The Effects of Exercise Intervention for Post-Operative Breast Cancer Patients in Korea: A Systemic Review and Meta-Analysis of Randomized Controlled Trials

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Purpose: This study aimed to systematically evaluate literature related to the effects of exercise intervention programs on physical or psychological variables of post-operative breast cancer patients in Korea, and identify the effectiveness of exercise intervention through meta-analysis. Methods: The review question was defined according to PICO-SD (Participants, Intervention, Comparisons, Outcomes, Study Design) to achieve a systematic literature review: “How does exercise intervention affect the physical or psychological outcome in post-operative breast cancer patients compared to the control group?” The subjects were randomized clinical trials (RCTs) studies released in Korea between 2010 and December 2020. Literature searches were conducted using four electronic databases, including Korean Studies Information Service System (KISS), Research Information Sharing Service (RISS), National Assembly Library, and DBpia. The search terms were ‘breast neoplasms’ or ‘breast cancer’ with ‘exercise’ or ‘exercise intervention’ or ‘exercise program’. A total of 13 RCTs were finally selected. Results: The outcome variables were in the upper extremity range of motion (ROM), shoulder disability, pain and edema. The effect size of exercise intervention on ROM was 0.95(95% CI:0.58, 1.33)(p<.001); shoulder disability was -1.16(95% CI:-1.77, -0.55)(p<.001); pain was -1.24(95% CI: -1.58, -0.89)(p<.001); and edema was -0.03(95% CI:-0.39, 0.33)(p=.858). Conclusion: This result suggests that oncology nurses may apply exercise intervention to improve ROM, shoulder disability, and to alleviate pain in post-op breast cancer patients.

Key Words: Breast neoplasm, Mastectomy, Exercise, Randomized Controlled Trial, Meta-analysis

INTRODUCTION

1. Background

In Korea, the incidence of breast cancer has increased rapidly since 1995, and it is now the most common among all cancers in women (23,547 cases in 2018, according to Statistics Korea). The incidence among women aged 40–50 was 62.6%, and the highest was among women aged 45–49, the most socially and economically active age group, increasing the severity of the breast cancer cases. Although the incidence of breast cancer patients is increasing, the 5-year relative survival rate of breast cancer in Korea has also increased, from 79.3% in 1995 to 93.3% in 2018, a higher survival rate than other cancers. The incidence of breast cancer patients is increasing, the 5-year relative survival rate of breast cancer in Korea has also increased, from 79.3% in 1995 to 93.3% in 2018, a higher survival rate than other cancers. The low age of onset and high survival rate of breast cancer means that breast cancer is becoming chronic, and there is thus a need for continuous adaptation in diagnosis, treatment, and even after completing treatment. The primary treatment for breast cancer patients is mastectomy, followed by chemotherapy, radiation therapy, and hormone therapy. Mastectomy patients not only experience side effects such as pain, nausea, and fatigue during treatment, but also are subject to long-term physical effects such as deformation and pain in the surgical site, swelling and sensory changes in the arms, decreased grip and muscle strength, and decreased upper extremity function, which leads to significant reductions in quality of life. These experiences last for one to two years after surgery, and breast cancer patients also experience physical changes after surgery, which leads to both physical discomfort and psychological pain due to losing a body part that is a symbol of their womanhood. For this reason, nursing interventions are needed to reduce the physical, psychological, and social discomfort experienced by post-operative breast cancer patients and help their treatment and rehabilitation.

Of the various nursing interventions, exercise interventions have been applied to cancer patients since the late 1980s. In addition to reducing pain and increasing the shoulder range of motion of breast cancer sur-
surgery patients, exercise interventions reduce anxiety and depression, accelerate return to daily life, strengthen the immune system, and improve quality of life.\textsuperscript{7-9} In particular, the significance of upper limb exercise programs to help restore upper limb functions and prevent symptoms from worsening has been emphasized, because post-operative breast cancer patients experience impaired upper limb functions due to the characteristics of breast cancer.\textsuperscript{10} Exercise interventions used for the treatment and rehabilitation of breast cancer patients consist of stretching, shoulder range of motion exercise, and strength training focusing on upper extremity exercise through various types of exercise such as yoga, aquatic exercise, rehabilitation exercise, Tai Chi, and elastic bands, and are effective in restoring upper limb functions and preventing symptoms from worsening.\textsuperscript{7,9}

A wide variety of studies have also been conducted in Korea since the 2000s, as exercise interventions have been applied in nursing and other disciplines (rehabilitation therapy, physical therapy, physical education, etc.) from before and after cancer surgery to chemotherapy and throughout the rehabilitation and survival period after treatment.\textsuperscript{7} With the demand to summarize the results of each study more scientifically and objectively, meta-analysis studies have been performed to integrate the results of these studies and present the effect size.\textsuperscript{8}

In terms of the meta-analysis studies on exercise interventions for breast cancer surgery patients in Korea, Lee et al.\textsuperscript{11} selected and analyzed 16 studies from 2000 to 2015, and Lee\textsuperscript{20} selected and analyzed 15 studies by searching only academic papers in the journals of the National Research Foundation of Korea from 2000 to April 2017 for exercise interventions applied to subjects six months after completing breast cancer treatment. However, these studies did not provide enough information on the systematic literature review and meta-analysis reporting standards, and lack quality assessment. On the other hand, studies by Kim\textsuperscript{7} and Park & Cho\textsuperscript{8} were conducted according to systematic literature review and meta-analysis reporting standards, and lack quality assessment. On the other hand, studies by Kim\textsuperscript{7} and Park & Cho\textsuperscript{8} were conducted according to systematic literature review and meta-analysis reporting standards. Kim\textsuperscript{7} selected and analyzed 13 studies published by 2012 without limiting the search period (year), but did not reflect the results of the studies after 2012. The most recent study by Park & Cho\textsuperscript{8} does not mention the search period but is presumed to reflect studies up to 2018 as it was published in mid-2019. It selected and analyzed seven studies by combining four randomized controlled trials (RCT) and three non-randomized controlled trials (NRCT), but with regard to extension, internal rotation, grip strength, upper extremity discomfort, and quality of life variables, which were reported as statistically insignificant, the analysis only included two to three studies. While the systematic literature review and meta-analysis guidelines of the National Evidence-based Healthcare Collaboration Agency state that it is technically possible to do a meta-analysis of only two studies, the results must be interpreted with caution.\textsuperscript{14}

Meanwhile, the results of meta-analysis studies conducted in Korea on the effect of exercise interventions for breast cancer surgery patients show that exercise interventions are effective in reducing abdominal fat ratio,\textsuperscript{7,14} increasing shoulder range of motion (flexion, extension, abduction, external rotation),\textsuperscript{7,12,13} improving quality of life,\textsuperscript{7} increasing grip strength,\textsuperscript{7,12} and increasing upper extremity flexibility,\textsuperscript{7,12} and that the effects on pain\textsuperscript{11,18} and edema\textsuperscript{21} were not statistically significant. However, some studies have reported that the effects on flexion,\textsuperscript{7,12} grip strength,\textsuperscript{7,12} and upper extremity flexibility\textsuperscript{7} were insignificant, highlighting some differences and inconsistencies between the meta-analysis studies. This means that these themes or topics should be analyzed again by accumulating new research results.

While most foreign meta-analysis studies on the effect of exercise interventions on post-operative breast cancer patients selected only RCT studies to present their analysis results,\textsuperscript{8,15-17} all four meta-analysis studies conducted in Korea were analyzed by mixing the results of randomized controlled trials (RCT) and non-randomized controlled trials (NRCT) in the meta-analysis process. Unlike RCT studies, the intervention effects obtained in NRCT studies are subject to various risks of bias, so the National Evidence-based Healthcare Collaboration Agency\textsuperscript{41} recommends a separate analysis for cases with different study design characteristics; so far, no Korean studies have performed a meta-analysis of RCT studies alone. Therefore, systematic literature reviews and meta-analyses on RCTs need to be conducted instead of mixing study designs with different levels of evidence to compare with foreign meta-analysis studies of RCTs.

Therefore, this study selected RCT studies that applied exercise interventions to post-operative breast cancer patients in Korea from 2010 to 2020 and analyzed the effects through a systematic literature review and meta-analysis to identify research trends in Korea and provide the latest valid evidence to compare with foreign RCT research results. In addition, providing evidence of exercise intervention effects on breast cancer patients in Korea will contribute to presenting future research directions for selecting evidence-based decision-making and interventions in oncology nursing practice.
2. Purpose
This study investigated the effects of exercise interventions on post-op breast cancer patients through a systematic literature review and meta-analysis of RCT studies in Korea.

RESEARCH METHOD

1. Design
This study conducted a systematic literature review and meta-analysis according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines to identify the effects of exercise interventions for post-op breast cancer patients in Korea.

2. Inclusion and exclusion criteria
The criteria for selecting literature consisted of questions according to the research purpose based on Participants, Intervention, Comparisons, Outcomes, Study Design (PICOS) by the PRISMA group. 1) The participants were those who received breast cancer surgery, 2) intervention was exercise interventions that included upper extremity exercises, 3) comparison was a control group that did not receive exercise interventions, 4) outcomes were studies that reported physical, social, and psychological variables, 5) study design was an RCT, and the published languages were limited to English and Korean.

The exclusion criteria included those who were diagnosed with breast cancer but did not receive surgery, studies in which the effect of only exercise interventions could not be confirmed due to the involvement of other interventions, single-group studies without control groups, studies that failed to present or validate the intervention results (cases that only published posters or abstracts, or if the original text was not available), and research types other than RCT (review, meta-analysis study, case study, and qualitative study).

3. Literature search and selection

1) Literature search
The search period was from December 2020 to January 2021 and was limited to studies published from 2010 to December 2020 to reflect the latest research trends. In terms of the academic search engines, this study searched all journal articles, reports, and theses on the Korean studies Information Service System (KISS), Research Information Sharing Service (RISS), the National Assembly Digital Library of Korea, and DBpia, which are the key databases presented by the Korea Health Information Service. The search terms were searched more than twice by combining 'Breast Neoplasms,' 'Breast Cancer,' and 'Exercise,' 'Exercise intervention,' 'Exercise program,' 'exercise,' 'exercise intervention,' and 'exercise program,' which correspond to P (Participants) and I (Intervention), using the MeSH (Medical Subject Headings) index. Duplicate articles were removed using RefWorks, and then the first round of literature that did not meet the criteria was excluded by checking the titles or abstracts. Inclusion and exclusion were decided by checking the entire original text of the articles that provided insufficient information through the titles or abstracts. In the case of duplicate publications, journal articles were selected over theses. Four researchers formed teams of two. The first team performed the literature search and screening process, and the second team reviewed the results. If any disagreement arose, all researchers reviewed the original text according to the inclusion and exclusion criteria until reaching an agreement to select the final studies for the analysis.

2) Literature selection
After excluding 72 duplicate studies using RefWorks from the 340 studies retrieved (n = 268), 213 studies with titles and abstracts unrelated to the selection criteria, one study which used interventions other than exercise, and seven studies without controls were also excluded (n = 47). The first screening process included studies with not enough information in the titles and abstracts to decide whether to exclude them. After reviewing the full text of the 47 studies that passed the first screening process, 13 final studies were selected for the meta-analysis by excluding 34 studies, including one study on participants who did not receive breast cancer surgery, one study which used interventions other than exercise, two studies which failed to confirm the effects of exercise interventions due to performing some exercise interventions on the control group, 11 single-group studies, 15 studies that were not control group pre-test/post-test designs, and four studies for which the original text was not available (Figure 1).

4. Quality assessment
This study consists of a meta-analysis of RCTs, and the quality of the literature was assessed using Version 2.0 of the Cochrane RoB (Risk of bias) tool. RoB 2.0 is a recent revision of the widely used RoB tool. The previous version of RoB made assessments based on the outcomes, but some studies using real-world tools raised issues with the tool, such as some areas having low inter-rater reliability, the need to reconsider the
theoretical background in ‘selective outcome reporting’ and the misuse of other areas of risk of bias. To address these issues, RoB 2.0 is structured to assess five domains: bias arising from the randomization process, bias due to deviations from intended interventions, bias due to missing outcome data, bias in measurement of the outcome, and bias in selection of the reported result. Each domain has three to seven assessment items, which are answered with Yes (Y), Probable Yes (PY), Probable No (PN), No (N), and No Information (NI). Based on the response, the algorithm programmed in RoB 2.0 calculates the assessment results in three stages (low, high, and some concerns of bias). In terms of the 13 RCTs in this study, first, the four researchers assessed the studies and shared the assessment results. Most assessments were consistent, but the ones that did not match each other were reviewed and discussed using the RoB 2.0 manual by Cochrane until an agreement was reached.

5. Data analysis

The effect sizes of 13 exercise interventions were analyzed using R version 4.0.3. These studies were conducted independently, so a random-effect model was used to estimate the mean of the distribution of effect sizes across different populations, including subjects, periods, and configuration of exercise interventions. The effect size was calculated using Hedge’s g by Hedges & Olkin, and the standardized mean difference (SMD) was used to correct the tendency of overestimating the effect size in studies with small samples. Based on Cohen’s criteria for effect size, values between 0.2–0.5 were considered to be ‘small,’ while 0.5–0.8 represented a ‘medium’ effect size, and 0.8 or higher a ‘large’ effect size. The heterogeneity of the effect sizes between the studies was

Figure 1. Flow diagram for study selection.
analyzed with the total variance (Q) and the actual variance (I^2) through a forest plot model (I^2≤25%: low, 25%<I^2≤75%: moderate, I^2>75%: high). Sensitivity analysis was performed on studies that showed a high heterogeneity to determine if they had a significant influence on the overall effect size and heterogeneity. After confirming the symmetry between the effect size and standard error through a funnel plot, publication bias was assessed through Egger's regression test if statistical analysis was enabled by the inclusion of 10 or more studies in the analysis. The effect sizes by adjusting publication bias by trim-and-fill analysis were also presented to validate the interpretation and application of the study results.

RESULTS

1. Quality assessment results

First, in the assessment of bias arising from the randomization process, the result was 'Low'(18.2%) as only two out of 13 RCT studies reported randomization processes through computer random number tables or lottery methods, and the remaining 11 studies had 'Some concerns'(81.8%) because there was no mention of the randomization processes.

Second, in terms of bias due to deviations from intended interventions, there were no specific reports in all 13 articles for the double-blind questions of '(1) whether the subjects were aware of their assigned intervention during the trial' and '(2) whether the people delivering the interventions were aware of the interventions assigned to the subjects during the trial,' among the six sub-questions, so the answers to questions (1) and (2) were No information (NI) and Probable Yes (PY), respectively. When responses to the two questions above indicated that double-blinding was not achieved, the third question that follows was '(3) whether important non-protocol interventions balanced across the two groups.' The control and experimental groups were basically treated under the same conditions (e.g., basic physical therapy), and only the experimental group received additional experimental treatment (exercise intervention designed in the study). Therefore, the answer was Yes (Y) since there were no exceptional non-protocol interventions. The fourth question was '(4) whether this affected the outcome,' and the answer was No (N). The final question, '(5) whether the subjects affected the outcome by not complying with the assigned interventions,' is a question that confirms whether the low compliance rate of the subjects led to dropouts and affected the study results. Each study reported that the subjects' compliance rates were checked in person or by phone at the hospitals or homes where exercise interventions were performed, so the answer was No (N). The final assessment of bias due to deviations from intended interventions by the algorithm was 'Low.' This domain is attributed to experimental treatment other than protocol, failure of intervention, and the dropout of subjects, and since there were only a few (one to three people) or no dropouts in the 13 studies for meta-analysis, there was no effect on the overall study results.

Third, in terms of bias due to missing outcome data, all 13 studies answered 'Yes (Y)' to the question of 'whether data for this outcome were available for all, or nearly all, subjects,' so the assessment was 'Low' 100%. Although some studies reported that dropouts (one to three people) were excluded from the final subjects, this was viewed as 'nearly all' subjects.

Fourth, in terms of bias in measurement of the outcome, the answer to '(1) whether the method of measuring the outcome was inappropriate' was No (N) because structured questionnaires were determined by their reliability and validity, and tools for measuring physical outcome variables, such as protractors, tape measurements, scales, and blood analysis, were considered as appropriate tools. The answer to '(2) whether measurement or ascertainment of the outcome was different between intervention groups' was No (N) because both groups were measured equally. The answer to '(3) whether the outcome assessors were aware of the experimental group' was 'Probable Yes (PY)' because the same person treated both groups in some studies. However, the answer to the final question of '(4) whether the assessors' awareness of the intervention group affected the assessment of the outcome' was 'Low' 100%. Where self-report questionnaires were used, the assessors could not intervene in the assessment; where physical variables were measured, the results were measured by blood tests or machines, and most studies applied a research design to reduce measurement-related errors, such as measuring more than two to three times and using the mean value as the assessment results.

Fifth, in terms of bias in selection of the reported result, the assessment was 'Low' 100% because all 13 studies reported the results honestly. Therefore, as a result of assessing the quality of literature in 13 RCTs, the risk of bias was 'Low'(Figure 2).

2. General characteristics of the literature for analysis

The general characteristics of the final 13 studies in the systematic literature review and meta-analysis on the effects of exercise interventions
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The effects of exercise intervention for post-operative breast cancer patients in Korea are presented in Table 1 by analyzing the authors, participants, intervention methods, and outcome variables. The studies consisted of three theses and 10 journal articles published since 2010, and they reported social and psychological effects and the recovery of physical functions. A total of 322 subjects participated in the individual studies (minimum: 14, maximum: 45, average: 24), consisting of post-op breast cancer patients who were diagnosed with lymphedema, receiving chemotherapy, or survivors who completed radiation therapy and chemotherapy. The exercises mainly consisted of stretching, shoulder range of motion (ROM) exercises, and resistance exercises (using elastic bands and dumbbells) to strengthen upper limb muscle strength for treatment and rehabilitation to reduce lymphedema and improve upper extremity function. In addition, home-based exercise education, rehabilitation exercises, aerobic exercises, treadmill exercises, sensory training exercises using Swiss balls, Smovey (an exercise product that creates resistance due to vibration swinging effects) exercise, and compound exercises were also used in stages depending on the patient’s condition. The exercise programs were applied for 2 weeks (1), 4 weeks (7), 8 weeks (4), and 12 weeks (1), for an average of three to five times a week for 30–50 minutes per session, for an average of 5.6 weeks.

The main outcome (dependent) variables were physical variables, including range of motion (ROM), shoulder disability, edema, pain, grip strength, hormones, and upper limb strength/muscle, and some studies also reported psychosocial variables, such as fatigue, depression, self-esteem, and self-efficacy. Several studies reported quality of life but used various measurement tools (Functional Assessment Cancer Therapy- Breast, Short-Form Health Survey-36, EORTC QLQ-30, EORTC QLQ-31, QLQ-BR23). Even if the measurement tools were consistent, it did not lead to meta-analysis because the number of studies was insufficient to derive results by selecting and applying consistent categories, such as reporting only some sub-domains among measurement tools or reporting only the total score without reporting the sub-domains. Therefore, meta-analysis was performed on ROM, shoulder disability, edema, and pain, which were presented in three or more papers among the physical and psychosocial variables.

In addition, the study by Song (Appendix 1, No. 8) applied exercise interventions for eight weeks on a scapular complex exercise group (a) and general exercise group (b), and the study by Ha (Appendix 1, No. 6) consisted of two experimental groups (flexor exercise group (a) and an extensor exercise group (b)) and one control, so each experimental group was analyzed separately during the meta-analysis.

3. The effects of exercise interventions after breast cancer surgery

1) Shoulder ROM

The overall effect size of exercise intervention for shoulder ROM was 0.95(95% CI: 0.58, 1.33), which is statistically significant (Z = 4.99, \( p < .001 \)), and the \( I^2 \) was 64%, indicating moderate heterogeneity (Q = 53.17, \( p < .001 \))(Figure 3-A). In particular, among ROM, flexion showed a large effect size of 1.10(95% CI: 0.13, 2.07), which was statistically significant (Z = 2.23, \( p = .025 \)), and the \( I^2 \) was 72%, indicating moderate heterogeneity (Q = 10.74, \( p = .013 \)). Abduction had a large effect size of 1.06(95% CI: 0.26, 1.87), which was statistically significant (Z = 2.23, \( p = .025 \)), and the \( I^2 \) was 72%, indicating moderate heterogeneity (Q = 10.74, \( p = .013 \)). Internal rotation, external rotation, and extension were not statistically significant. Therefore, post-op exercise intervention had a significant effect on flexion and abduction among shoulder ROM.

2) Shoulder disability

Shoulder disability is a structured questionnaire for assessing functional upper extremity levels and measures the subjective evaluation score for each item. The measurement tools used in this study were Disabilities of Arm, Shoulder, and Hand (DASH) and Shoulder Pain And Disability Index (SPADI), and both tools were consistent and measured the same concept, as the questions in each tool evaluated upper extremity function in terms of pain and discomfort in everyday events (lifting...
heavy objects, bathing, etc.). According to the analysis results, the effect size of exercise intervention for shoulder disability was -1.16(95% CI: -1.77, -0.55), which was a large effect size that decreased pain and discomfort of shoulder function by 1.16, and was also statistically significant (Z = -3.72, p < .001), and the I² was 71%, indicating moderate heterogeneity (Q = 23.79, p = .001)(Figure 3-B). Therefore, exercise intervention significantly reduced the subjects’ shoulder disability

3) Pain
The effect size of exercise intervention for pain was -1.24(95% CI:
-1.58, -0.89), which was a large effect size that decreased pain by 1.24, and was also statistically significant ($Z = -7.03, p < .001$), and the $I^2$ was 0%, indicating no heterogeneity ($Q = 3.38, p = .761$) (Figure 3-C). All of the studies identified used the same measurement method, which was the visual analogue scale (VAS). In other words, post-op exercise interventions significantly reduced pain.

4) Edema

The effect size of exercise intervention for edema was -0.03 (95% CI: -0.39, 0.33), which was not statistically significant ($Z = -0.18, p = .858$), and the $I^2$ was 0%, indicating no heterogeneity ($Q = 0.33, p = .955$) (Figure 3-D). In other words, post-op exercise intervention had no effect on reducing edema.

4. Publication bias and sensitivity analysis

Sensitivity analysis was performed to identify whether the studies with a high degree of heterogeneity had a significant influence. Pain and edema were considered to be non-heterogeneous, and the $I^2$ for ROM was 64%, indicating moderate heterogeneity. Further sensitivity analysis showed the effect of Bae and Lee’s study (Appendix 1, No. 2) on the overall effect size (reduced from 0.95 to 0.77) and heterogeneity ($I^2 = 64\%$ to 59.8%). In terms of shoulder disability, the study by Song (8a) (Appendix 1, No. 8, complex exercise group a) had an effect on the overall effect size (reduced from -1.16 to -0.85) and heterogeneity ($I^2 = 71\%$ to 58.7%).

In terms of publication bias, Egger’s regression test was conducted for statistical verification under the subjective judgment that there were asymmetric funnel plots, and trim-and-fill analysis was also performed if the results showed there was publication bias. Trim-and-fill analysis validates the relationship between the effect size and standard error using regression analysis to detect statistical asymmetries, calculates an adjusted average effect size for asymmetry, and compares it with the original average effect size to evaluate the influence of the errors.20

Trim-and-fill analysis was conducted to determine whether there was publication bias when the results of the published studies did not represent the results of all the selected studies by analyzing and confirming the impact of studies (missing data) that were not included in the meta-analysis because they were not published, but it does not actually change the analyzed mean effect size, and as such caution is required in interpreting such results.20 This study compared the effect size (small, medium, large) and statistical significance before and after trim-and-fill analysis to determine whether 1) the influence of error was insignificant, 2) the influence of error was not insignificant, but not large enough to affect the outcome, 3) the error was serious enough to question the study results.21,22

As shown in the funnel plots in Figure 4, pain and edema were generally symmetrical around the mean, and ROM and shoulder disability were generally asymmetrical, with studies with small sample sizes distributed mainly in the lower right corner of the mean. In terms of ROM, statistical analysis was possible due to having more than 10 studies in the analysis, and the result of Egger’s regression test indicated there was publication bias, with bias $= 7.97$ ($t = 4.88, df = 18, p < .001$). The effect size corrected for the publication bias in ROM by performing trim-and-fill analysis was still statistically significant ($Z = 2.74, p = .006$) with a medium effect size of 0.58 (95% CI: 0.16, 1.00). However, the effect size before trim-and-fill was 0.95, so the influence of the error was not insignificant because of the large difference between before and after adjusting for publication bias, but the effect was still above medium and was not statistically significant enough to affect the results.

Although the funnel plot for shoulder disability was asymmetric, Egger’s regression test was not applicable because there were less than 10 studies included in the analysis. According to the results of trim-and-fill analysis, the effect size was -1.16, so the effect of publication bias was insignificant due to showing the same results as before trim-and-fill analysis.

DISCUSSION

This study conducted a systematic literature review and meta-analysis by selecting 13 RCTs in Korea that applied exercise interventions, including upper extremity exercises, for post-operative breast cancer patients. All 13 studies showed the latest trends as they were published from 2010 to the present day.

Through assessing the quality of the literature, the risk of bias was determined as ‘Low’ 100% in all domains (bias due to deviations from intended interventions, bias due to missing outcome data, bias in measurement of the outcome, and bias in the selection of the reported result) other than bias arising from the randomization process, so the overall quality assessment result was that there was a ‘low’ risk of bias. The quality assessment tool used in this study was RoB 2.0, the latest version (revised in August 2019) of the widely used RoB tool. Compared to the previous version, RoB 2.0 aims for objectivity through more de-
Figure 3. Forest plots of the effects of exercise intervention for post-op breast cancer patients.
tained sub-questions for each assessment domain and helps the assessor’s judgment by providing algorithmic results for reference. For example, among the six sub-questions for assessing ‘bias due to deviations from intended interventions,’ the answers for (1) whether the subjects were aware of their assigned intervention during the trial' and (2) whether the people delivering the interventions were aware of the interventions assigned to the subjects during the trial,' were ‘No information (NI) and ‘Probable Yes (PY), respectively. However, if this had been assessed with the previous version of the RoB tool, the risk of bias would have been ‘uncertain’ or ‘high.’ The RoB 2.0 tool is structured to assess the impact of the risk of bias more specifically by using additional sub-questions rather than assessing the risk of bias to be ‘high’ based solely on the fact that double-blinding was not achieved. The fact that the assessment was ‘low’ in this study is a notable difference from the previous version of the RoB tool because the experimental group and the control group received the same treatment under the same conditions, the dropouts from the interventions did not affect the results, and due to the subjects’ high compliance rate for exercise interventions. Another difference from previous quality assessments includes assessing the ‘bias in measurement of the outcome’ to be ‘low’ due to the use of appropriate tools for the measurement variables, the same measurement and evaluation of experimental and control groups, and applying a study design to minimize bias associated with the assessors’ measurement even if it is affected by physical variables (participants’ self-reported questionnaires, weight, and blood test results) that were not affected by situations where blinding the assessors was not possible. Therefore, the RoB 2.0 tool reflects all existing risk of bias assessment items while constructing algorithms of more specific sub-questions for the risk of bias affecting the outcome, so the quality assessment of the literature does not depend on the subjective judgment of the meta-analysis researchers.

The quality assessment of the study by Park & Cho, one of the most recent studies that performed a meta-analysis on a similar topic to this study and used a previous version of the RoB tool, was ‘low,’ and there was no significant difference from the quality assessment results of this study. However, in a foreign study by Furmaniak et al., which also used a previous version of the RoB tool, most of the identified studies were assessed to have a ‘high’ risk of bias in the areas of ‘bias of participants and researchers’ and ‘bias of outcome evaluation’ while
most of the other domains were assessed to be ‘low’ or ‘uncertain.’

In the 13 studies identified in this meta-analysis, the overall risk of bias was ‘Low’ in the quality assessment, but they still lack specific information on the randomization method and blinding items. Eleven studies did not provide specific information on the randomization method between the experimental and control groups during the randomization process, and none of the 13 studies reported the blinding of study participants and assessors. According to a study by Kyung et al., which evaluated the quality of RCT studies published in domestic medical SCI journals based on the CONSORT guidelines, only 19% of the studies reported the randomization methods, and more than 50% did not report blinding items. Therefore, to conduct a well-rounded, randomized double-blind RCT study, researchers need to improve the quality of their research from the design by referring to standardized research reporting frameworks, such as CONSORT.

In this study, the effects of exercise intervention were found to increase ROM, decrease shoulder disability (pain and discomfort), and reduce pain. First, in terms of shoulder ROM, the effect of exercise intervention was significant, and the heterogeneity between the selected studies was moderate. In terms of sensitivity analysis, the heterogeneity decreased the most when the study by Bae & Lee was excluded, which showed the largest effect size in flexion among ROM. In addition, the funnel plots and Egger’s regression test showed that there was publication bias. Studies with small sample sizes are more likely not to be published, but may be published when they have a large effect size, so among the studies included in the meta-analysis, studies with small sample sizes are more likely to have a relatively large effect size, and if there is a significant relationship between the sample size and effect size, this demonstrates the existence of a ‘small-study effect,’ or publication bias. The studies included in the meta-analysis also consisted of a relatively small population of 24 on average, ranging from a minimum of 14 to a maximum of 45. Therefore, the effect of exercise interventions on ROM was large, but caution is required in interpreting the results due to publication bias. However, Ribeiro et al. performed a meta-analysis on RCTs that identified the effect of exercise intervention in early rehabilitation treatment within three months after breast cancer surgery, and the results showed that flexion (1.4–2.4) and abduction (1.3–1.9) had large effects and that external rotation was not significant, which was consistent with the findings of this study.

Second, in the case of shoulder disability, shoulder pain and discomfort were reduced significantly, and the heterogeneity between the selected studies was moderate. Excluding the study by Song (8a) from the sensitivity analysis produced the greatest decrease in heterogeneity. Although the funnel plot suggested the possibility of publication bias, Egger’s regression test was not applicable because there were only eight studies that analyzed shoulder disability as a variable. In a trim-and-fill analysis, the effect of publication bias was considered to be insignificant because the effect size was large and showed the same results as before trim-and-fill analysis. Therefore, the effect of exercise intervention for shoulder disability was found to be a significant reduction in shoulder pain and discomfort, and the effect of publication bias was insignificant. A previous study by Park & Cho was a meta-analysis on two studies (measured shoulder disability by DASH) and showed a large effect size of 0.81, but was not statistically significant, which differed from the results of this study. In a meta-analysis, the results of studies that analyze only two to three papers must be interpreted with caution, and the two studies analyzed by Park & Cho found statistically significant and non-significant effect sizes, which eventually influenced the conclusion, which was not statistically significant. Therefore, the results of this study, which analyzed eight articles on shoulder disability, provide more reasonable evidence than the conclusions of previous studies in which the effect of exercise interventions on shoulder disability was not significant.

Third, in terms of pain, all seven RCTs included in the pain analysis measured pain using the same visual analogue scale (VAS), and the effect of reducing pain showed a large effect size with no heterogeneity between the selected studies. The funnel plot also showed that there was no publication bias. This result supports the findings of a previous study that reported exercise intervention after surgery has a significant effect on reducing pain in post-op breast cancer patients. On the other hand, in terms of previous studies in Korea, the meta-analysis by Lee et al. on four studies measuring pain by VAS showed a small effect (0.21) that was not statistically significant, and the meta-analysis by Park & Cho on three studies measuring pain by VAS showed a medium effect (-0.69) that was not statistically significant, which differed from the results of this study. This is because the studies by Lee et al. and Park & Cho combined RCTs and NRCTs in the analysis, which influenced the intervention effect of NRCTs that are subject to various risks of bias. Therefore, the results of this study are of great significance due to it being limited to analyzing RCTs as recommended by the National Evidence-based Healthcare Collaboration Agency.

Meanwhile, the effect of exercise intervention on reducing edema...
was not significant. The analysis involved four articles, all of which measured the upper arm circumference (cm) as the edema values, and there was no heterogeneity between the studies ($I^2 = 0\%$). Some previous studies also reported that the effect on edema was not significant. This is because many post-op breast cancer patients experience upper extremity edema during surgery and radiation therapy, so most studies provide physical therapy to reduce edema for both the experimental and control groups (Table 1), and the studies in this meta-analysis reported that physical therapy, such as Manual Lymphatic Drainage (MLD) and Complete Decongestive Therapy (CDT), had a significant effect on reducing edema. Therefore, there was no significant difference between the two groups because the physical therapy received by both the experimental and control groups was effective in reducing the edema, not because exercise intervention did not contribute to reducing edema.

In summary, exercise interventions for post-op breast cancer patients have a significant effect in improving shoulder ROM, reducing shoulder function discomfort, and reducing pain. However, caution should be used in interpreting the results involving improvement of shoulder ROM due to publication bias.

Meanwhile, the exercise interventions analyzed in this study were applied to subjects diagnosed with lymphedema after breast cancer surgery, or survivors receiving adjuvant chemotherapy or those who completed surgery and treatment. The types of exercise were complex exercises consisting of stretching, strength exercise, and aerobic exercise to improve upper extremity function, or rehabilitation exercises, such as resistance exercise or strength exercise using elastic bands. According to a study by McNeely et al., there was no uniform standard for exercise intensity, and the wide range of outcome variables and measurement tools indicating various types of exercise and exercise effects made it difficult to compare the effects of exercise interventions. This study has its significance in that it provided evidence for the effectiveness of a single exercise intervention because the exercise interventions were limited to programs composed of upper extremity exercise, the tools for measuring physical variables were consistent among the identified studies, and cases that applied interventions other than exercise were excluded from the analysis. Furthermore, this study is differentiated from previous meta-analysis studies because the studies included in the meta-analysis reflect recent research trends as they were published in the last 10 years, and due to combining only RCTs, the risk of bias was minimized, providing more objective and reliable evidence for comparing the effects and results.

A limitation of this study is that the analysis consists of the effects of exercise interventions centered around physical variables. Although this study tried to analyze the effects of exercise interventions on psychological variables, fewer than three studies used the same psychological variables because each of them had various psychological outcome variables, and different and inconsistent tools for measuring even the same variables, so the corresponding variables were excluded from the analysis.

**CONCLUSION**

This study selected randomized controlled trials from 2010 to 2020 to conduct a systematic literature review and meta-analysis to investigate the effects of exercise interventions on post-op breast cancer patients in Korea.

A total of 13 RCT studies were included in the meta-analysis, and the overall risk of bias was ‘Low’ in the quality assessment of the literature, but most studies had insufficient information on the randomization method and blinding items for participants and assessors. There also was a lack of studies reporting the psychological effects, because the effects of exercise intervention were mainly reported in terms of physical variables.

For breast cancer surgery patients, post-op exercise interventions had significant effects in reducing pain and shoulder disability. In terms of shoulder ROM, exercise interventions were particularly effective in flexion and abduction. However, there was a publication bias in shoulder ROM, which was not significant, but caution is required in interpreting the results.

In the future, RCT studies that apply exercise interventions on post-op breast cancer patients need to expand the dependent variables to include physical and psychological variables. In addition, sample size effects should be considered to reduce publication bias, and research plans and reports that meet RCT reporting standards, such as CONSORT, should be made from the design stage.

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Appendix 1. Studies Included in Meta-analysis

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