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An Overview of Systematic Reviews: Complementary Therapies for Cancer Patients

Seong Min Lee[1], Ho Cheol Choi[1], and Min Kyung Hyun, KMD, PhD[2]

Abstract

Introduction: This article critically examines the systematic reviews (SR) and meta-analysis (MA) of complementary therapies for cancer patients to appraise the evidence level, and offers suggestions for future research and practice. **Methods:** The Cochrane Library and MEDLINE were searched from their inception to January 2018, to identify SR and MA of complementary therapies available for cancer patients. Final selected SR and MA were methodologically evaluated for their quality by applying the Assessing the Methodological Quality of Systematic Reviews 2 (AMSTAR2) instrument. Data extraction and risk of quality assessments were performed by 2 independent reviewers. **Results:** A total of 104 studies were included in the analysis. The majority of the individual clinical trials included in the SR and MA were performed in China (48%) and the United States (26.9%). Breast cancer was the most studied cancer type (25%), and acupuncture was the most studied intervention (21%). Side effects of cancer such as pain, depression, and fatigue were effectively managed with complementary therapies. The methodologically problematic items included not listing the excluded studies and lack of protocol or protocol registration. **Conclusions:** With increasing interest in research, complementary therapies appear to be beneficial in reducing side effects and raising the quality of life of cancer patients. Complementary therapies have generally been studied for all cancers, with acupuncture being the most researched, regardless of the cancer type. Since AMSTAR2 is a stricter assessment tool than before, future studies need to consider the risk of methodological bias with caution and discuss appropriate overall quality assessment tools.

Keywords

Complementary therapies, cancer, Assessing the Methodological Quality of Systematic Reviews 2, AMSTAR2

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Introduction

Cancer is a major global public health concern and is the second leading cause of mortality in the United States of America.[1] Because of an aging population and population growth, there has been a 33% increase in cancer cases between 2005 and 2015.[2]

The World Health Organization statistics provided about 12.7 million cancer cases in 2008, and this number is expected to increase to 21 million by 2030. Cancer patients are challenged with various side effects, including fatigue, chemotherapy-induced pain, and depression, which induce severe impairment in their quality of life (QOL).[3] According to the World Health Organization, one aim of cancer treatment is to considerably prolong the life of patients and ensure QOL for cancer survivors.[4] Complementary therapies have emerged as adjuvant therapies that are able to increase the QOL of cancer patients. In recent times, the use of complementary therapies is much more prominent and popular than previously considered, as an efficacious segment of cancer treatments.[5] Cancer patients use complementary therapies mainly for enhancing the immune system, relieving pain, and controlling adverse side effects caused by the disease or treatment.[6] Complementary therapies contain a broad range of therapeutic approaches.[7] Several studies state that complementary therapies promote the QOL of cancer patients during

[1]College of Korean Medicine, Dongguk University, Gyeongju, Republic of Korea
[2]Department of Preventive Medicine, College of Korean Medicine, Dongguk University, Gyeongju, Republic of Korea

Corresponding Author:
Min Kyung Hyun, Department of Preventive Medicine, College of Korean Medicine, Dongguk University, 123, Dongdae-ro, Gyeongju-si, Gyeongsanbuk-do 38066, Republic of Korea.
Email: mk3three@dongguk.ac.kr

and after treatment by reducing adverse symptoms.[6,8] Recent research has reported that 60% of cancer patients have used at least one type of complementary therapy after being diagnosed with cancer.[8] Furthermore, leading cancer centers in the United States offer evidence-based complementary therapies coupled with conventional medicine, a process known as integrative medicine.[9] In addition, systematic reviews (SR) and meta-analysis (MA) for evaluating the effects of complementary therapies are also increasing. This study, therefore, critically reviews the SR and MA of complementary therapies in cancer patients to appraise the evidence level and provides suggestions for future research and practice.

Methods

Protocol and Registration

The protocol of this review was registered on PROSPERO 2018 (Registration Number: CRD42018090318).

Search Strategy

Two databases, The Cochrane Library and MEDLINE, were searched from their inception through January 2018.

The Cochrane Library

#1 MeSH descriptor: [Neoplasms] explode all trees in Cochrane Reviews
#2 MeSH descriptor: [Complementary Therapies] explode all trees in Cochrane Reviews
#3 #1 and #2 in Cochrane Reviews

MEDLINE

#1 systematic[sb] AND (neoplasms[MeSH] or neoplasm*)
#2 systematic[sb] AND (Complementary Therapies[MeSH] or Complementary Therapie*)
#3 #1 and #2

Study Selection

Types of Participants. All cancer patients treated with complementary therapies were included. There were no restrictions with respect to age, sex, ethnicity, or type of setting.

Types of Interventions. This review included all types of complementary therapies. We classified the interventions according to the guidelines set by the National Center for Complementary and Integrative Health (NCCIH). These were natural products, mind and body practices, and other complementary health approaches. Since acupuncture belongs to 2 groups (mind and body practices and traditional Chinese medicine of other complementary health approaches), we added one more subgroup and classified it separately. Any control that is compared with complementary and alternative therapies is included.

Types of Outcome Measures

- QOL, assessed by any validated instrument.
- Overall survival, including survival rate or survival time or overall survival, assessed by any validated instrument.
- Pain, assessed by any validated instrument.
- Depression, assessed by any validated instrument.

Types of Study. SR and MA were included in this study.

Language Restriction. Only articles written in English were included.

Data Extraction and Quality Assessment

Two independent reviewers extracted data using standardized data extraction, and assessed the methodological quality of each included study by applying Assessing the Methodological Quality of Systematic Reviews 2 (AMSTAR2). Any discrepancies were resolved by consensus or consultation with a third reviewer. The data extraction form comprised the name of author, publication year, publication country, sample size, study conducted country, search period, study design, type of cancer, interventions, and outcomes.

AMSTAR2 comprises 16 items for assessing the methodological quality of SR. It rates the overall confidence of the review results as high, moderate, low, and critically low.[10] Appraisal is based on the number of critical or noncritical flaws: "critically low," more than one critical flaw regardless of whether it has noncritical weaknesses; "low," only one critical flaw regardless of the presence of noncritical weaknesses; "moderate," more than one noncritical weakness with no critical flaws; and "high," none or one noncritical weakness.

Results

Study Selection

A total of 601 studies were identified; 32 duplicated studies were deleted. After checking all titles and abstracts, 247 possible relevant studies were retained. After the second screening through full text review, 104 studies were finally selected for analysis (Figure 1).

Study Characteristic

Of the 104 studies, 17 studies were published in 2012, and 23 studies were published in 2016 (Table 1). The affiliation country of corresponding author for SR and MA were China (30%), Republic of Korea (15%), the United Kingdom

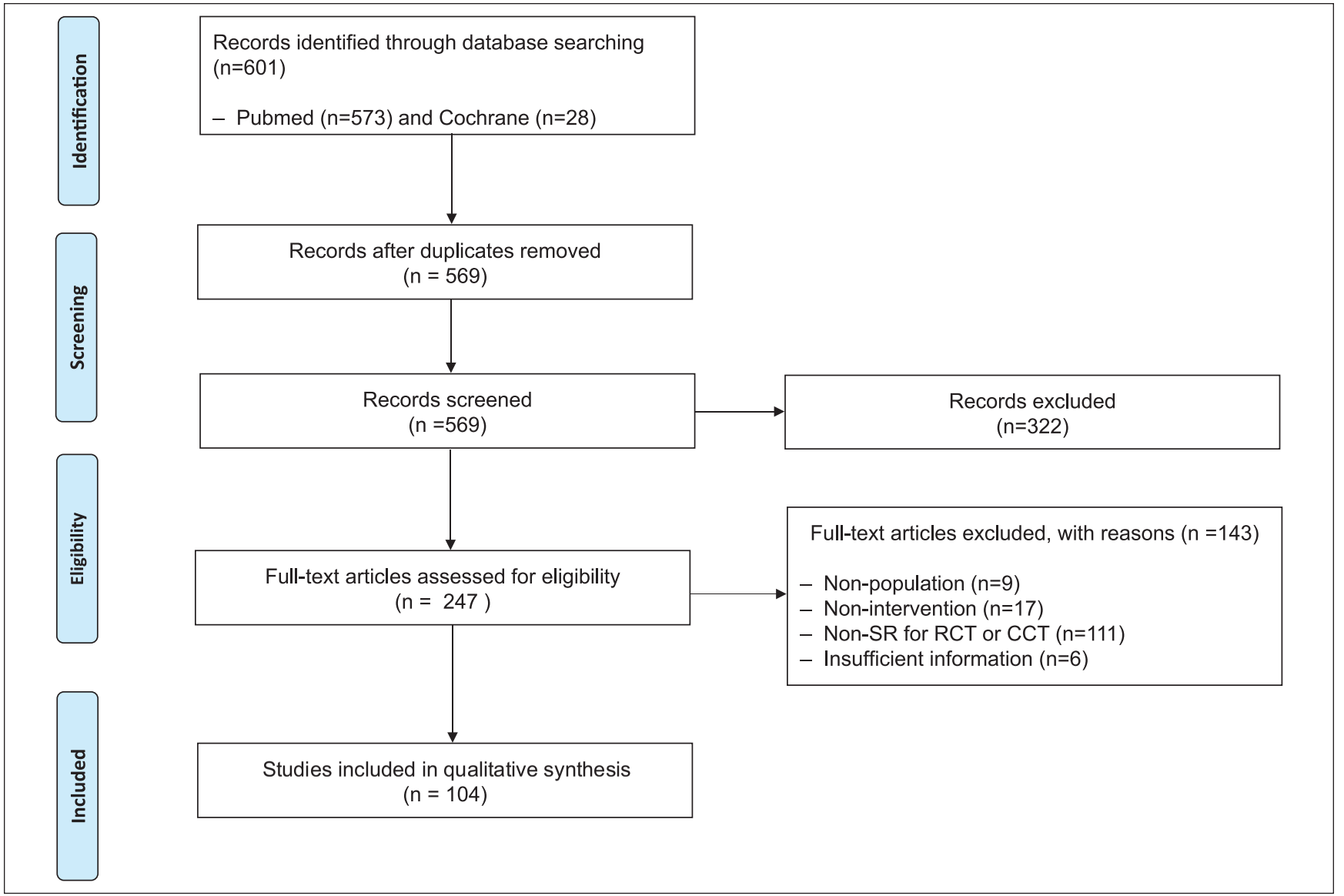

Figure 1. Flow chart of study selection.

Table 1. The Number of Studies by the Year and Lead Authors' Affiliation[a].

Country of Lead Authors' Affiliation	2003	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	Total N	Total %
Australia									2 (2)		1 (1)	1 (1)	2 (2)		6	6
Brazil													1 (1)		1	1
China				1 (1)		2 (1)		1 (1)	7 (6.5)	2 (2)	8 (8)	1 (1)	9 (9)	2 (2)	33 (31.5)	32 (30)
Canada						(1)									(1)	1
France												1 (1)			1	1
Germany	(1)								2 (2)		2 (2)	1 (1)	1 (1)	1 (1)	7 (8)	7 (8)
Hong Kong						(1)									(1)	1
Iran													1 (1)		1	1
Ireland							1 (1)								1	1
Republic of Korea						1 (1)	3 (3)		2 (2)	1	2 (2)	5 (5)	2 (2)	1 (0.5)	17 (15.5)	15
The Netherlands						1 (1)			1 (1)						2	2
Taiwan						1						1 (1)	2 (2)	1 (1)	5	5
United Kingdom	1	1 (1)	2 (2)	3 (3)	1 (1)	2 (2)			1 (1)	1 (2)		2 (2)	1 (1)		15	14
United States			2 (2)						2 (2.5)	4 (4)		3 (3)	4 (4)	(0.5)	15	14
Total	1	1	4	4	1	7	4	1	17	8	13	15	23	5	104	100%

[a]Numbers in parentheses represent corresponding authors; those outside parentheses are based on first authors.

Table 2. Countries Where Clinical Trials of the Included studies Were Conducted.

Country	N	%
China	748	48.0%
United States	419	26.9%
United Kingdom	65	4.2%
Sweden	50	3.2%
Germany	33	2.1%
India	33	2.1%
Canada	32	2.1%
Australia/New Zealand	29	1.9%
Republic of Korea	28	1.8%
Taiwan	26	1.7%
Italy	14	0.9%
Norway	12	0.8%
Spain/Portugal	10	0.6%
Denmark	9	0.6%
France	8	0.5%
Brazil	5	0.3%
Israel	5	0.3%
Slovenia	5	0.3%
Iran	4	0.3%
The Netherlands	4	0.3%
Unknown	4	0.3%
Japan	3	0.2%
Other	13	0.8%
Total	1559	100.0%

(14%), and the United States (14%) (Table 1). On the other hand, most clinical trials included in the SR and MA were performed in China (48%, 748/1559) and the United States (26.9%, 419/1559) (Table 2). The most researched cancer types included all cancers (56%), followed by studies on breast cancer (25%) Figure 2). In addition, the most studied complementary therapy was acupuncture (21%), followed by herbal medicines (14%) Figure 3).

Methodological and Reporting Quality

Studies were not rated moderate or high confidence if there were more than just one weakness in critical domain and high percentage of studies had difficulty in achieving every critical domain of AMSTAR2 evaluation. As a result, only 17 (16%) studies were rated high. Failure to provide a list of excluded studies (Item 7) was the main reason for being rated critically low. Furthermore, several studies lacked explicit statements of review methods established prior to performing the research, and failed to explain any modifications from previously published protocols (Item 2). Only 23 cases (22.1%) met the requirement of Item 2, and 20 (19.2%) studies provided Item 7.

Confirming noncritical items was relatively easy as compared with critical items, resulting in the absence of moderate grade. Overall, although AMSTAR2 has been simplified, it is more demanding to mark a study as high in methodological quality, as compared with the previous version (Figure 4).

Outcomes of Included Studies

Overall, the included SR and MA suggest potential encouraging effects for each outcome. However, the studies also reveal low evidences or low numbers of methodologically rigorous trials. We present below the result of each outcome measurement.

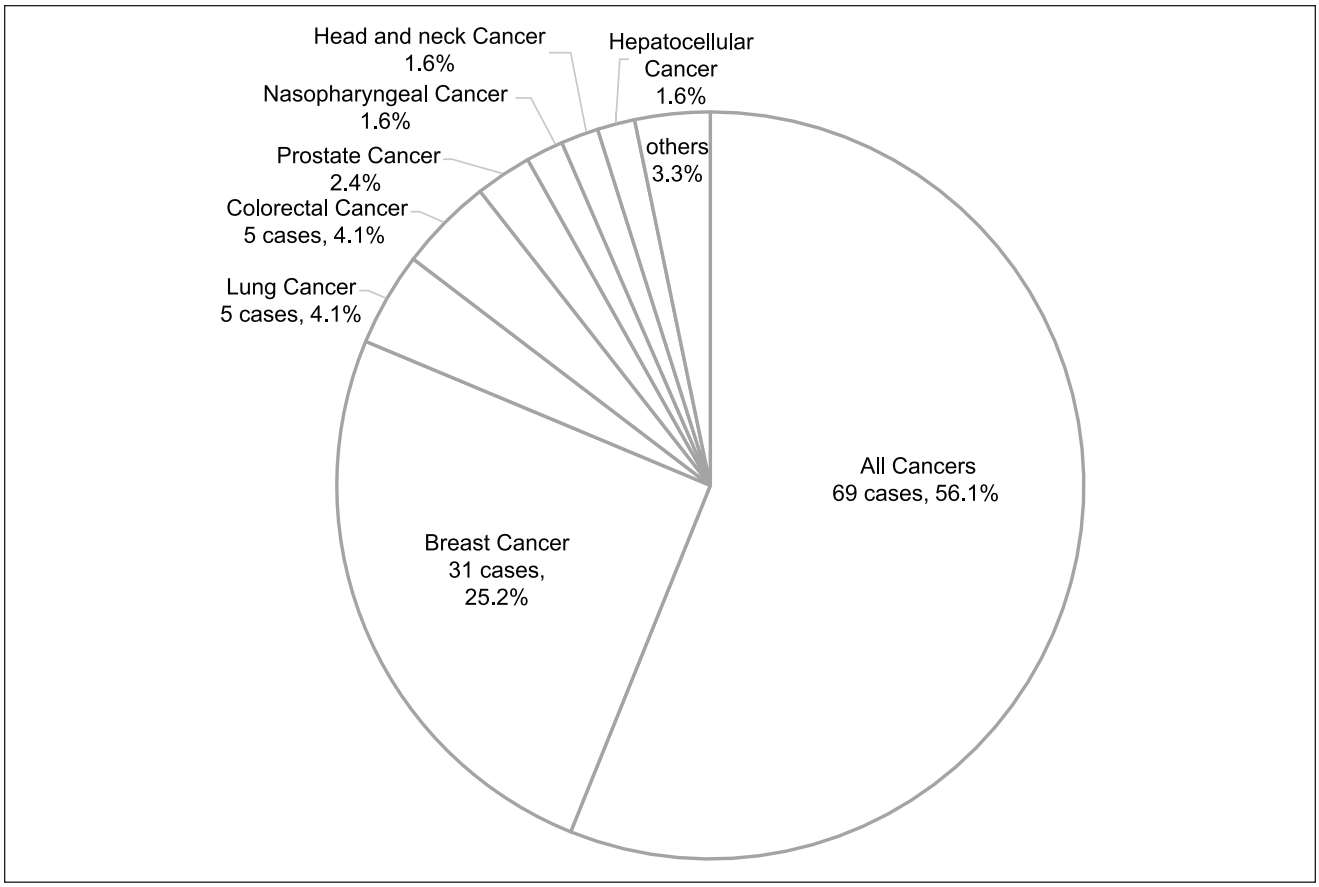

Figure 2. The cancer types of the included studies.

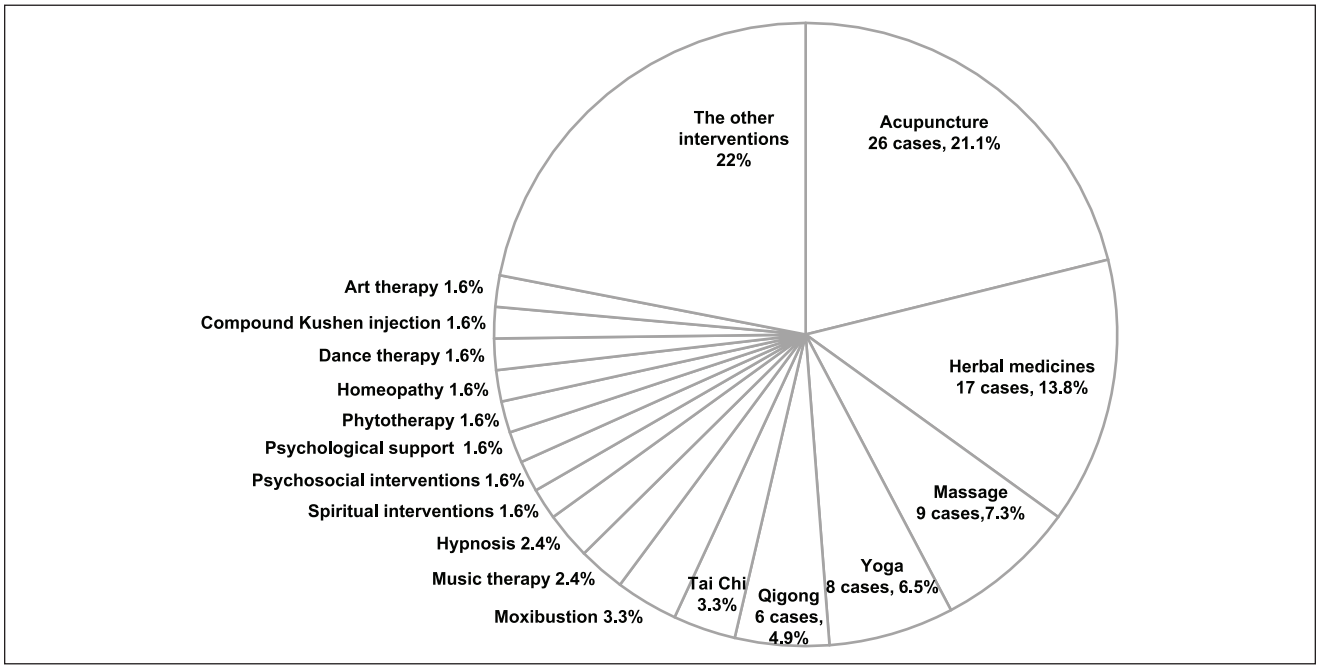

Figure 3. The type of CAM intervention of the included studies.

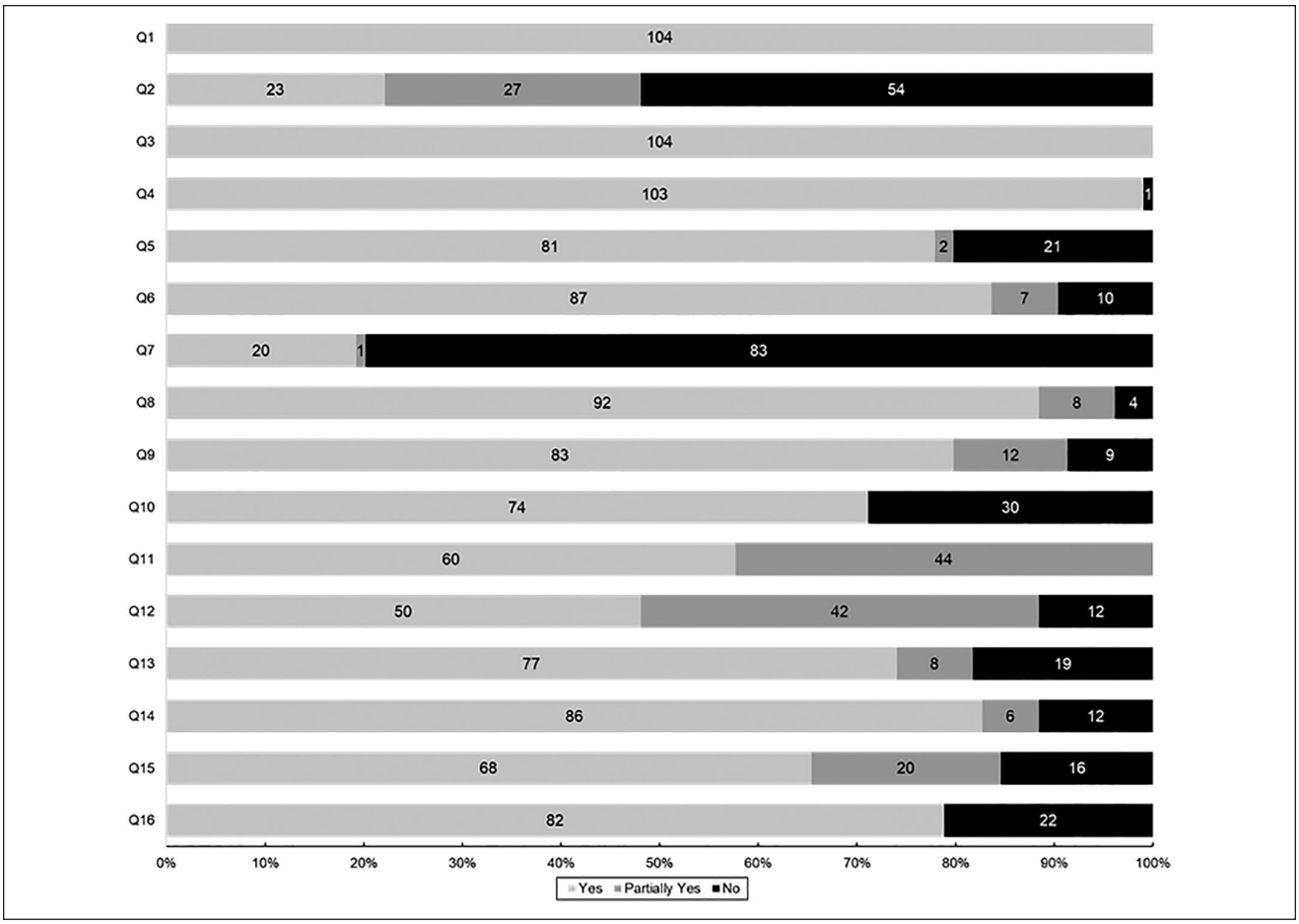

Figure 4. Methodological and reporting quality: evaluation results of each AMSTAR2 question of included studies.

The Items of AMSTAR2 are as Below, and the Bold Items (Q2, 4, 7, 9, 11, 13, 15) are Critical Domains.

Q1	Did the research questions and inclusion criteria for the review include the components of PICO? (population, intervention, control group, and outcome)
Q2	**Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?**
Q3	Did the review authors explain their selection of the study designs for inclusion in the review?
Q4	**Did the review authors use a comprehensive literature search strategy?**
Q5	Did the review authors perform study selection in duplicate?
Q6	Did the review authors perform data extraction in duplicate?
Q7	**Did the review authors provide a list of excluded studies and justify the exclusions?**
Q8	Did the review authors describe the included studies in adequate detail?
Q9	**Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review?**
Q10	Did the review authors report on the sources of funding for the studies included in the review?
Q11	**If meta-analysis was performed, did the review authors use appropriate methods for statistical combination of results?**
Q12	If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?
Q13	**Did the review authors account for RoB in primary studies when interpreting/discussing the results of the review?**
Q14	Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?
Q15	**If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?**
Q16	Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?

Quality of Life

Systematic review

- Among 91 randomized controlled trials (RCTs) and controlled clinical trials (CCTs) in 21 SRs,[11-31] 58 reported beneficial aspects of complementary therapies on increasing the QOL for cancer patients (64%, 58/91). (Online appendix 1-1).

Meta-analyses

- Among 33 MAs in 28 studies,[32-59] 22 reported significant effects of complementary therapies on increasing the QOL for cancer patients (72%, 24/33). (Online appendix 1-2).

Overall Survival

Systematic review

- Among 57 RCTs and CCTs in 7 SRs,[14,17,22,28,30,34,55,60] 12 reported beneficial aspects of complementary therapies on the overall survival (OS) improvement for cancer patients (21%, 12/57). (Online appendix 2-1).

Meta-analysis

- Among the 16 MA in 9 studies,[23,40,45,61-66] 15 reported significant effects of complementary therapies on OS improvement for cancer patients (94%, 15/16). (Online appendix 2-2).

Pain

Systematic review

- Among 62 RCTs and CCTs in 11 SRs,[12,16,24,27,67-73] 53 reported beneficial aspects of complementary therapies on relieving pain for cancer patients (85%, 53/62). (Online appendix 3-1).

Meta-analysis

- Among 20 MA in 19 studies,[35,36,38,42,43,48,53,54,56,57,74-82] 16 reported significant effects of complementary therapies on relieving pain for cancer patients (80%, 16/20). (Online appendix 3-2).

Depression

Systematic review

- Among 101 RCTs and CCTs in 14 SRs,[12,13,15,17,18,25,29,30,35,55,69,71,72,83] 34 reported beneficial aspects of complementary therapies on relieving depression for cancer patients (34%, 34/101). (Online appendix 4-1).

Meta-analysis

- Among 17 MA in 14 studies,[23,32,33,36-38,41-43,54,57,84-86] 10 reported significant effects of complementary therapies on relieving depression for cancer patients (59%, 10/17). (Online appendix 4-2).

Discussion

This comprehensive review finally included a total of 104 SR and MA of complementary therapies for cancer patients. Considering the increase in number of studies, we could confirm the increased interest in application of complementary therapies for cancer patients.

Most of the SR and MA were published by lead authors affiliated to China, Republic of Korea, the United Kingdom, and the United States. Ironically, approximately 75% clinical trials, including in SR and MA, were performed in China and the United States. The Republic of Korea and the United Kingdom were somewhat lacking in efforts to generate evidence by conducting primary research (ie, clinical studies) and were more focused toward evidence syntheses, as compared with China and the United States.

Meanwhile, we found that complementary therapies were generally applied to all cancers and the most studied complementary therapy was acupuncture. Breast cancer was the most investigated single cancer type. It is assumed that the purpose of complementary therapies for cancer patients is not to eradicate specific cancer cells, but to manage side effects and improve the QOL with the aid of biomedicine.

Similar to our findings, acupuncture (55.3%) was the most frequently provided complementary therapy in a survey of cancer centers across 26 European countries.[87] If the disease was not limited to cancer, the most commonly used complementary therapy was herbal medicine (data collected from SR of surveys) in the United Kingdom, and natural products in the US National Health Interview Survey in 2007.[88,89]

The methodological and reporting quality of SR and MA were found to be low due to the absence of research protocols and failure to provide the list of excluded studies. Other articles assessed by AMSTAR2 were also rated critically low for similar reasons.[90,91] Because there is a limitation for the SR and MA conducted before the AMSTAR2 was published, further studies are required to carefully consider methodology from the protocol stage for being appraised high quality. Conversely, of the 17 methodologically high research studies, yoga (17.6%, 3/17)[32,33,84] and herbal medicines (17.6%, 3/17)[11,34,92] were most widely studied, and were indicative of bestowing a positive effect on the patients' QOL. However, several research studies deferred a definitive conclusion due to paucity of high-quality evidence.

Many cancer patients experience one or more adverse side effects during their treatment period; 86% of patients report chemotherapy-associated side effects.[93] Complementary therapies have been used in the management of side effects caused by cancer or cancer treatment. Similarly, the outcomes of included SR and MA reveal that complementary therapies can be effective for improving the QOL and managing side effects of cancer patients.

We acknowledge that there are few limitations to this study. First, in most research on complementary therapies, the definition and scope of complementary therapies remains unclear; hence, it is difficult to set the inclusion/exclusion criteria. We therefore applied the complementary therapies classification of NCCIH. Second, despite every effort to provide a comprehensive and systematic review, language restrictions of our study might have resulted in omission of several studies conducted in Asian or other countries. However, China has published the most articles despite English-language restriction.

Conclusions

In our overview, we found that SR and MA on complementary therapies in cancer patients have increased in China and the United States. Although there are methodological and reporting quality limitations based on AMSTAR2, several complementary therapy interventions were used to manage side effects such as pain, fatigue, and depression in cancer patients. Therefore, future studies must treat the risk of methodological bias with caution. High-quality SR in which selection of high-quality studies is combined with adequate methodology, are needed to clarify the true efficacy of complementary therapies for cancer patients.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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ORCID iD

Min Kyung Hyun https://orcid.org/0000-0003-0212-8633

Supplemental Material

Supplemental material for this article is available online.
Appendix 1-1. Quality of life in SR
Appendix 1-2. Quality of life in MA
Appendix 2-1. Overall survival in SR
Appendix 2-2. Overall survival in MA
Appendix 3-1. Pain in SR
Appendix 3-2. Pain in MA
Appendix 4-1. Depression in SR
Appendix 4-2. Depression in MA

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