The effects of physical activity on physiological markers in breast cancer survivors
A meta-analysis

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Abstract

Methods: To systematically evaluate the effects of physical activity on physiological markers in breast cancer survivors.

Results: A total of 11 articles with 941 cases were eligible in this meta-analysis. The results of the meta-analysis showed that physical activity could decrease the levels of insulin (SMD = −1.90, 95% CI: −3.2 to −0.60; I² = 92.3%, P < .001), insulin-like growth factor 1 (IGF-I) (WMD = −4.67, 95% CI: −23.14 to 13.79; I² = 96.2%, P < .001), insulin-like growth factor binding protein-3 (IGFBP-3) (WMD = −20.09, 95% CI: −47.15 to 6.97; I² = 93.3%, P < .001). However, compared with the control group, there was not the significant change of insulin-like growth factor 2 (IGF-II), insulin-like growth factor binding protein-1 (IGFBP-1), leptin, adiponectin, glucose, C-reactive protein (CRP), Interleukin-6 (IL-6), Interleukin-10 (IL-10), and tumor necrosis factor alpha (TNF-α) levels after the intervention.

Conclusions: Physical activity could improve the insulin function that might be associated with decreasing the levels of IGF-I, IGFBP-3 and insulin in breast cancer survivors.

Abbreviations: IGF-1 = insulin-like growth factor 1, IGF-II = insulin-like growth factor 2, IGFBP-1= insulin-like growth factor binding protein-1, IGFBP-3 = insulin-like growth factor binding protein-3, CRP = C-reactive protein, Interleukin-6 (IL-6), Interleukin-10 (IL-10), and tumor necrosis factor alpha (TNF-α) levels after the intervention.

Keywords: breast cancer survivors, meta-analysis, physical activity, physiological markers

1. Introduction

Global cancer cases will present rapid growth, according to the American cancer society, as the growth and aging of global population, the new cancer cases increased quickly, the numbers of global cancer cases will reach 19.3 million from 2016 to 2025 and 24 million by 2035.[1] Exercise can offer a variety of psychological and physiological benefits, relieve the pressure and pain of patients in the process of treatment, relate to reducing the risk of cancer mortality. Studies have shown that exercise can improve the cancer-related fatigue and sleep symptoms, etc., and improve the survival quality of cancer patients effectively.[2] In addition, it can also improve the CD 16+ cells to shift doubly, increase the dissolving activity and improve the immune function of cancer patients. The biomarkers like insulin, insulin-like growth factor, IGF-binding protein, C-reactive protein, leptin, adiponectin, interleukin, etc played important roles in improving the body of cancer patients.[3] Moreover, the inflammatory factors including IL-6, IL-10, and TNF-α were associated with breast cancer and suggested as potential mediators of physical activity on breast cancer.[4] Therefore, we used the method of evidence-based medicine to conduct a meta-analysis that focus on the concentration changes of insulin, IGF-I, IGFBP-1, IGFBP-3, leptin, adiponectin, glucose, CRP, IL-6, IL-10, and TNF-α of cancer patients that exercise intervention caused.

2. Materials and methods

The ethical approval is not necessary in this study because it is a meta-analysis. This meta-analysis is strictly followed by the PRISMA scheme of evidence-based medicine.

2.1. Information retrieval

We searched the foreign databases such as PubMed, Web of Science, Medline and Chinese databases such as Wanfang and...
2.2.2. Object of study. The breast cancer patients diagnosed at any periods; the diagnosis is in accordance with “the China association of breast cancer diagnosis and treatment guidelines and standards (2015 edition).”

2.2.3. Intervention. The experimental group carried out the exercise intervention, the control group did not or the normal measures.

2.2.4. Final indicator. The concentration of IL-6, IL-10, TNF-α, leptin, adiponectin, glucose, insulin-like growth factor, IGF-binding protein, and C-reactive protein in plasma, which was unlimited measurement.

2.2.5. Exclusion criteria.
1) The repeated or poor-quality literatures;
2) The literatures that the average and the standard deviation of the ending index cannot be calculated according to the experimental data.

2.3. Literatures screening
The searching results from different databases were imported into the Endnote X6 to rearrange. Screening the literatures using independently incorporated and excluded standards and mutual blindness by 2 researchers, first, reading the title and abstract of the literatures and weeding out the clearly not related literatures, then getting the literatures we may need preliminarily, downloading the full text and reading carefully to judge whether the literatures qualified. After screening, the results would be cross-checked, and we would communicate with the corresponding author when 2 judged results not inconsistent to discuss whether the document would be included.

2.4. Data extraction
The 2 researchers extracted the data from the final included literature, which was designed in advance. The extracted content included the first author, the published age, the experimental area, the average age, the sample size, the experimental period, the interventions of the experimental group and the control group, and the average and standard deviation of concentration of the final indicator such as IL-6, IL-10, TNF-α, leptin, adiponectin, glucose, insulin-like growth factor, IGF-binding protein and C-reactive protein in the experimental group and the control group.

2.5. Evaluation of trials quality
Using the Cochrane collaboration’s tool for assessing risk of bias to define the methodological quality of the included literatures. This tool defined the methodological quality of the included literatures from 6 fields included selection bias, performance bias, detection bias, attrition bias, reporting bias, other bias. Every index included 3 options that are low risk of bias/unclear risk of bias/high risk of bias. If the above quality standards are fully met, which remind us that the risk of partial reclining is the minimum and grade A; while one or more of these criteria is met, the likelihood of partial reclining is moderate and grade B; and the above criteria are not met at all, the migration risk is high and grade C.

2.6. Statistical processing
The outcomes of this study are continuous variables, if the data unit of the same variable is different, we chose the SMD (standardized mean difference) and 95%CI as the effect magnitude to calculate the amount of the combined effect, and the data unit of the same variable is same, we used the weighted mean difference (WMD) and 95%CI as the effect magnitude to calculate the amount of the combined effect. First, analyzing the characteristics of the clinical population and methods included in the study, if there is a clinical heterogeneity, only carried out the descriptive analysis, whereas the next stage is meta-analysis. Before merging of the meta-analysis, we should carry out the heterogeneity test by Q inspection (the range of I² is 0%~100%), if the I² ≤ 50%, P > .1, showing that the heterogeneity between studies is small and can use a fixed effects model to do the meta-analysis; on the contrary, when the I² > 50%, P < .1, indicating that there is an obvious heterogeneity between studies and can use a randomized effects model to do the meta-analysis. In addition, we should conduct the sensitivity analysis to explore the heterogeneity of the research when necessary. In order to control the impact of publication bias, the meta-analysis results were examined by Begg test and the Egger test. The STATA 13.0 software was used for statistical analysis. The test level was statistically significant by P < .05.

3. Results
3.1. The searching results and the basic characteristics of the included studies
Retrieving 1312 references from all databases, using the Endnote X6 to eliminate 237 repeated references, eliminating the 1029 uncorrelated references by reading the titles and abstracts, going back to 6 references, eliminating the 41 unqualified references by downloading and reading the full text of 52 possible qualified references, including 11 randomized controlled trials eventually. The screening process as shown in Figure 1.

The included articles were all retrieved by the SCI, 7 were from the United States, 2 were from Canada, 1 was from the UK, and 1 was from Germany. There were 941 patients totally that 476 belonged to intervention groups and 465 belonged to control group, the average age was 56.3±6.4. The duration of the
intervention is from 6 weeks to 12 months. The quality level of
the literature was grade A, all of which were low-grade bias.

3.2. The results of meta-analysis
3.2.1. The level of Insulin. Seven studies analyzed the effects of
exercise on the levels of insulin in the blood of breast cancer
patients had statistical heterogeneity, and so we used the
randomized effects model to do the merging analysis. The results
showed that compared with the control group, exercise had lower
levels of insulin in breast cancer patients (SMD = −1.90, 95% CI:
−3.2 to −0.60; I² = 92.3%, P < .001), as shown in Figure 2.

3.2.2. The level of IGF-I. Four studies analyzed the effects of
exercise on the levels of IGF-I in the blood of breast cancer
patients had statistical heterogeneity, and so we used the
randomized effects model to do the merging analysis, the results
showed that the IGF-I of 2 groups had statistical significance
(WMD = −4.67, 95% CI: −23.14 to 13.79; I² = 96.2%, P < .001), as shown in Figure 3.

3.2.3. The level of IGFBP-1. Three studies analyzed the effects
of exercise on the levels of IGFBP-1 in the blood of breast cancer
patients had no statistical heterogeneity, and so we used the
fixed effects model to do the merging analysis, the results showed that
the IGFBP-1 of 2 groups had no statistical significance (WMD
= −2.90, 95% CI: −3.90 to −1.90; I² = 0%, P = .66), as shown in
Figure 4.

3.2.4. The level of IGFBP-3. Four studies analyzed the effects of
exercise on the levels of IGFBP-3 in the blood of breast cancer
patients had no statistical heterogeneity, and so we used the fixed
effects model to do the merging analysis, the results showed that
the IGFBP-3 of 2 groups had statistical significance (WMD = −
20.09, 95% CI: −47.15 to 13.97; I² = 93.3%, P < .001), as shown in
Figure 5.

3.2.5. The level of IGF-II. Two studies analyzed the effects of
exercise on the levels of IGF-II in the blood of breast cancer
patients had no statistical heterogeneity, and so we used the fixed
effects model to do the merging analysis, the results showed that
the IGF-II of 2 groups had no statistical significance (WMD = −
54.21, 95% CI: −61.41 to −47.00; I² = 0%, P = .66), as shown in
Figure 6.

3.2.6. The level of Leptin. Two studies analyzed the effects of
exercise on the levels of Leptin in the blood of breast cancer
patients had no statistical heterogeneity, and so we used the fixed
effects model to do the merging analysis, the results showed that
the Leptin of 2 groups had no statistical significance (WMD = −
7.69, 95% CI: −21.46 to 6.08; I² = 0%, P = .87), as shown in
Figure 7.
3.2.7. The level of Adiponectin. Two studies analyzed the effects of exercise on the levels of Adiponectin in the blood of breast cancer patients had no statistical heterogeneity, and so we used the fixed effects model to do the merging analysis, the results showed that the Adiponectin of 2 groups had no statistical significance (WMD = 0.21, 95%CI: –3.05 to 3.46; I² = 0%, P = .80), as shown in Figure 8.

3.2.8. The level of glucose. Three studies analyzed the effects of exercise on the levels of glucose in the blood of breast cancer patients had no statistical heterogeneity, and so we used the fixed effects model to do the merging analysis, the results showed that the glucose of 2 groups had no statistical significance (WMD = 0.02, 95%CI: –0.40 to 0.36; I² = 0%, P = .47), as shown in Figure 9.

3.2.9. The level of CRP. Two studies analyzed the effects of exercise on the levels of CRP in the blood of breast cancer patients had no statistical heterogeneity, and so we used the fixed effects model to do the merging analysis, the results showed that the CRP of 2 groups had no statistical significance (WMD = –0.02, 95%CI: –0.40 to 0.36; I² = 0%, P = .47), as shown in Figure 10.

3.2.10. The level of IL-6. Five studies analyzed the effects of exercise on the levels of IL-6 in the blood of breast cancer patients had no statistical heterogeneity, and so we used the fixed effects model to do the merging analysis, the results showed that the IL-6 of 2 groups had no statistical significance (WMD = –0.21, 95%CI: –0.46 to 0.04; I² = 0%, P = .67), as shown in Figure 11.

3.2.11. The level of IL-10. Two studies analyzed the effects of exercise on the levels of IL-10 in the blood of breast cancer patients had no statistical heterogeneity, and so we used the fixed effects model to do the merging analysis, the results showed that the IL-10 of 2 groups had no statistical significance (WMD = –0.10, 95%CI: –0.31 to 0.11; I² = 0%, P = .82), as shown in Figure 12.

3.2.12. The level of TNF-a. Three studies analyzed the effects of exercise on the levels of TNF-a in the blood of breast cancer patients had no statistical heterogeneity, and so we used the fixed effects model to do the merging analysis, the results showed that the TNF-a of 2 groups had no statistical significance (WMD = –0.15, 95%CI: –0.44 to 0.14; I² = 12%, P = .32), as shown in Figure 13.

3.3. The sensitivity and publication bias analysis

Due to the quantitative limitations of the literature, we were only able to analyze the sensitivity of meta-analysis of the effects of exercise on the levels of insulin in the blood of breast cancer patients, the results showed that the end is stable and reliable as shown in Figure 14. In addition, the Begg test and the Egger test showed that there was no risk of publication bias ($P > .1$), and because of fewer than 10 references, we did not have a funnel analysis (Table 1).
Figure 3. Forest plot of comparison for IGF-1.

Figure 4. Forest plot of comparison for IGFBP-1.
Figure 5. Forest plot of comparison for IGFBP-3.

Figure 6. Forest plot of comparison for IGF-II.
Figure 7. Forest plot of comparison for Leptin.

Figure 8. Forest plot of comparison for Adiponectin.
Figure 9. Forest plot of comparison for Glucose.

Figure 10. Forest plot of comparison for CRP.
Figure 11. Forest plot of comparison for IL-6.

Figure 12. Forest plot of comparison for IL-10.
Figure 13. Forest plot of comparison for TNF-α.

Figure 14. Sensitivity analysis of the meta-analysis.
4. Discussion

4.1. The quality analysis of the literature included in the study

All 11 studies included in this meta-analysis were conducted with high quality randomized controlled trials. The detailed description of the allocation concealment, blind, intention analysis and loss of the interview was given. Therefore, the evidence was higher.

4.2. Exercise affects the biochemical index of breast cancer patients

Despite the inconsistencies of past evidences, the recent observational studies have shown that breast cancer patients who have an active body have a better prognosis than sedentary patients. According to the study of American nurses, the female breast cancer patients who have an active body have a better prognosis and lower risk of death than sedentary women.16,17 Although the mechanism of how exercise improve the prognosis of patients with breast cancer have not studied completely, but a lot of research have confirmed that breast cancer patients with high weight are related with higher recurrence rate and mortality notably.18 The study of Goodwin found that compared with the patients with the lowest quartile of insulin levels, the patients with the highest quartile of insulin levels have increased times risk of cancer recurrence and 3 times the risk of death, and high levels of IGFBP-3 can predict the distant metastasis of breast cancer in postmenopausal women. The people who do not exercise regularly and have obesity usually have higher insulin levels and insulin sensitivity.18 The studies have shown that insulin and cytokines may be a critical media for weight gain. Our study found that exercise can reduce the levels of IGF-I (WMD = −4.67, 95%CI: −23.14 to 13.79), IGFBP-3 (WMD = −20.09, 95%CI: −47.15 to 6.97) and Insulin (SMD = −2.32 to −0.60) effectively. However, our study did not find that exercise can alter the level of IGF-II, IGFBP-1, IGFBP-3, which can block the proliferation of abnormal cells and reducing relapse and death.

In breast cancer, only 5% to 10% patients with breast cancer attributed to genetic inheritance. The physical activity is one of prevention efforts that focused on the modifiable risk factors of breast cancer.19 The growth of breast cancer cells could be promoted by increased IGF-I which produced by polyploid adipose stem cells.20 In the further study, IGF-I was proved that it could modulates biological responses via inducing the adhesion of adipose stem cells.20 In the previous study demonstrated that the ratios of IGF-I/IGFBP3 were increased in the postmenopausal women with breast cancer in Taiwanese.21 Not only IGF-I, but also IGFBP-3 have been demonstrated that they were related with the prognosis of breast cancer.22 In the patients with breast cancer, physical activity could improve the expression levels of IGF, which the molecular mechanism of physical activity on the tumor microenvironment.23 Moreover, the IGFBP3 expression was upregulated by physical activity in breast cancer, which implied

### Table 1

The basic characteristics of included studies.

| Included Studies | Country | Sample Size | Age | Experimental Treatment | Control Group | Intervention Time | Outcome Indicators | Quality Evaluation |
|------------------|---------|-------------|-----|------------------------|---------------|-------------------|-------------------|-------------------|
| Rogers et al, 2012 | America | 13 | 15 | 58.6±3.9 | Strength training intervention | Usual care | 3 months | IL-6, IL-10, TNF-α, leptin, adiponectin, Insulin, IGF-1, IGFBP-3, IL-6 | A |
| Janelins et al, 2011 | America | 9 | 10 | 54.3±7.6 | Tai Chi Chuan | Non-physical activity control | 12 weeks | Insulin, IGF-1, IGFBP-3, IL-6 | A |
| Lahart et al, 2016 | England | 40 | 40 | 52.4±8.3 | Home-based PA intervention | Usual care | 6 months | Insulin | A |
| Irwin et al, 2009 | America | 37 | 38 | 56.4±9.5 | Aerobic exercise | Usual care | 6 months | Insulin, IGF-1,IGFBP-3, IL-6 | A |
| Schmidt et al, 2016 | Germany | 48 | 44 | 57.1±5.7 | Resistance Exercise | Relaxation control group | 6 months | Insulin, IGF-1,IGFBP-3, IL-6 | A |
| Fairey et al, 2003 | Canada | 25 | 28 | 50.5±6.6 | The exercise group | The delayed control group | 15 weeks | Insulin, Glucose, IGF-1, IGF-2, IGFBP-1, IGFBP-3 | A |
| Schmidt et al, 2016 | America | 39 | 40 | 53.3±8.7 | Weight training | The delayed control group | 6 months | Insulin, Glucose, IGF-1, IGF-2, IGFBP-1, IGFBP-3 | A |
| Ligibel et al, 2008 | America | 51 | 49 | 52.9±3.9 | Strength training exercise intervention | Usual care | 16 weeks | Insulin, Glucose, IGF-1, IGF-2, IGFBP-1, IGFBP-3 | A |
| Swisher et al, 2015 | America | 18 | 10 | 53.8±3.6 | Moderate-intensity aerobic exercise | Usual care | 12 weeks | CRP, IL-6, TNF-α, insulin, leptin, adiponectin | A |
| Connroy et al, 2016 | Canada | 160 | 160 | 61.2±5.4 | Aerobic exercise intervention | Control group | 12 months | IL-10 | A |
| Jones et al, 2013 | America | 36 | 31 | 56.4±9.6 | Aerobic exercise intervention | Usual care | 6 months | CRP, IL-6, TNF-α | A |

IGF-1 = insulin-like growth factor 1, IGF-II = insulin-like growth factor 2, IGFBP-1 = insulin-like growth factor binding protein-1, IGFBP-3 = insulin-like growth factor binding protein-3, CRP = C-reactive protein, IL-6 = Interleukin-6, IL-10 = Interleukin-10, TNF-α = tumor necrosis factor alpha.
that the role of physical activity on the breast cancer were associated with the IGF-1/IGFBP3 axis.\textsuperscript{[23]}

4.3. The limitation

Even if this meta-analysis was conducted via PRISMA approach of evidence-based medicine, which made rigorous literature inclusion and exclusion criteria, but there are no guidelines on how to exercise for cancer patients. Therefore, there are differences in the duration and intervention in different studies, and the sample is smaller, which may affect the stability of the results. However, the included studies were all high quality randomized controlled trials, which increased the reliability of the study. Although we do not restrict the language of publication, the research and study group we have included is Caucasian, which may influence our conclusions in other populations. Although our analysis showed that there is no publication bias, we have included only published randomized controlled trials, and because of no unpublished randomized controlled trial and limited literatures, we could not draw the all funnel diagrams, so the potential publication bias could not be ruled out.

5. Conclusion

Exercise can reduce the levels of Insulin, IGF-I and IGFBP-3 in blood of breast cancer patients significantly, but cannot alter the levels of IGF-II, IGFBP-1, leptin, adiponectin, glucose, CRP, IL-6, IL-10, and TNF-a significantly. Because of there is no related study that exercise affects the level of biochemical index in Asian crowd, so it is necessary to do such large multicenter randomized controlled trials to explore the differences that exercise affects the biochemical index in different races.

Author contributions

This study was designed by Lv X and Xu QY, performed by Kang XY, Yu Z and Han SF. The data was analyzed by Kang XY, Lv X and Zhu YF. This paper was written by Xu QY and reviewed by Kang XY.

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