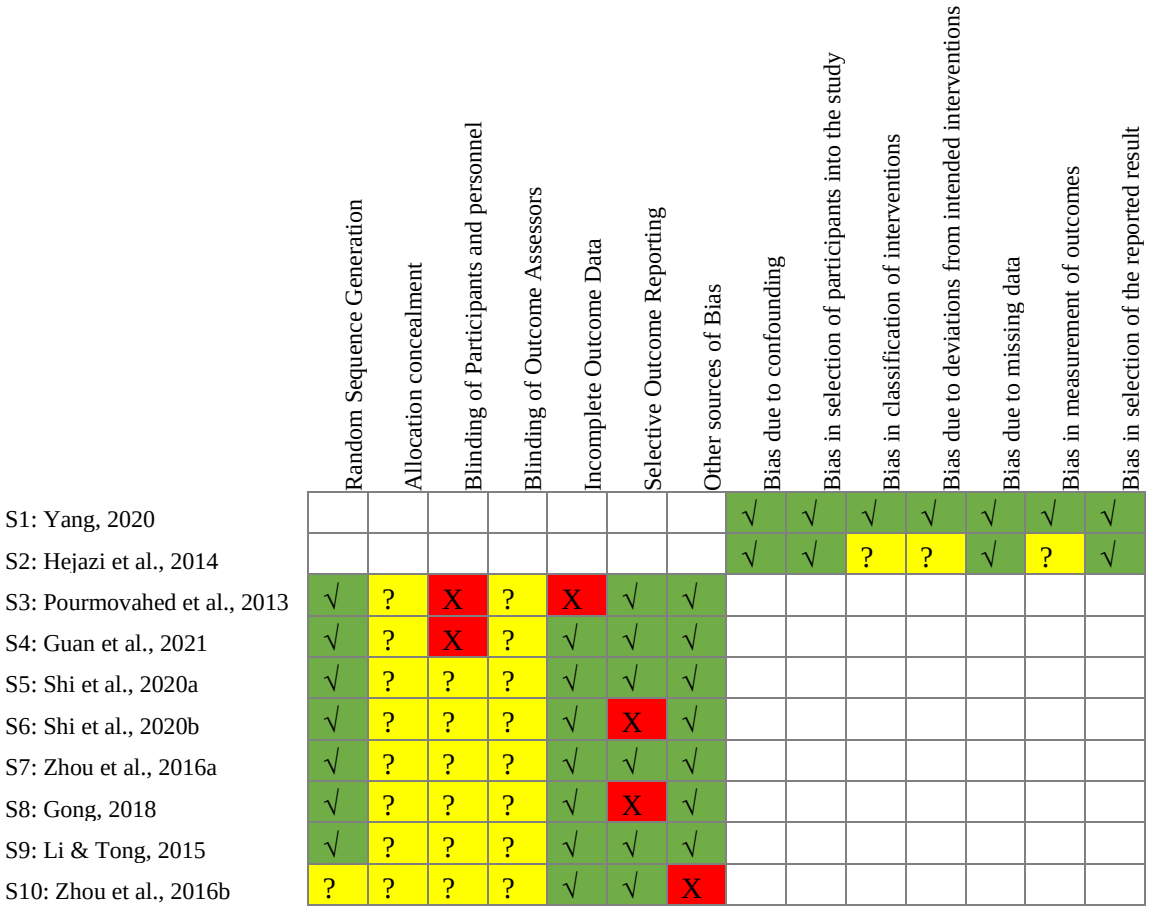

Figure 2. *Risk of bias summary. Cochrane Risk of Bias Tool for randomised controlled trials is used to assess bias for 8 randomized trials (Higgins et al., 2011). ROBINS-I (Sterne et al., 2016) is used to assess bias of 2 quasi-experimental studies. √indicates low risk, X indicates high risk, and ? indicates unclear/insufficient information.*

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Table 2: Breathing exercise protocols in the included studies

Study	Description of Breathing Exercise Intervention	Frequency	Duration	Instructor
S1: Yang, 2020	Active Cycle of Breathing Technique (ACBT): Consists of 3-4 controlled breath, 3-4 thoracic expansion, and 2-3 forced expiratory exercises. Controlled breath exercises: In relaxed sitting or semi-recumbent position, inhale through the nose, then exhale from the mouth slowly, expanding abdomen while inhaling with breath controlled until ready for the next active breath; ratio of inhaling to exhaling is 1:2-3; Thoracic expansion exercises: Using inhalation device to facilitate active inhalation and passive exhalation, after 3 breaths, hold breath for 3 seconds; Forced expiratory exercises: Short breath through the nose, open mouth for forced exhalation, and after 1-2 times make a quick cough.	10-15 minutes/session 3 times/day	One month	Nurse
S2: Hejazi et al., 2014	Slow deep breathing exercise (details of the intervention were not reported).	Not reported	Not reported	Not reported
S3: Pourmovahed et al., 2013	Hey-Hu regular breathing technique: First, the child takes a deep breath and exhales while whispering “hey”, and then inhales deeply again and exhales while whispering “hu”.	One-off practice	One minute before and during the procedure until the end of the procedure	Not reported
S4: Guan et al., 2021	Five-minute mindful breathing guided by the researchers, who were psychiatrists trained in mindfulness therapy.	One-off practice	5 minutes	Psychiatrists
S5: Shi et al., 2020a	Enhanced Recovery After Surgery (ERAS): In sitting or standing position, with the goal of reaching desired tide volume (body weightx10ml/kg) (the feeling of not being able to inhale or exhale any further), inhale through the nose with mouth closed, and then hold breath for 30-60 seconds, then exhale slowly with lips pursed; the ratio of inhaling to exhaling is 1:2-3.	20 minutes/session 3 times/day	5 days	Not reported
S6: Shi et al., 2020b	Enhanced Recovery After Surgery (ERAS): In sitting or standing position, with the goal of reaching desired tide volume (body weightx10ml/kg) (the feeling of not being able to inhale or exhale any further), inhale through nose with mouth closed, and then hold breath for 30-60 seconds, then exhale slowly with lips pursed; the ratio of inhaling to exhaling is 1:2-3.	Duration/session not reported 3 times/day	7 days	Not reported
S7: Zhou et al., 2016a	In a supine position, inhale through the nose slowly, relax diaphragm and extend abdomen, hold breath for 1-2 seconds, and then exhale slowly with lips pursed; the ratio of inhaling to exhaling is 1:2.	30 minutes/session 3 times/day	1 day before surgery and 3 days post-surgery	Nurse
S8: Gong, 2018	In a comfortable position, inhale through the nose slowly, relax diaphragm and extend abdomen, hold breath for 1-2 seconds, and then exhale slowly with effort and lips pursed; the ratio of inhaling to exhaling is 1:2.	20-30 minutes/session 3 times/day	1 month	Not reported

S9: Li & Tong, 2015	Pursed lip breathing exercise and balloon blowing exercise. Pursed lip breathing exercise: In a comfortable position, inhale through the nose slowly and then exhale slowly with lips pursed, adjusting respiration volume with the aim of blowing a candle out at a distance of 15-20 cm (4-6 in); the ratio of inhaling to exhaling is 1:2. Balloon blowing exercise: Choose a 5-30 cm (2-12 in) size balloon, inhale through the mouth and nose, and then blow air forcefully into the balloon.	30 minutes/per session 3 times/day	Until discharge from hospital	Not reported
S10: Zhou et al., 2016b	Active slow nose breathing while relaxing the diaphragm and expanding the abdomen, hold breath for 1-2 seconds, and exhale slowly with lips pursed and relax; the ratio of inhaling to exhaling is 1:2.	6-10 breaths/min 15-20 minutes/session 3-5 times/day	1 day before surgery and 3 days post-surgery	Nurse

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Appendix 1: Search strategies for the systematic review

Database	Search Strategies	
PubMed (502)	#1	"breathing exercises"[MeSH Terms] OR "respiration"[MeSH Terms]
	#2	("breathing exercise*"[Title/Abstract] OR "Breath*"[Title/Abstract] OR "inhal*"[Title/Abstract] OR "exhal*"[Title/Abstract])
	#3	("breathing exercises"[MeSH Terms] OR "respiration"[MeSH Terms]) OR (("breathing exercise*"[Title/Abstract] OR "Breath*"[Title/Abstract] OR "inhal*"[Title/Abstract] OR "exhal*"[Title/Abstract]))
	#4	"Pain" [MeSH Terms] OR "Pain Management"[MeSH Terms] OR "analgesia" [MeSH Terms]
	#5	"sore"[Other Term]
	#6	("Pain" [MeSH Terms] OR "Pain Management"[MeSH Terms] OR "analgesia" [MeSH Terms]) OR ("sore"[Other Term])
	#7	"Neoplasm*"[MeSH Terms]
	#8	(((((((((neoplasm*[Title/Abstract]) OR tumo*[Title/Abstract]) OR tumou*[Title/Abstract]) OR neoplasia[Title/Abstract]) OR cance*[Title/Abstract]) OR carcinom*[Title/Abstract]) OR chemo*[Title/Abstract]) OR antineoplasti*[Title/Abstract]) OR malignant[Title/Abstract]) OR Oncolog*[Title/Abstract]
	#9	("Neoplasm*"[MeSH Terms]) OR ((((((((((neoplasm*[Title/Abstract]) OR tumo*[Title/Abstract]) OR tumou*[Title/Abstract]) OR neoplasia[Title/Abstract]) OR cance*[Title/Abstract]) OR carcinom*[Title/Abstract]) OR chemo*[Title/Abstract]) OR antineoplasti*[Title/Abstract]) OR malignant[Title/Abstract]) OR Oncolog*[Title/Abstract])
	#10	((("breathing exercises"[MeSH Terms] OR "respiration"[MeSH Terms]) OR (("breathing exercise*"[Title/Abstract] OR "Breath*"[Title/Abstract] OR "inhal*"[Title/Abstract] OR "exhal*"[Title/Abstract]))) AND (("Pain" [MeSH Terms] OR "Pain Management"[MeSH Terms] OR "analgesia" [MeSH Terms]) OR ("sore"[Other Term]))) AND (("Neoplasm*"[MeSH Terms]) OR ((((((((((neoplasm*[Title/Abstract]) OR tumo*[Title/Abstract]) OR tumou*[Title/Abstract]) OR neoplasia[Title/Abstract]) OR cance*[Title/Abstract]) OR carcinom*[Title/Abstract]) OR chemo*[Title/Abstract]) OR antineoplasti*[Title/Abstract]) OR malignant[Title/Abstract]) OR Oncolog*[Title/Abstract]))
Medline (14); **CINAHL (15);** **SocINDEX (0);** **PsycInfo (0);** **Scopus (20);** **Web of Science (17)**	#1	("breathing exercise*" or "respiration" or "breath*" or "inhal*" or "exhal*").mp. [mp=text, heading word, subject area node word, title]
	#2	(pain or sore or analgesia).mp. [mp=text, heading word, subject area node word, title]
	#3	(neoplasm* or tumo* or cance* or carcinoma* or chemo* or antineoplastic* or malignan* or oncolog* or radi*therapy).mp. [mp=text, heading word, subject area node word, title]
	#4	#1 and #2 and #3

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Science Direct (0)		("Breathing exercise" or "respiration" or "Breath" or "breathing" or "inhalation" or "inhale" "exhalation" or "exhale") AND ("pain" or "pain management" or "pain reduction" or "pain control" or "sore") AND ("neoplasm" or "cancer" or "anticancer" or "chemotherapy" or "radiotherapy" or "radiation therapy" or "metastasis" or "malignant" or "tumour" or "tumor" or "carcinoma" or "oncology")
JBI (153)	#1	("breathing exercise" or "respiration" or "breath*" or "inhal*" or "exhal*").mp. [mp=text, heading word, subject area node word, title]
	#2	(pain or sore or analgesia).mp. [mp=text, heading word, subject area node word, title]
	#3	(neoplasm* or tumo* or cance* or carcinoma* or chemo* or antineoplastic* or malignan* or oncolog* or radi*therapy).mp. [mp=text, heading word, subject area node word, title]
	#4	#1 and #2 and #3
EMBase (64)	#1	("breathing exercise" or "respiration" or "breath*" or "inhal*" or "exhal*").m_titl.
	#2	(pain or sore or analgesia).m_titl.
	#3	(neoplasm* or tumo* or cance* or carcinoma* or chemo* or antineoplastic* or malignan* or oncolog* or radi*therapy).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]
	#4	#1 and #2 and #3
Cochrane Central Register of Controlled Trials (10)		breathing or breathing exercise or breathing technique or respiration in Record Title AND pain or pain relief or pain management or analgesia in Title Abstract Keyword AND cancer or tumo* in Title Abstract Keyword - (Word variations have been searched)
CNKI (599)		主题=呼吸；AND 主题=疼痛；AND 主题=癌症， 同义词扩展
Wanfang (102)		主题=呼吸；AND 主题=疼痛；AND 主题=癌症， 同义词扩展