Effects of Exercise on Inflammatory Factors and IGF System in Breast Cancer Survivors: A Meta-analysis

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Abstract

Background: To analyze the effects of exercise on IGF system and inflammatory factors in breast cancer survivors, and to provide evidence for the relationship between exercise and the hypothetical mechanism of preventing the development of breast cancer and improving its prognosis.

Methods: Pubmed, Embase, Web of science, CNKI , Wanfang and VIP (China Science and Technology Journal) were systematically searched until April 2021. Search terms included “exercise”, "inflammatory factors", "IGF system" and "breast cancer". A total of 1066 related articles were searched. All the statistical results were analyzed by STATA 14.0 and Rstudio 4.1.1.

Results: We found that exercise significantly reduced the level of IGF-1 (WMD, -19.947ng/ml; 95%CI, -22.669 to -17.225; P=0.000). Subgroup analysis showed that in the studies with intervention period> 12 weeks, exercise could significantly reduce the level of IL-6 (WMD,-0.761 pg/ml; 95%CI,-1.369 to -0.153 ; p= 0.014), while in the studies with intervention period ≤ 12 weeks, exercise could significantly reduce the level of CRP (WMD,- 2.381 mg/ L; 95% CI,-4.835 to 0.073, P=0.001) and IL-10 (WMD,-7.141 pg/ml, 95% CI,-10.853 to -3.428; P=0.000) .In addition, aerobic exercise plus resistance training can significantly reduce the IL-6 level (WMD,-1.474 pg/ml; 95% CI,-1.653 to - 1.296; P=0.000). The results of sensitivity analysis showed that after excluding the high heterogeneity study, exercise can significantly reduce the level of TNF- α in patients with breast cancer (WMD, -1.399 pg/ml; 95%CI, -1.718 to -1.080; P=0.000).

Conclusion: Exercise can reduce the levels of IGF-1, IL-6, CRP, IL-10 and TNF- α in woman with breast cancer. This may be due to the period or type of exercise.

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1. Background

Breast cancer is the most common cancer among women all over the world, and it is also the most frequent cause of cancer death in women[1]. Therefore, how to improve the survival rate of breast cancer patients and reduce the incidence of breast cancer is the main research content. At present, several mechanisms have been speculated about the etiology and progress of breast cancer [2], including inflammatory factors, IGF system and so on. The effect of chronic inflammation on tumorigenesis and tumor microenvironment is widely considered to play a key role in the risk of cancer occurrence, development and recurrence[3]. Some studies have shown that systemic inflammation characterized by elevated TNF-α, IL-6 and CRP is associated with an increased risk of breast cancer progression and death[4–7]. In addition, compared with the serum of patients with benign tumor, the expression of insulin-like growth factors-1(IGF-1) was higher in patients with breast cancer. Therefore, some scholars have proposed that the increase of IGF-1 level may indicate the progression and metastasis of tumor [8]. In addition to IGF-1, insulin-like growth factor binding proteins (IGFBPs) can also be considered as part of the IGF system, which can indirectly regulate the activity of IGFs [9]. A large number of studies have shown that IGF-1 is involved in the occurrence and development of tumors and is closely related to the prognosis of tumors. Insulin-like growth factor binding protein-3 (IGFBP-3) inhibits its anti-apoptotic effect in breast cancer cells by regulating the mitosis of IGFs[10]. In view of the effect of inflammatory markers and IGF system on breast cancer, improving the inflammatory state and IGF system of breast cancer high-risk population may be a new way to reduce the risk of breast cancer. Studies have shown that inflammatory factors such as TNF-α, IL6, IL-10 and CRP are considered to be potential mediators between exercise and breast cancer[11]. In addition, exercise is related to the levels of IGF-I and IGFBPs [12, 13]. Exercise can inhibit the IGF signal pathway by reducing the level of IGF-1. An increasing number of evidence shows that exercise can improve the levels of inflammatory factors and IGF system in breast cancer patients and reduce the risk of breast cancer patients. However, the point from individual studies is inconsistent. Sprod et al [14] found no significant changes in insulin-like growth factor binding protein-1 (IGFBP-1) and IGFPB-3 after 12 weeks of Taijiquan intervention in 21 breast cancer survivors. In addition, other meta-analyses have come to different conclusion [15, 16]. Therefore, this meta-analysis will focus on the effects of exercise on IL-6, IL-10, IL-1β, CRP, TNF- α and IGF-1, IGFBP-3 in patients with breast cancer, and use subgroup analysis to further explore the effects of different intervention time and mode on outcome indicators in order to determine the relationship between intervention period, intervention type and inflammatory factors, IGF system. To provide evidence for the hypothetical mechanism of exercise to prevent the development of breast cancer and improve its prognosis.

2. Methods

2.1 Search strategy

This meta-analysis followed the PRISMA scheme of evidence-based medicine.Pubmed, Embase, Web of science, CNKI ,Wanfang and VIP (China Science and Technology Journal) were systematically searched until April 2021. Search terms included "physical activity or exercise or sport or training" and "breast cancer or breast tumor or breast oncology" and "inflammatory or IL-6 or IL-10 or IL-1β or CRP or TNF-α or IGF or IGF-1 or IGFBP-3". The protocol for this systematic review was registered on INPLASY (ID=INPLASY2021100101) and is available in full on the inplasy.com (https://doi.org/10.37766/inplasy00000000).

2.2 Eligibility criteria:

All the retrieved literatures were screened and excluded. The screening criteria are as follows:

Inclusion criteria: (1) subjects: breast cancer survivors; (2) intervention measures: exercise intervention (including aerobic exercise, resistance exercise, resistance exercise combined with aerobic exercise, high-intensity interval training, etc.); (3) study content: effects of exercise group (physical activity) and control group on inflammatory factors or IGF system in patients with breast cancer; (4) intervention time: during the period of postoperative rehabilitation; (5) study type: randomized controlled trial and include at least one blank group.

Exclusion criteria: (1) intervention measures are not simple exercise, but exercise intervention combined with other therapies (such as exercise combined with diet, exercise combined with drugs, etc.); (2) only experimental design, there is no specific implementation process; (3) review literature, repeated publication and unable to obtain the full text; (4) the main research indicators are not consistent or the data are incomplete.

2.3 Data extraction:

Two evaluators independently carry out retrieval and screening, and then check and compare the results. If there are any differences, it will be decided by a third party. The extracted data include basic information (title, original study author, year of publication, country), basic characteristics of subjects (sample size, mean age, gender, cancer stage, etc.), characteristics of exercise intervention (exercise type, exercise frequency, exercise time, intensity, etc.), characteristics of control group (routine treatment, placebo control, etc.) and outcome indicators (the changes of indicators before and after intervention, P value and / or CI).

2.4 Risk of bias assessment:

The Cochrane manual evaluation standard (version 5.0.2) was used to comprehensively evaluate the literature quality, and objectively evaluate whether there were methodological errors and subjective biases. In summary, risk of bias was assessed in the following six domains: (1) Random sequence Generation; (2) Allocation Concealment; (3) Blinding; (4) Incomplete outcome data; (5) selective outcome reporting; (6) Other sources of bias. Use the above criteria to evaluate the quality of the article, and the results are judged by "low risk", "high risk" or "unclear risk".

2.5 outcome indicators:

The outcome indicators included the levels of IL-6, IL-10, IL-1β, CRP, TNF- α, IGF-1 and IGFBP-3 in each group.

2.6 Statistical analysis:

This study used stata14.0 and Rstudio 4.1.1 software to perform a meta-analysis of the differences between endpoint and baseline indicators (formula: $SD_{change}=\sqrt{SD_1^2+SD_2^2-(2*R*SD_1*SD_2)}$R taken as 0.5). The extracted data were all continuous variables, and the individual test units were converted. Since the study of Karimi et al.[17]only mentioned endpoint indicators, it made sense to combine differential data with endpoint data according to previous studies[18], so we combined the posttest data from this study with differential data from other studies. Mean±SD was chosen as the standard scale of effect in the article, and the statistics were expressed as weighted mean difference (WMD) with 95% confidence interval (CI), $P < 0.05$ as a statistically significant difference. The I^2 value was used to perform heterogeneity analysis among studies. when $I^2= 0$, no heterogeneity among studies was considered, and a fixed-effects model was used; when $I^2\geq 50\%$, heterogeneity among studies was found and a random-effects model was used. When there was heterogeneity between studies, subgroup analysis was used to analyze the sources of heterogeneity, such as grouping different intervention period and type for computational analysis of I^2 values. In addition, in order to increase the credibility of the meta-analysis, sensitivity analysis were conducted to analyze whether there was a significant effect of each article on the combined results.

3. Result

3.1 Article search results:

After searching by subject terms and excluding duplicates, 1066 relevant articles were retrieved. By reading the titles, 364 articles remained. And 289 articles are manually excluded using abstracts, leaving 75 articles. A total of 17 articles met the criteria by reading the full text, of which 6 articles did not mention specific data. Therefore 11 articles were finally included. A flow diagram for study selection is presented in Figure 1.

3.2 Characteristics of selected studies:

Table 1 summarizes the details of the 11 included articles. In brief,11 articles were reported from 10 RCTs. Of the 10 trials, 8 studies were 2-arm randomized controlled trials[19] with exercise group and control group; one study was a 3-arm randomized controlled trial including two exercise groups (high-intensity interval exercise plus resistance exercise, high-intensity interval exercise plus aerobic exercise) and control group, which were analyzed separately in the text; another study was a 4-arm randomized controlled trial including an exercise group, a ginger-taking group, the taking ginger plus exercise group and the placebo group, then we extracted data only from the exercise and placebo groups. Among the 11 articles, nine of the outcome indicators included IL-6[14, 19-26], five included CRP [17, 21, 23-25] and TNF-α[19-22, 26], respectively, four included IL-10[17, 19, 20, 22],three included IGF-1[14, 24, 27] and IGFBP-3[14, 24, 27],and 1 included IL-1β[20] (not analyzed). The number of individuals in a study ranged from 16 to 240, with a total number of 696 individuals. Exercise intervention types included aerobic, resistance training, aerobic plus resistance training, yoga, water-based exercise, HIIT plus aerobic exercise, HIIT plus resistance training, and tai chi; settings included supervised, home-based or mixed; intensity included moderate, vigorous, or increasing, and frequency ranged from 1 session per week to 5 sessions per week; and period varied from 8 to 24 weeks; duration varied from 30-90 min.

Table 1
Characteristics of the selected studies

Author(year)	Deign	Participants	Intervention	Adherence	biomarkers	Other variables
Irwin, etc.* (2009)	Two-arm RCT. AT;UC	N=75, stage□-□A BCS,AT mean age:56.4±9.5	AT,24wks, 5d/wk, 150min/wk		IGF-1,IGF-3	Insulin, etc.
Lisa, etc. (2011)	Two-arm RCT.TCC; SST	N=21, □-□B BCS,TCC mean age: 54.33±10.64	TCC, 12wks, 3d/wk,60min	72%	IL-6 IGF-1 IGFBP-3	HRQOL, etc.
Gomez, etc. (2011)	Two-arm RCT.AT+RT;UC	N=16, stage□-□BCS, mean age:50±5	AT+RT 8wks,3d/wk, 90min, supervised	91%	IL-1, IL-10 IL-1β IL-6, IL-10/TNF-α TNF-α,	VO2max weight, etc.
Rogers, etc. (2012)	Two-arm RCT.AT+RT;UC	N=28, □-□A BCS, mean age: 56±10.5	AT+RT, 12wks,2d/wk, 150min/wk supervised		IL-10, IL-6, Il-1β, IL-6/IL-10,TNF-α/IL-10	BMI, Fatigue, etc.
Jones, etc.* (2012)	Two-arm RCT. AT;UC	N=75, stage□-□A BCS,AT mean age:56.4±9.5	AT,24wks, 5d/wk, 150min/wk		CRP□IL-6□ TNF-α	BMI, etc.
Bower, etc. (2013)	Two-arm RCT. yoga; HE	N=31,stage□-□BCS;mean age:54±5.7	Yoga,12wks, 2d/wk, 90min, supervised	78%	IL-6, CRP	Fatigue, depression, etc.

Abbreviations: AT: aerobic training ; RT:resistance training ;HE: health education ;GS: ginger supplement

SST: standard support therapy ;UC: usual care ;TCC: tai chi chuan.

*two articles from the same experiment

Abbreviations:Karimi, etc.(2015)is endpoint indicators;

Anouk E, etc. (2020)* RT+HIIT group;Anouk E, etc. (2020)#AT+HIIT group

Author(year)	Deign	Participants	Intervention	Adherence	biomarkers	Other variables
Karimi, etc. (2015)	Four-arm RCT. exercise;placebo□GS□exercise+GS	N=40, stage□-□BCS, exercise mean age:47.3±8.1	Water-Based Exercise, 6wks,4d/wk, 40-80min		IL-10, hs-CRP	Insulin, etc.
Christina, etc. (2017)	Two-arm RCT.AT+RT; delayed intervention control	N=20, stage□-□BCS,AT+RT mean age:53.0±10	AT+RT, 16wks,3d/wk 80min, supervised	97%	CRP, IL-6	Body composition, etc.
Christina, etc. (2018)	Two-arm RCT. AT+RT; UC	N=100, stage 0-□BCS, mean age:53.5±10.4	AT+RT, 16wks,3d/wk AT:150min/wk, supervised	95%	IGF-1, CRP, IL-6, TNF-α	Weight, BMI, etc.
Kim, etc. (2019)	Two-arm RCT. exercise; no exercise	N=50, stage□-□A BCS ,exercise mean age:49.95±8.12	stretching and resistance exercise, 12wks,1d/wk	90%	IL-6,TNF-α	Fatigue, etc.
Anouk E, etc. (2020)	Three-arm RCT.HIIT+RT;HIIT+AT;UC	N=240, stage□-□A BCS, mean age: RT:52.2±10.1 AT:53.9±7.4	HIIT+RT; HIIT+AT, 16wks, 2d/wk,60min	RT:79.5%; AT:82.1%	IL-6, TNF-α	Muscular strength, etc.
Abbreviations: AT: aerobic training ; RT:resistance training ;HE: health education ;GS: ginger supplement						
SST: standard support therapy ;UC: usual care ;TCC: tai chi chuan.						
*two articles from the same experiment						
Abbreviations:Karimi, etc.(2015)is endpoint indicators;						
Anouk E, etc. (2020)* RT+HIIT group;Anouk E, etc. (2020)#AT+HIIT group						

3.3 Methodologic quality of selected studies:

All 10 randomized controlled trials mentioned randomized grouping; 2 studies mentioned the method of randomization, the others did not; 3 studies mentioned allocation concealment, the others did not; only one study implemented blinding as the interventions were exercise interventions and blinding was difficult to implement; and 7 studies mentioned participants dropout or lost to follow-up. The end result was shown in figure 2 and figure 3.

3.4 Results of meta-analyses

3.4.1 Meta-analysis results of the effect of exercise on IL-6

9 studies analyzed the effect of exercise on IL-6 and a total of 318 participants were included in the study (Figure 4). A random effects model was used due to the high Heterogeneities of pooled studies (I^2 =88.2%). The analysis showed a trend towards a decrease in IL-6 levels following the exercise intervention, but there was no statistically significant change in IL-6 levels in the exercise group compared with the control group (WMD, -0.479 pg/ml; 95% CI, -1.107 to 0.149, p=0.195).

3.4.2 Meta-analysis results of the effect of exercise on CRP

5 studies reported the effects of exercise on CRP (Figure 5). A random effects model was used due to the high Heterogeneities of pooled studies (I^2 =99.0%). Analysis showed a trend toward a decrease in CRP after exercise intervention, but the effect of exercise on CRP was not statistically significant (WMD, -2.381 mg/L; 95% CI, -4.835 to 0.073; P=0.057).

3.4.3 Meta-analysis results of the effect of exercise on TNF-α

5 studies reported the effect of exercise on TNF-α (Figure 6). A random effects model was used due to the high Heterogeneities of pooled studies (I^2 =92.3%). Analysis showed a trend towards a decrease in TNF-α after exercise intervention, but the effect of exercise on TNF-αwas not statistically significant (WMD, -1.399 pg/ml; 95% CI, -1.718 to -1.080; P=0.245).

3.4.4 Results of Meta-Analysis of the Effect of Exercise on IL-10

4 studies analyzed the effect of exercise on IL-10 (Figure 7), with a total of 150 participants included in the study. A random effects model was used due to the high Heterogeneities of pooled studies (I^2 =78.5%). The results showed a trend towards a decrease in IL-10 levels after exercise intervention, but the effect of exercise on IL-10 was not statistically significant (WMD, -0.029 pg/ml; 95% CI, -0.367 to 0.309; P=0.866).

3.4.5 Meta-analysis results of the effect of exercise on IGF-1

3 studies reported the effect of exercise on IGF-1 (Figure 8). A fixed effect model was used due to the no statistical Heterogeneities of pooled studies (I^2 =0.0%). I^2 was 0.0%, and there was no statistical heterogeneity, so fixed effect model was used. The analysis showed a significant effect of exercise on IGF-1 (WMD, -19.947ng/ml; 95% CI, -22.669 to -17.225; P=0.000).

3.4.6 Meta-analysis results of the effect of exercise on IGFBP-3

3 studies reported the effect of exercise on IGFBP-3 (Figure 9). A random effects model was used due to the high Heterogeneities of pooled studies (I^2 =95.1%). I^2 was 95.1% and there was a high degree of heterogeneity between studies, so a random effects model was used. There was a trend for an increase in IGFBP-3 levels after the exercise intervention, but the statistical results were not significant (WMD, 4.501ng/ml; 95% CI, -1.099 to 10.101; P=0.115).

3.5 Subgroup analysis

Considering the large differences in intervention period among all studies, we grouped them according to different intervention period: >12 weeks and ≤12 weeks. To analyze the heterogeneity of the included studies, we performed subgroup analyses for some of the studies, as shown in Table 2. (1) Subgroup analysis of the effect of exercise intervention on IL-6: A total of 9 studies about IL-6 levels were included, including 5 studies with an intervention period≤12 weeks and 4 studies with an intervention period>12 weeks. The results of the subgroup analysis showed that the effect of exercise on IL-6 was more significant in studies with exercise intervention period>12 weeks (WMD, -0.761 pg/ml; 95% CI, -1.369 to -0.153; p=0.014),and in studies with exercise intervention period≤12 weeks, there was no significant effect of exercise on IL-6 levels (WMD, 0.615 pg/ ml; 95% CI, -0.763 to 1.993; p=0.382); (2) subgroup analysis of the effect of exercise intervention on CRP and IL-10: In studies with an intervention period≤12 weeks, exercise had significant effects on CRP (WMD, -2.381 mg/L; 95% CI, -4.835 to 0.073, p=0.001)and IL-10 (WMD, -7.141 pg/ml; 95% CI, -10.853 to -3.428; P=0.000).

Table 2
subgroup analysis of different intervention period

group	standard	total	WMD	95%CI	P	I^2	P(heterogeneity)
IL-6	≤12wks	5	0.615	-0.763 to 1.993	0.382	50.1%	0.091
	>12wks	4	-0.761	-1.369 to-0.153	0.014	91.3%	0.000
CRP	≤12wks	2	-2.381	-4.835 to 0.073	0.001	0.0%	0.760
	>12wks	3	-3.068	-6.908 to 0.772	0.117	99.5%	0.000
TNF-α	≤12wks	3	-1.132	-6.782 to 4.517	0.694	0.0%	0.716
	>12wks	2	-0.723	-2.036 to 0.590	0.280	98.0%	0.000
IL-10	≤12wks	3	-7.141	-10.853 to-3.428	0.000	0.0%	0.415
	>12wks	1*#	0.027	-0.110 to 0.164	0.698	60.7%	0.111
*Anouk E, etc. (2020) RT+HIIT group;#Anouk E, etc. (2020) AT+HIIT group							

In addition, we performed a subgroup analysis of exercise intervention type, but due to the volume of articles, we only performed a subgroup analysis of studies involving IL-6, and the results are shown in Table 3. Among the studies about IL-6, there were 4 studies on aerobic plus resistance training; two studies on Tai Chi and yoga; and one study each on aerobic exercise, resistance exercise, high-intensity interval exercise plus resistance exercise, and high-intensity interval exercise plus aerobic exercise. Subgroup analyses showed that the effect of aerobic plus resistance exercise on IL-6 was more significant (WMD, -1.474; 95% CI, -1.653 to -1.296; P=0.000).

Table 3
subgroup analysis of different intervention type of IL-6

group	total	WMD	95%CI	P	I^2	P(heterogeneity)
AT+RT	4	-1.474	-1.653 to -1.296	0.000	0.0%	0.879
Mindbody	2	0.867	-1.214 to 2.947	0.414	86.9%	0.006
AT	1	0.04	-0.564 to 0.644	0.897	.	.
RT	1	-0.210	-2.913 to 2.493	0.879	.	.
HIIT+RT	1	-0.490	-0.954 to -0.026	0.038	.	.
HIIT+AT	1	-0.240	-0.833 to 0.153	0.176	.	.
Abbreviations: AT+RT: aerobic training +resistance training;Mindbody：taiji，yoga.						

3.6 Sensitivity analysis

Due to the quantitative of the articles, we only performed sensitivity analyses on the relevant articles on IL-6, TNF-α and CRP. Sensitivity analyses of the effects of exercise on IL-6 and CRP are shown in Figures 10 and 11, and the results were relatively stable and reliable. Whereas sensitivity analysis of the 5 studies on TNF-α revealed (Table 4) a high degree of heterogeneity in one of the studies by Jones et al. This study was excluded and meta-analysis was performed, the results are shown in Figure12. A fixed effects model was used due to the I^2=0.0%. The results showed a significant difference in TNF-α levels in the exercise group compared to the control group (WMD, -1.399 pg/ml; 95% CI, -1.718 to -1.080; P=0.000).

Table 4
sensitivity analysis of CRP

Study omitted	Estimate	[95% CI]
Gomez,etc. (2011)	-.73597163	-1.9933293 to 0 .52138609
Jones,etc. (2012)	-1.3991472	-1.7181057 to -1.0801886
Rogers,etc. (2012)	-.74548692	-2.0388248 to 0.54785085
christina,etc. (2018)	-.06109226	-.24138363 to 0.11919912
Kim,etc. (2019)	-.72941327	-1.9951227 to 0.53629613
Combined	-.74299052	-1.9951979 to 0.50921682
Jones,etc. (2012) has obvious heterogeneity		

3.7 Publication bias

Begg (p=0.602) test and Egger (p=0.068) test showed no risk of publication bias, and we did not perform a funnel analysis because there were fewer than 10 references.

4. Discussion

Most of the current studies on the effects of exercise on inflammatory factors and IGF systems in breast cancer survivors involve IL-6, IL-10, IL-1β, TNF-α, CRP, IGF-1, IGFBP-3, etc. Some researchers used meta-analysis to quantify the effects of exercise on the levels of inflammatory factors and IGF systems [28, 29], but no quantitative analysis was performed in terms of exercise period and type, and our article refines the effects of different intervention period and different intervention type on the combined effects of outcomes based on previous studies. Further quantitatively evaluate the effects of exercise on inflammatory factors and IGF systems, so as to provide a basis for more individualized studies.

Our meta-analysis showed that exercise intervention significantly reduced IGF-1 levels in breast cancer survivors, and further subgroup analyses showed significant improvements in IL-6 levels in the exercise group compared with control group when the intervention period was longer than 12 weeks, and a significant effect of exercise on CRP and IL-10 when the intervention period was less than or equal to 12 weeks; in addition, aerobic exercise plus resistance training significantly reduced IL-6 levels. Sensitivity analysis showed that exercise had a significant effect on TNF-α levels in breast cancer survivors after excluding highly heterogeneous studies.

4.1 Exercise improves the prognosis of breast cancer patients

The American Cancer Society (ACS) and the American Society of Clinical Oncology (ASCO) in their breast cancer survivorship care guidelines suggests that breast cancer survivors should engage in regular exercise consistent with ACS guidelines, should avoid lack of exercise, and should engage in at least 150 minutes of moderate or 75 minutes of vigorous aerobic exercise per week plus strength training at least two days per week [30].

A meta-analysis involving 16 breast cancer survivors showed that the mean relative risks of breast cancer mortality and all-cause mortality for breast cancer survivors who participated in exercise were 0.72 (95% CI, 0.60-0.85) and 0.52 (95% CI, 0.42-0.64) [31], respectively. Another strong piece of evidence comes from a prospective evaluation involving 8 cohorts breast cancer patients. There is an association between post-treatment exercise and breast cancer-specific mortality and various mortality rates. 8-9 Met-hours of exercise per week associated with a 50% reduction in mortality from cancer and all causes [32]. A meta-analysis also found that exercise was negatively associated with all-cause, breast cancer-related mortality, and risk of breast cancer recurrence in breast cancer survivor [33]. In addition, numerous studies [34-36] have shown that lack of exercise is also associated with postoperative fatigue, psychological distress, and poor overall quality of life in breast cancer patients. Therefore, exercise is one of the better prognostic rehabilitation tools for breast cancer patients.

4.2 Inflammatory factors

Tumor-associated inflammation is one of the hallmarks of breast cancer [37],IL-6, TNF-α and CRP are widely recognized as biomarkers of breast cancer-associated systemic inflammation [38].IL-6, TNF-α and CRP are all pro-inflammatory factors that have been widely studied. In addition, IL-1β is also a pro-inflammatory cytokine that plays a role in the pathogenesis of cancer [39, 40].IL-1β levels are significantly higher in tumors of breast cancer patients than in normal breast tissue [41]. Studies have shown that increases in chronic pro-inflammatory factors, particularly IL-6, are associated with elevated levels of fatigue and psychological symptoms in breast cancer survivors [42-44]. The mechanism may be the ability of pro-inflammatory cytokines to affect brain function through various signaling modalities (vagal activation, hormonal effects, direct interactions between circulating cytokines and brain cytokines), leading to complex cancer complications such as fatigue and depression [42-45]. In addition to pro-inflammatory cytokines, anti-inflammatory cytokines are also important in the development of tumors, such as IL-10. IL-10 is a powerful anti-inflammatory cytokine that promotes the formation of a microenvironment, then inhibits anti-tumor immune responses and promotes the growth of cancer cells [46-48]. Studies have shown that serum levels of IL-10 are significantly higher in breast cancer patients than in healthy individuals [49]. Given these characteristics of inflammatory factors, these biomarkers can be used to diagnose female breast cancer and identify patients with a poorer prognosis.

Studies have shown that exercise is associated with lower levels of various pro-inflammatory cytokines [50, 51]. A study on breast cancer patients found a negative association between exercise and IL-6 levels; other meta-analyses have also shown a significant decrease in IL-6 and CRP levels after exercise intervention [52]. However, in our meta-analysis we only found that exercise intervention significantly reduces TNF-α levels after excluding highly heterogeneous studies, but we did not found significant correlation between exercise and other inflammatory factors. Further subgroup analyses showed that exercise significantly reduced IL-6 levels when the intervention period >12 weeks, but exercise had a nonsignificant effect on IL-6 levels when the intervention period ≤12 weeks. In contrast, the exercise significantly reduced CRP and IL-10 levels when the intervention period ≤12 weeks. This suggests a possible effect of different intervention period on the experimental results. There was significant heterogeneity in the results of the intervention period subgroup analysis (91.3%, 99.5%, 98.0%, 60.7%), suggesting that the effect of exercise on IL-6, CRP, TNF-α, and IL-10 levels in breast cancer patients with different intervention period is a high probability of being a source of heterogeneity in the currently included studies. Therefore, we hypothesized that there may be a complex correlation between the period of intervention and changes in inflammatory factors. A study analysis [52] concluded that for the elderly population, short-term intervention training hardly leads to significant changes in the organism at the level of indicators. However, long-term exercise may not show changes in inflammatory markers, as older adults are susceptible to other uncontrolled environmental factors, which in turn affect the levels of inflammatory factors. In addition, we found that aerobic plus resistance training significantly reduced IL-6 levels. Previous studies [53, 54] have identified the benefits of aerobic plus resistance training, which improves the overall functional capacity of breast cancer patients. As a result, a growing number of studies have now evolved from just one type of exercise to a more complex exercise prescription of aerobic exercise combined with resistance training. However, we included too few studies on other inflammatory factors to analyze the effects of other intervention types on outcomes. More studies should be included in the future to analyze the effects of exercise intervention period and type on inflammatory markers in breast cancer patients and to determine the most appropriate intervention period and intervention type for breast cancer patients.

4.3 IGF system

The IGF system is one of the important mechanisms in breast cancer pathogenesis. IGF -1 has anti-apoptotic effect on breast cancer cells [55, 56] and IGFBP-3 is a highly relevant binding protein for IGF-1. IGFBP-3 is able to inhibit IGF-1 binding to IGF-1R (IGF-1 receptor) by competitive binding to IGF -1 to exert activity [57, 58].Studies have shown that high circulating levels of IGF-1 and low levels of IGFBP-3 are associated with an increased risk of premenopausal breast cancer [9, 59, 60]. In addition, a meta-analysis of prospective studies on the relationship between IGF-1 and breast cancer incidence in premenopausal women showed a statistically significant positive association between IGF-1 and breast cancer risk [61]. The IGF signaling system plays an important role in breast cancer development and progression [62, 63]. In addition, the IGF signaling system is an important mediator in tumorigenesis more than 90% of breast cancer patients have overexpression of IGF-1R [64]. So targeting the IGF system is a better option.

Studies have shown that exercise can reduce IGF-1 levels and increase IGFBPs levels [65]. Exercise is thought to cause physiological changes in systemic IGF ligand and binding protein bioavailability, which may indirectly affect IGF-1R signaling [66]. In our meta-analysis, we included three studies on IGF-1, and all three studies reported that exercise significantly decreased IGF-1 levels. In a meta-analysis [29] involving 7 studies of breast cancer patients also found a trend towards decreased IGF-I levels after exercise, but this was not statistically significant (WMD, -5.23 ng/mL; 95% CI, 13.00 to 2.53; p=0.19).However this meta-study found no significant effect of exercise on IGFBP-3 (WMD, 0.01; 95% CI, -0.96 to 0.98; p=0.99) levels. This is similar to the findings of our study, in which although there

was a tendency for exercise to improve IGFBP-3, the results were not statistically significant. Among the studies on IGFBP-3 that we included, two of them [21, 25] reported elevated IGFBP-3 levels after exercise, while in another 6-month aerobic exercise study [28] found a significant reduction of 4.1% (p=0.006) in IGFBP-3 levels in the intervention group compared to the control group. The results showed a significant discrete pattern, which may be related to intervention type. In a 6-month study [67] of prostate cancer patients with aerobic or resistance exercise programs significant increase in serum IGFBP-3 of 12.1% ($P \leq 0.05$) was observed in the resistance exercise group, while IGFBP-3 was reduced by 23.7% ($P \leq 0.05$) in the aerobic exercise group. However, this may be only a conjecture, as baseline levels of IGFBP-3 were significantly higher in the aerobic exercise group than in the resistance training group in this study, and participants in this study also differed significantly from those in our study.

4.4 Limitations of the study

The article included fewer studies and included only English and Chinese studies, which may have incomplete study inclusion; second, this study did not adjust for potential confounders such as age, BMI, and gender, which may have a potential effect on the study results; third, due to the small number of included studies and the lack of available data, the subgroup analysis only discussed the effect of different exercise period and type on the result in some studies, and did not analyze the effects of all studies on the type and intensity of the intervention. A comprehensive subgroup analysis of the characteristics of exercise intervention is warranted for future studies.

4.5 Conclusion

This study affirms the trend that exercise positively affects the inflammatory factors and IGF system in breast cancer survivors. Exercise is feasible for breast cancer survivors, and exercise not only reduces side effects, but also improves survival rates in breast cancer patients. However, the most beneficial exercise period, type and intensity for inflammatory factors and IGF systems in breast cancer patients are not clear. Future studies should include more randomized controlled trials to analyze the appropriate exercise intervention for breast cancer patients to improve inflammatory factors and IGF systems, and to provide a basis for developing individualized exercise prescriptions for breast cancer patients.

Abbreviations

AT
aerobic training
RT
resistance training
HE
health education
GS
ginger supplement
SST
standard support therapy
UC
usual care
TCC
tai chi chuan.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for pulication

Not applicable.

Availability of data and materials

All data generated or analysed during this study are included in this published article [and its supplementary information files].

Competing interests

The authors declare that they have no competing interests.

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Authors' Contributions

YZ and MD planned the structure of the manuscript. YZ and NJ analyzed the data .YZ wrote the manuscript and designed the figures. NJ and MD participated in its design and coordination, and helped to draft the manuscript. All authors read and approved thefinal manuscript.

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Figures

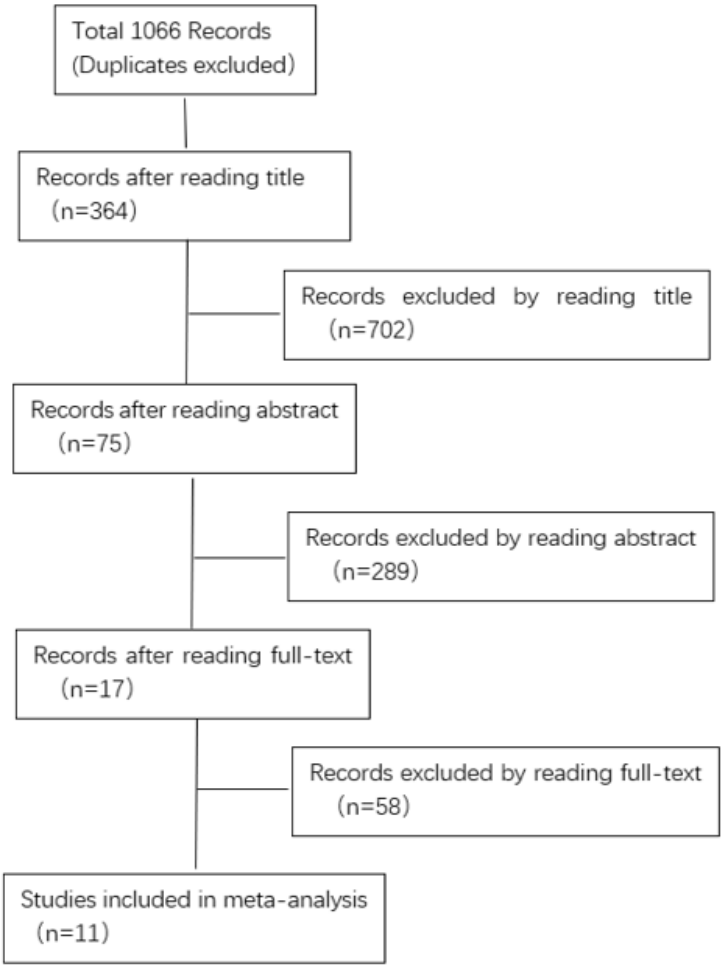


Figure 1

studies selection flow diagram

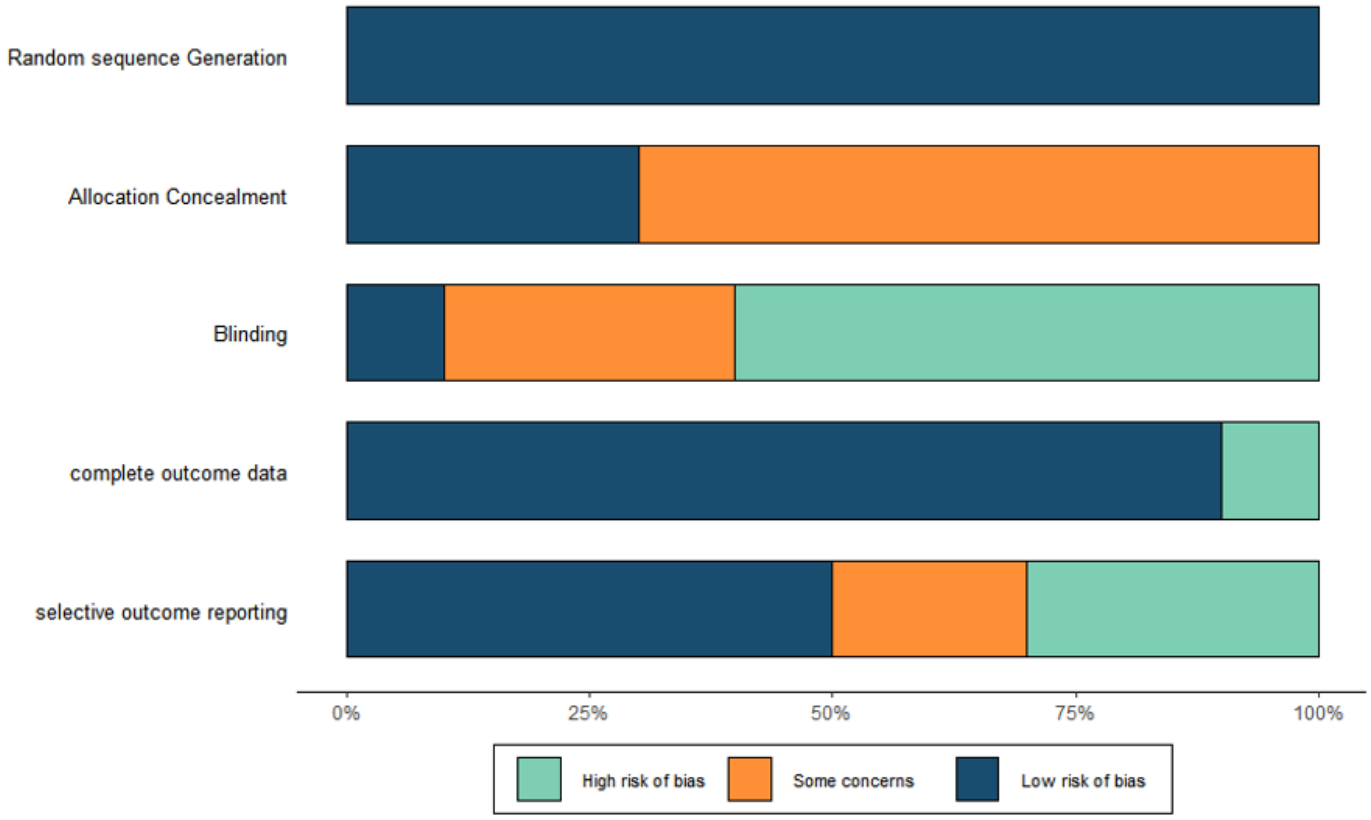


Figure 2

Risk of bias proportion

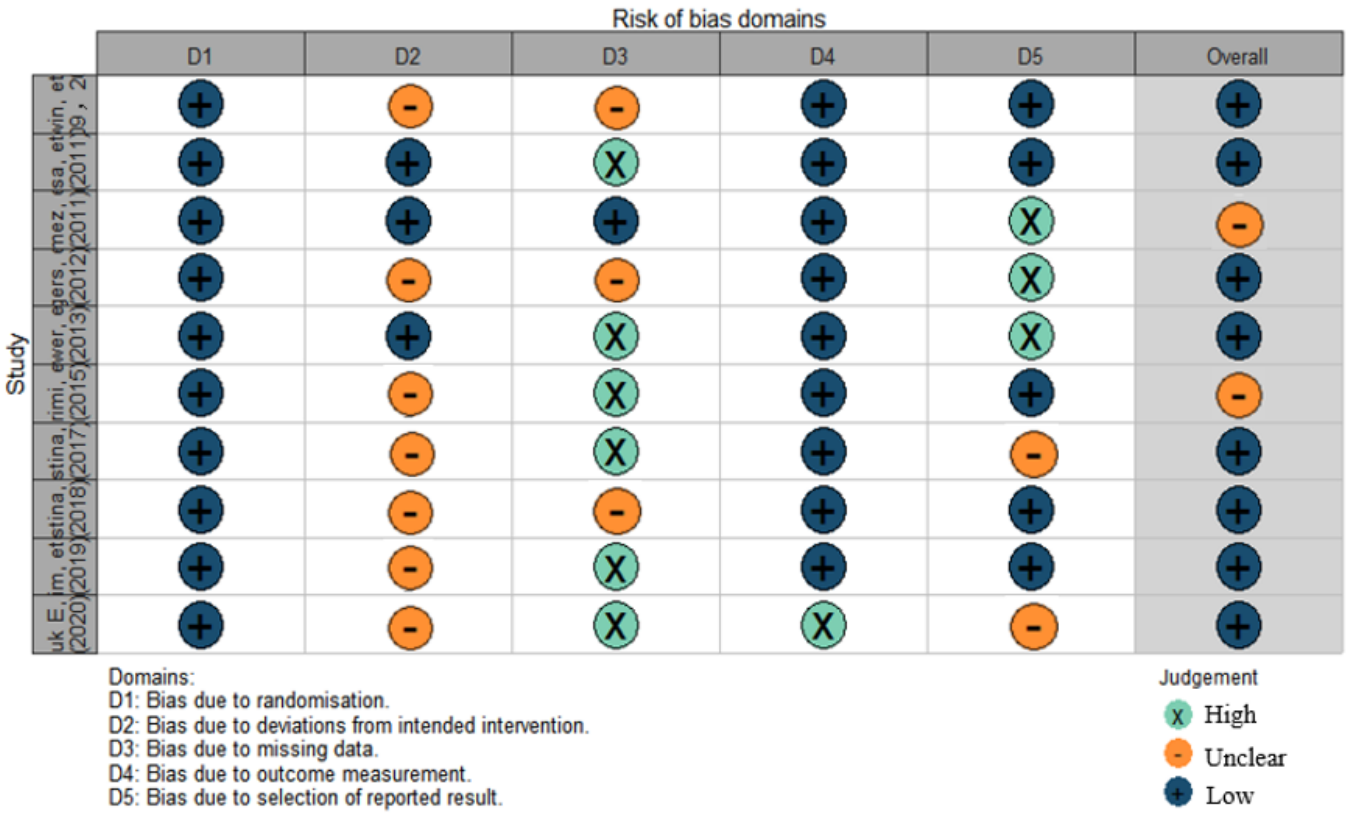
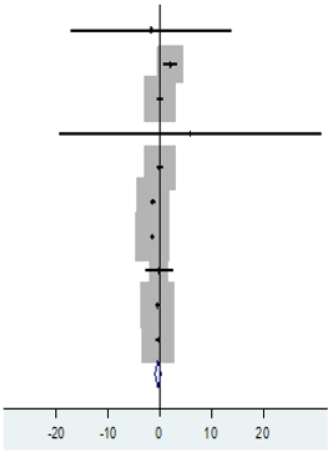


Figure 3

Risk of bias domains

Study: Irwin, etc.(2009,2012); Lisa, etc.(2011); Gomez, etc.(2011); Rogers,etc.(2012);Bower,etc.(2013);Karimi,etc.(2015); Christina, etc. (2017); Christina, etc. (2018); Kim, etc.(2019); Anouk E, etc.(2020)

		Exercise		Control		
Author(year)	n	Mean±SD	n	Mean±SD	Weight (%)	WMD【95%CI】
IL-6 (pg/ml)						
Gomez,etc. (2011)	8	-4.5±22.48	8	-2.81±0.45	0.15	-1.690 (-17.271 to 13.891)
Lisa,etc. (2011)	9	2±2.02	10	-0.02±0.56	8.81	2.020 (0.655 to 3.385)
Jones, etc. (2012)	36	0.04±1.32	31	0.00±1.2	13.82	0.040 (-0.564 to 0.644)
Rogers,etc. (2012)	15	3.9±46.17	13	-2±18.02	0.06	5.900 (-19.435 to 31.235)
Bower,etc. (2013)	16	0.16±0.73	15	0.27±1.06	13.56	-0.110 (-0.755 to 0.535)
christina,etc. (2017)	10	-4.17±0.51	10	-2.81±0.45	14.88	-1.360 (-1.782 to 0.938)
christina,etc. (2018)	50	-1.4±0.44	50	0.1±0.56	15.77	-1.500 (-1.697 to -1.303)
kim,etc. (2019)	12	-0.26±2.14	6	-0.05±3.02	3.80	-0.210 (-2.913 to 2.493)
Anouk E,etc. (2020) *	30	0.03±0.79	29	0.52±1.01	14.66	-0.490 (-0.954 to -0.026)
Anouk E,etc. (2020) #	27	0.18±0.87	29	0.52±1.01	14.49	-0.340 (-0.833 to 0.153)
Overall	177		170		100.00	-0.479 (-1.107 to 0.149)



Heterogeneity: Tau^2 =0.5903, df = 9 (P = 0.000); I^2 = 88.2%

Test for overall effect: Z = -1.295 (P =0.195)

Figure 4

Forest plot of comparison for IL-6

Anouk E, etc. (2020)* RT+HIIT group；Anouk E, etc. (2020)#AT+HIIT group

Figure 5

Forest plot of comparison for CRP

Karimi, etc.(2015): endpoint indicators

Figure 6

Forest plot of comparison for TNF-α

Figure 7

Forest plot of comparison for IL-10

Abbreviations:Karimi, etc.（2015）is endpoint indicators；

Anouk E, etc. (2020)* RT+HIIT group，Anouk E, etc. (2020)#AT+HIIT group

Figure 8

Forest plot of comparison for IGF-1

Author(year)	n	Exercise Mean±SD	n	Control Mean±SD	Weight (%)	WMD【95%CI】
IGFBP-3 (ng/ml)						
Irwin, etc. (2009)	37	-190±80	38	-150±100	1.80	-40.000 (-80.931 to 0.931)
Lisa, etc. (2011)	9	0.89±1.04	10	-1.7±1.19	49.57	2.590 (1.587 to 3.593)
christina, etc. (2018)	50	6.9±4.17	50	-1.2±3.4	48.63	8.100 (6.609 to 9.591)

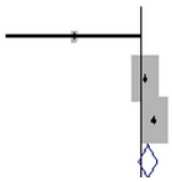


Figure 9

Forest plot of comparison for IGFBP-3

Figure 10

sensitivity analysis of IL-6

Anouk E, etc. (2020)* RT+HIIT group，Anouk E, etc. (2020)# AT+HIIT group

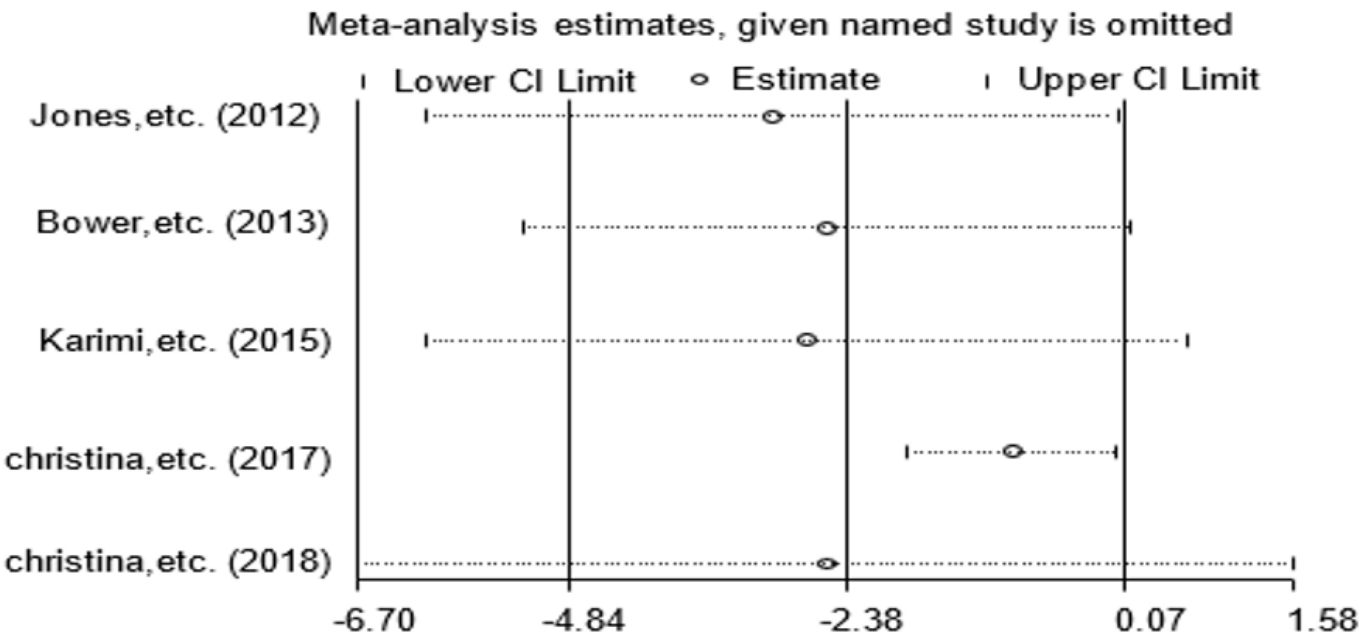


Figure 11

sensitivity analysis of CRP

Figure 12

Forest plot of comparison for TNF-α after excluding highly heterogeneous studies

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- PRISMAchecklist.docx
- PRISMA2020checklist.docx