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Research Article

Cancer Epidemiology, Biomarkers & Prevention

Effects of Exercise on Insulin, IGF Axis, Adipocytokines, and Inflammatory Markers in Breast Cancer Survivors: A Systematic Review and Meta-analysis

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Abstract

Background: Insulin, IGF axis, adiponectin, and inflammatory markers are associated with breast cancer. Given that physical activity improves prognosis of breast cancer survivors, we investigated the effects of exercise on these markers as potential mediators between physical activity and breast cancer.

Methods: PubMed, EMBASE, CENTRAL, CINAHL, and SportDiscus were searched up to December 3, 2015, to identify randomized controlled trials (RCT) that investigated the effect of exercise on insulin, IGF axis, and cytokines in breast cancer survivors. Weighted mean difference (WMD) was calculated using either fixed- or random-effects models on the basis of the heterogeneity of the studies.

Results: A total of 18 studies involving 681 breast cancer survivors were included, and these numbers were reduced for individual biomarker analyses. We found that exercise significantly reduced fasting insulin levels [WMD, −3.46 μU/mL; 95% confidence interval (CI), −5.97 to −0.95; $P = 0.007$]. Furthermore, potentially meaningful but statistically nonsignificant changes were observed in insulin resistance (WMD, −0.73; 95% CI, −0.54 to 0.13; $P = 0.23$), adiponectin (WMD, 1.17 μg/mL; 95% CI, −0.87 to 3.20; $P = 0.26$), and C-reactive protein (WMD, −1.10 mg/L; 95% CI, −2.39 to 0.20; $P = 0.10$). Subgroup analyses showed that fasting insulin levels were significantly more impacted in studies in which intervention participants experienced a weight reduction (WMD, −7.10 μU/mL; 95% CI, −10.31 to −3.90; $P < 0.001$).

Conclusions: Exercise reduces fasting insulin levels in breast cancer survivors. This may be due to exercise-induced reductions in body weight.

Impact: Practitioners and clinicians may better help breast cancer prognosis be improved through exercise, anticipating physiological effects on cancer. *Cancer Epidemiol Biomarkers Prev; 26(3); 355–65. ©2016 AACR.*

Introduction

Physical activity is a well-known lifestyle factor that is positively associated with breast cancer prognosis (1–3). In one study, patients with breast cancer who participated in physical activity of more than 9 to 14.9 metabolic equivalent task (MET)-hours per week demonstrated significantly reduced breast cancer mortality [relative risk (RR), 0.5; 95% confidence interval (CI), 0.31–0.82], compared with those who participated in less than 3 MET-hours per week of physical activity (1). Moreover, a recent exploratory follow-up of a randomized controlled trial (RCT) suggested that patients with breast cancer who exercise during chemotherapy may have a lower risk of recurrence (HR, 0.68; 95% CI, 0.37–1.24) and an improved overall survival rate (HR, 0.60; 95% CI, 0.27–1.33; ref. 3).

The mechanisms linking physical activity and breast cancer risk and mortality are unclear. However, numerous studies have reported that high levels of fasting insulin and metabolic risk factors are associated with greater breast cancer risk, recurrence, and mortality (4–6). In a cohort of 512 women with newly diagnosed breast cancer, Goodwin and colleagues (5) reported that individuals with higher levels of fasting insulin at the time of cancer diagnosis had an increased risk of breast cancer recurrence and greater overall mortality as compared with women with lower levels of fasting insulin. The mechanisms through which insulin could impact breast cancer risk and outcomes are not clear, but research suggests that insulin can stimulate breast cancer cell proliferation (6), mediated through binding of insulin to IGF receptors (7). In addition, upregulated inflammation-related cytokines adipocytokines and inflammatory markers, including IL6, TNFα, and C-reactive protein (CRP), are associated with breast cancer and are also poor prognosticators in breast cancer patients., which have also been suggested as potential mediators between physical activity and breast cancer (8). A number of RCTs have examined the changes in insulin, IGF axis, adiponectin, IL6, TNFα, and CRP after exercise interventions in patients with breast cancer.

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However, the results from individual studies are inconsistent (9, 10). Therefore, in this study, we investigated the effects of several biomarkers that have been proven to be associated with breast cancer and physical activity, and we performed a meta-analysis of the RCTs to summarize the collective evidence of the effects of exercise on insulin, IGF axis, adiponectin, IL6, TNFα, and CRP in breast cancer survivors.

Materials and Methods

Search strategy

We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Supplementary Table S1; ref. 11) and Cochrane Handbook for Systematic Reviews of Interventions (12). PubMed (MEDLINE), EMBASE, Cochrane CENTRAL, CINAHL, and SportDiscus databases were searched up to December 3, 2015 and Medical Subjects Headings (MeSH) Terms for PubMed and CENTRAL, and Emtree terms for EMBASE were also used. Search terms included breast cancer–related terms ("breast cancer," "breast neoplasm," "breast tumor," "breast tumor," or "breast carcinoma"), exercise-related terms ("exercise," "physical activity," or "sport"), and study design ("RCT" or "controlled clinical trial"). The articles found via databases were then manually screened for eligible studies using title and abstract. Two independent researchers (D.-W. Kang and J. Ligibel) completed the literature search and screening from databases, and the reference lists from previous systematic reviews and meta-analyses were screened.

Eligibility criteria

Eligible studies were RCTs that examined the effects of exercise or physical activity compared with control (usual care) on insulin, IGF axis, adipocytokines, and/or inflammatory markers in breast cancer survivors. The included studies provided any types of exercise intervention, including aerobic exercise, resistance exercise, aerobic and resistance combined exercise, yoga, or tai chi. The exercise intervention must not have been combined with diet or other intervention factors and must have been compared with a control group. Participants were those who were diagnosed with stage 0–IV breast cancer survivors who had completed treatment.

Data extraction

The data extracted from the selected studies included characteristics of the participants [sample size, mean age, mean body mass index (BMI), gender, cancer type, cancer stage, current treatment status, and menopausal status], characteristics of exercise intervention and control (exercise type, setting, period, frequency, duration, intensity, and treatment for control group), and results (changes in mean/SD after intervention, *P* value and/or CI, missing data/participants, and units of the measurements). When there were missing or conflicting data, emails were sent to the corresponding author for further information and clarification. Data were retrieved by 2 reviewers (D.-W. Kang and J. Ligibel), discrepancies in the results of data extraction were mediated by a third reviewer (J.Y. Jeon), and consensus was achieved via discussion.

Risk of bias assessment

The Cochrane Collaboration's Risk of Bias Tool (13) was used to assess the risk of bias in selected studies. In summary, risk of bias was assessed in the following 7 domains: (i) random sequence generation, (ii) allocation concealment, (iii) blinding of participants and personnel, (iv) blinding of outcome assessment, (v) complete outcome data, (vi) selective reporting (intention-to-treat analysis), and (vii) other bias (bias due to problems not covered elsewhere in other domains). Studies that had no serious flaws were rated as having a low risk of bias and studies that showed substantial bias were rated as having a high risk of bias (14).

Statistical analysis

When at least 2 studies were available for an outcome, a meta-analysis was performed. A summary estimate of each study was calculated and weighted. In this study, SD was referenced for the weighting of each study, and a weighted average was calculated for the meta-analysis. All dependent variables in this study are continuous, and the number of participants in the exercise and control groups was calculated to determine the weighted mean difference (WMD). WMD with a 95% CI was provided as the difference in mean changes between groups divided by the pooled SD. Analysis models for each outcome were determined on the basis of the results of heterogeneity tests. Heterogeneity was tested using Higgin I^2 statistic. $I^2 \leq 50\%$ was used to determine the absence of heterogeneity, and a fixed-effects model was used. If I^2 was greater than 50% and heterogeneity was found between studies, a random-effects model was used. Subgroup analyses were conducted to test the robustness of significant results depending on whether groups in the studies showed weight reduction (15).

Results

Study selection

A study selection flow diagram (11) is presented in Fig. 1. In brief, of a total of 597 records after duplicates removed, 570 articles were manually excluded using titles and abstracts. Of 27 full-text articles screened, 18 articles met inclusion criteria and were then quantitatively analyzed.

Characteristics of selected studies

Details of the 18 selected articles are summarized in Table 1. In brief, 18 articles were reported from 14 RCTs. Of 14 trials, 12 studies were 2-arm RCTs with one exercise group and one control group. One study (16) was a 3-arm RCT with a home-based aerobic exercise group, a supervised resistance exercise group, and a control group, and these two exercise groups were separately analyzed in the meta-analyses. Another study (17) was a 4-arm RCT comprising an exercise group, a diet group, an exercise plus diet group, and a placebo group, and therefore only the results from the exercise group and the placebo group were extracted and analyzed. Participants in the included studies were stage 0–IIIb patients with breast cancer who completed treatments including surgery, chemotherapy, and/or radiation therapy with/without hormonal or endocrine therapy. The number of participants in a study ranged from 20 to 101, with a total number of 681 participants. Exercise intervention programs varied in type (aerobic exercise, resistance exercise, aerobic plus resistance exercise, yoga, or Tai Chi), setting (supervised, home-based, or combined), intensity (moderate, moderate-vigorous, or vigorous), period (from 6 to 24 weeks), and duration (from 15 to 90 minutes per session).

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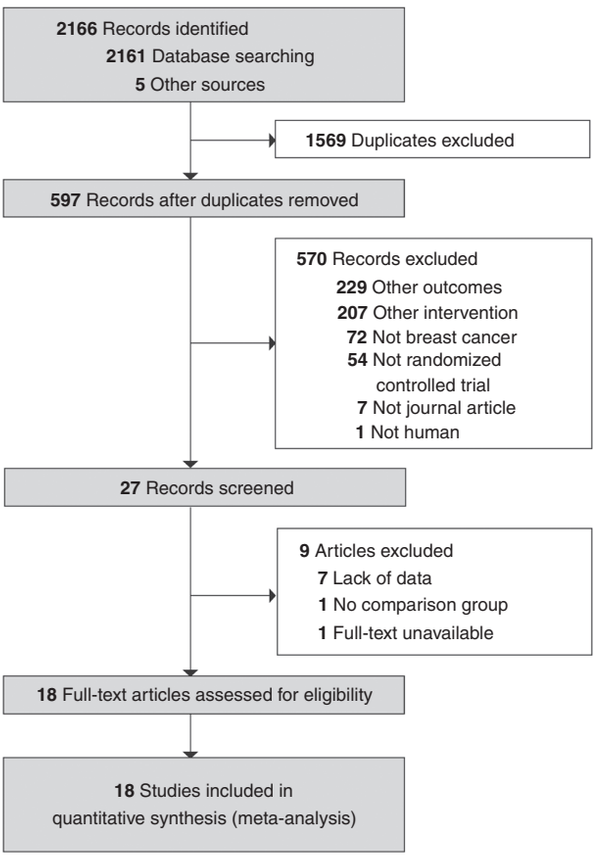

Figure 1.
PRISMA flow diagram.

Methodologic quality of selected studies

The results of risk of bias and quality assessment for the selected studies are summarized in Table 2. Quality assessment results are provided for each individual study, and the total scores are not presented because it has been suggested that cutoff scores for the assessment of methodologic quality of studies have not been clearly established, and therefore, there may be ambiguity in determining the overall quality of selected studies (18).

Results of meta-analyses

Effects of exercise on insulin. A total of 7 studies (19–25) involving 369 participants were included in the analysis (Fig. 2). The average length of exercise intervention was approximately 16 weeks. I^2 was 96%, indicating that the studies are highly heterogeneous, and a random-effects model was therefore used. The analysis showed that fasting insulin level was significantly reduced in the exercise group compared with the control group (WMD, −3.46 μU/mL; 95% CI, −5.97 to −0.95; $P = 0.007$).

To understand the impact of weight change in the intervention studies on changes in fasting insulin levels (15), studies were subcategorized according to whether there was weight reduction after the exercise intervention (Supplementary Table S2). A subgroup analysis showed that exercise significantly more impacted fasting insulin levels in studies where intervention participants experienced a weight reduction (WMD, −7.10 μU/mL; 95% CI, −10.31 to −3.90; $P < 0.001$), whereas there was not significant insulin reduction when intervention participants did not experience a weight reduction (WMD, −0.78 μU/mL; 95% CI, −2.32 to 0.77; $P = 0.32$).

Effects of exercise on glucose, insulin resistance, and IGF axis. The effects of exercise on glucose (19, 20, 22–26), insulin resistance (IR; refs. 19, 20, 22–24), and IGF axis (19, 21, 24, 25) in breast cancer survivors are presented in Fig. 3. There was no significant difference in change in glucose, IR, IGF1, and IGF-binding protein-3 (IGFBP3) between the exercise group and the control group. However, a potentially meaningful, but statistically insignificant, change in IR was observed after the exercise intervention (WMD, −0.20; 95% CI, −0.54 to 0.13; $P = 0.23$).

Effects of exercise on adipocytokines and inflammatory markers. Effects of exercise on adiponectin, IL6 (17, 27, 28), TNFα (16, 27, 29–33), and CRP (16, 27, 30, 32, 33) in breast cancer survivors are presented in Fig. 4. There was no significant change in adipocytokines and inflammatory markers before and after exercise intervention compared with control group. Although there was not statistically significant change, adiponectin (WMD, 1.17 μg/mL; 95% CI, −0.87 to 3.20; $P = 0.26$) and CRP (WMD, −1.10 mg/L; 95% CI, −2.39 to 0.20; $P = 0.10$) showed potentially meaningful results.

Discussion

Our meta-analysis demonstrated that exercise interventions significantly reduced fasting insulin levels in breast cancer survivors. Further subgroup analyses showed that reductions in insulin were greater when weight loss occurred. For IR, adiponectin, and CRP, significant changes were not seen, but potentially meaningful changes were found in response to exercise interventions, although fewer studies included these markers, limiting the power of this analysis to observe differences.

Insulin has been known to play a critical role in carcinogenesis in various sites on the human body including breast tissue (34, 35), and patients with cancer have shown increased insulin levels in the blood. In addition, IR, which represents an elevated concentration of serum insulin, is the main characteristic of patients with type II diabetes mellitus (T2DM). Given that fasting insulin acts as a promoter of tumorigenesis, the association between cancer and T2DM has in fact been well-documented in a number of prospective cohort studies (36). Because a high concentration of fasting insulin, or hyperinsulinemia, is known to increase the risk of cancer recurrence and mortality (5, 37), the effect of exercise on circulating insulin level was of interest. In the present study, our findings in insulin reduction after exercise intervention in patients with breast cancer are in agreement with previously reported studies showing that exercise enhances insulin signaling. In conjunction with fasting insulin reduction, our finding in a potentially meaningful but insignificant IR reduction may be driven by an enhanced insulin sensitivity through exercise (38, 39). This is particularly relevant given that breast cancer is strongly associated with obesity and physical inactivity (1), and insulin has been proposed as a mediator of the effect of physical activity on breast cancer prognosis (40–42).

Furthermore, in our subgroup analyses to further understand the insulin reductions after exercise intervention, a larger reduction

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Table 1. Characteristics of the selected studies

Author (year)	Design	Participants	Intervention	Adherence	Results	
					Biomarkers	Other variables
Bower and colleagues (2014)	Two-arm RCT; yoga intervention vs. health education control	31 stage 0–II breast cancer patients (29 completed); mean age = 54.4 ± 5.7 y; BMI > 31; posttreatment; postmenopausal only	Iyengar yoga, supervised, group-based, 12 wks, 2 d/wk, 90 min	77.5%	IL6, CRP, TNF receptor type II, IL1, gene expressions, salivary cortisol	Fatigue, depression, stress, sleep, physical performance
Rogers and colleagues (2014)	Two-arm RCT; exercise vs. usual care	46 stage I–II breast cancer patients (42 completed); mean age = 56.2 ± 7.7 y; mean BMI = 31.2; at least 4 wks posttreatment; postmenopausal only	Combined, 12 wks; aerobic exercise, 160 min/wk, moderate-intensity walking; resistance exercise with resistance bands, 2 d/wk	92%	IL6, IL8, IL10, TNFα	Fatigue, physical activity level, BMI, WHR, %BF, muscle strength, VO_{2max}, depression
Ergun and colleagues (2012)	Three-arm RCT; Resistance EG + education (REG) vs. Aerobic EG + education (AEG) vs. education only (ED)	60 breast cancer patients (58 completed); aged 18 to 65 y; mean BMI (kg/m^2) = 26.6 ± 4.4 (REG), 28.6 ± 5.2 (AEG), 28.6 ± 5.1 (ED); posttreatment; postmenopausal only	Resistance exercise, supervised, 12 wks, 3 d/wk, 45 min Aerobic brisk walking, home-based, 3 d/wk, 30 min Education program was provided to all 3 groups for 30 min/wk	Not reported	IL6, TNFα, and angiogenesis- and apoptosis-related molecules	Not reported
Guinan and colleagues (2013)	Two-arm RCT; exercise vs. usual care	26 stage I–III breast cancer patients (22 completed); mean age = 48.1 ± 8.8 y; BMI (kg/m^2) > 35; 2 to 6 mo posttreatment; 69.2% postmenopausal	Aerobic program, 8 wks, from 35% to 75% HRR; supervised, 2 d/wk, 60 min; home-based, from 1 to 5 d/wk	Not reported	Insulin, glucose, IR, HbA1c, CRP	WC, SBP, DBP, TC, HDL-C, LDL-C, TC:HDL-C ratio, TG
Karimi and colleagues (2013)	Four-arm RCT; water-based exercise (EX) vs. ginger supplement (GS) vs. EX + GS vs. placebo	40 stage I–II breast cancer patients; mean age = 48 ± 6 y; mean BMI (kg/m^2) = 32.4; posttreatment	Aerobic exercise, water-based, 6 wks, 4 d/wk, 50%–75% HRR	Not reported	Adiponectin[a,b] and oxidative stress markers	Not reported
Thomas and colleagues (2013) Jones and colleagues (2012) Irwin and colleagues (2009)	Two-arm RCT; exercise (EG) vs. usual care (CG)	75 stage 0–IIIA breast cancer patients (68 completed); mean age = 56.4 ± 9.6 y for EG, 55.4 ± 7.6 y for CG; mean BMI = 30.6 ± 6.0 (EG), 29.4 ± 7.3 (CG); 6 mo posttreatment; postmenopausal only	Aerobic exercise (primarily walking), 24 wks, supervised 3 d/wk and home-based 2 d/wk, 45–150 min	56%	Insulin, glucose[b], IGF1[b], IGFBP3[b], IL6, CRP, TNFα	WC, SBP, DBP, HDL-C, TG, metabolic syndrome score
Nuri and colleagues (2012)	Two-arm RCT; exercise (EG) vs. usual care (CG)	32 stage I–IIIB breast cancer patients (29 completed); aged 50—65 y; mean BMI (kg/m^2) = 27.9 ± 3.5 (EG), 27.4 ± 3.4 (CG); 6 mo posttreatment; postmenopausal only	Combined; aerobic walking exercise, supervised, 15 wks, 2 d/wk, 35 to 45 min, 45% to 65% THR; resistance training; 15 wks, 2 d/wk	Not reported	Insulin[a,b], glucose[a,b], IR	Weight[a,b], BMI[a,b], WC, HC, WHR[a,b], SBP[a,b], VO_{2peak}[a,b], HDL-C[a,b], TG[a,b]
Rogers and colleagues (2012)	Two-arm RCT; exercise (EG) vs. usual care (CG)	28 stage I–IIIA breast cancer patients (22 completed); mean age = 56 ± 10.5 y; mean BMI (kg/m^2) = 33.9 ± 7.4 (EG), 30.3 ± 7.1 (CG); posttreatment; 86% postmenopausal	Combined, 12 wks (supervised 6 wks, unsupervised 6 wks); aerobic exercise, 150 min/wk, moderate intensity; resistance exercise, 2 d/wk	86.5%	Adiponectin, HMWA, IL6, TNFα, leptin[b], other inflammatory-related markers	BMI, FM, WHR, muscle strength

(Continued on the following page)

Table 1. Characteristics of the selected studies (Cont'd)

Author (year)	Design	Participants	Intervention	Adherence	Results	
					Biomarkers	Other variables
Sprod and colleagues (2012)	Two-arm RCT; Tai Chi Chuan (TCC) exercise vs. standard support therapy (SST)	35 stage 0–IIIB breast cancer patients (21 completed); mean age = 54.3 ± 3.6 (TCC) y, 52.7 ± 2.1 (SST) y; mean BMI (kg/m^2) = 24.9 ± 1.9 (TCC), 25.0 ± 1.4 (SST); 1 wk to 30 mo posttreatment	Aerobic TCC exercise, supervised, 12 wks, 3 d/wk, 60 min, low to moderate intensity	72%	Insulin, glucose, IGF1, IGFBP1, IGFBP3, IL6, and other cytokines	Weight, BMI[b], FM, LM
Gomez and colleagues (2011)	Two-arm RCT; exercise vs. usual care	20 stage I–II breast cancer patients (16 completed); aged 40 to 60 y; 2–5 y posttreatment; postmenopausal	Combined, aerobic (primarily cycle ergometer) and resistance exercise, 8 wks, 3 d/wk, 90 min, 70%–80% HR_{max}	91%	IL6, TNFα, and other cytokines	Weight, %BF[b], FM, LM[b], $VO2_{peak}$[b], muscle strength[b]
Ligibel and colleagues (2008, 2009)	Two-arm RCT; exercise (EG) vs. usual care (CG)	101 stage I–III breast cancer patients (82 completed); mean age = 52 ± 9 (EG) y, 53 ± 9 (CG) y; BMI (kg/m^2) > 25 or %BF > 30, mean BMI = 30.3 ± 5.9 (EG), 31.4 ± 6.8 (CG); 3 months post-treatment; 84% postmenopausal	Combined, 16 wks; aerobic exercise, home-based, 90 min/wk; resistance exercise, supervised, 2 d/wk, 50 min	73%	Insulin, glucose, IR, adiponectin, HMWA, leptin	Weight, BMI, %BF, WC[a], HC[a,b], WHR
Hutnick and colleagues (2005)	Two-arm RCT; exercise (EG) vs. usual care (CG)	49 stage I–III breast cancer patients; aged 25 to 80 y, mean age = 48.5 ± 10 (EG) y, 52.3 ± 9.2 (CG) y; mean BMI (kg/m^2) = 26.7 ± 5.4 (EG), 26.6 ± 4.1 (CG); immediately after treatment	Combined, aerobic and resistance exercise, 24 wks (supervised 12 wks and unsupervised 12 wks), 3 d/wk., 40–90 min, 60%–75% functional capacity	Not reported	IL6 and lymphocyte activation markers	Weight, BMI, %BF, muscle strength*
Schmitz and colleagues (2005)	Two-arm RCT; immediate exercise (IE) vs. delayed exercise (DE)	85 stage I–III breast cancer patients (78 completed); mean age = 53.3 ± 8.7 (IE) y, 52.8 ± 7.6 (DE) y; mean BMI (kg/m^2) = 25.9 ± 0.7 (IE), 25.8 ± 0.7 (DE); 4–36 mo posttreatment; 77.8% postmenopausal	Resistance exercise, 24 wks (supervised 12 wks and unsupervised 12 wks), 2 d/wk, 60 min	92%	Insulin, glucose, IR, IGF1, IGF2[b], IGFBP1, IGFBP2, IGFBP3	Insulin, glucose, IR, IGF1, IGF2[b], IGFBP1, IGFBP2, IGFBP3
Fairey and colleagues (2003, 2005)	Two-arm RCT; exercise vs. usual care	53 stage I–IIIA breast cancer patients (42 completed); aged 50 to 69 y, mean age = 59 ± 6 y; mean BMI (kg/m^2) = 29.2 ± 6.6; posttreatment; 12 mo postmenopausal	Aerobic exercise (recumbent or upright cycle ergometer), 15 wks, 3 d/wk, 15–35 min, 70%–75% maximal oxygen consumption	98.4%	Insulin, glucose, IR, IGF1[b], IGF2, IGFBP1, IGFBP3[b], IGF1: IGFBP3 ratio[b], CRP	Weight, BMI, skinfolds, TC, HDL-C, LDL-C, TG[b], TC:HDL-C ratio, SBP, DBP, RHR, HRR[b], VO_{2peak}[b]

Abbreviations: %BF, percent body fat; DBP, diastolic blood pressure; FM, fat mass; HbA1c, glycosylated hemoglobin A1c; HC, hip circumference; HDL-C, high-density lipoprotein cholesterol; HMWA, high-molecular-weight adiponectin; HRR, heart rate reserve; LDL-C, low-density lipoprotein cholesterol, LM, lean mass; RHR, resting heart rate; SBP, systolic blood pressure; TC, total cholesterol; TG, triglycerides; WC, waist circumference; WHR, waist–hip ratio.

[a]Significantly different within exercise group after intervention.

[b]Significantly different between exercise and control groups after intervention.

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Table 2. Methodologic quality and risk of bias of the selected studies

Author (year)	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Complete outcome data	Selective reporting (ITT analysis)	Other bias
Bower and colleagues (2014)	+	+	−	+	+	−	+
Rogers and colleagues (2014)	+	+	+	?	+	−	+
Ergun and colleagues (2013)	+	?	?	+	+	?	+
Guinan and colleagues (2013)	+	?	−	+	−	+	+
Karimi and colleagues (2013)	+	?	−	?	+	?	?
Thomas and colleagues (2013)	+	?	?	?	−	+	+
Jones and colleagues (2012)	+	?	?	+	+	+	+
Nuri and colleagues (2012)	+	?	?	+	+	?	+
Rogers and colleagues (2012)	+	?	?	+	+	−	+
Sprod and colleagues (2012)	+	+	−	−	+	−	+
Gomez and colleagues (2011)	+	+	−	+	+	−	+
Irwin and colleagues (2009)	+	?	?	+	+	+	+
Ligibel and colleagues (2008, 2009)	+	?	?	−	+	+	+
Hutnick and colleagues (2005)	+	?	−	?	+	−	+
Schmitz and colleagues (2005)	+	+	+	+	+	+	+
Fairey and colleagues (2003, 2005)	+	+	+	+	+	+	+

Abbreviations: +, low risk of bias; −, high risk of bias; ?, unclear risk of bias; ITT, intention-to-treat.

was found in studies that reported concurrent weight reduction with exercise. These findings support previous studies that modest weight loss was associated with improvement in insulin sensitivity and glucose tolerance (43–45). Mason and colleagues (46) performed a 12-month-long lifestyle modification program (diet alone, diet + exercise, exercise alone) and found that the magnitude of weight loss was associated with metabolic improvement in insulin, C-peptide, glucose, and HOMA-IR. However, there are also studies which found significant improvement in insulin sensitivity in response to exercise without significant weight loss (47, 48). However, our study found that weight loss is necessary to observe the effect of exercise on circulation insulin level. Because both lack of physical activity and obesity contribute to IR via different pathophysiology, an exercise intervention accompanied with a reduction in adiposity increases the chance of improvement in insulin sensitivity (38, 39, 49, 50).

Given that higher serum insulin levels indirectly lead to elevated IGF1 and reduced levels of the binding proteins (51, 52), contributing to carcinogenesis and increased risk of cancer development (53, 54), we further performed a meta-analysis to study the effect of exercise on circulating IGF axis, but no significant changes in IGF1 and IGFBP3 after the exercise intervention were found. However, a few previous meta-analysis (10, 55) found that exercise significantly reduced IGF1 (WMD, −12.0 ng/mL; 95% CI, −23.3 to −0.5; $P = 0.04$) in posttreatment breast cancer survivors, which was inconsistent with our findings. This discrepancy may be explained when considering that our study updated by adding data from Sprod and colleagues (25) in this meta-analysis. Given that Sprod and colleagues (25) found a substantial but insignificant decrease in IGF1 (−10.68 ng/mL; 95% CI, −27.00 to 5.64; $P = 0.69$) in the exercise group compared with the control group, the pooled effect of exercise on IGF1 did not reach statistical significance in our analysis. This may be a result of lack of statistical power due to small sample sizes of individual studies, as well as the heterogeneity between the studies.

Adiponectin did not significantly increase after the exercise intervention in this meta-analysis. A previous meta-analysis from 13 cohort studies with 3,578 breast cancer cases and 4,363 controls reported that an elevated level of adiponectin was associated with a decreased breast cancer risk (OR, 0.838; 95% CI, 0.744–0.943; ref. 56). Other observational studies have also supported that adiponectin is inversely related to a risk of breast cancer (57–59). *In vivo* and *in vitro* studies have reported that adiponectin may play an important role in promoting apoptotic and antiproliferative responses against breast cancer cells (60, 61). In a normal healthy population, 8 RCTs have examined the effects of exercise on adiponectin; however, only one third of the RCTs demonstrated a positive effect of exercise, indicating that exercise increases serum adiponectin level with small-to-moderate effect sizes (62). In our meta-analysis, we found a statistically nonsignificant but noteworthy increment in the adiponectin level (WMD, 1.17 μU/mL; 95% CI, −0.87 to 3.20; $P = 0.26$), indicating that the positive effect of exercise on adiponectin in patients with breast cancer is still uncertain.

Upregulated inflammation-related adipocytokines, including IL6 and TNFα, are poor prognosticators in patients with breast

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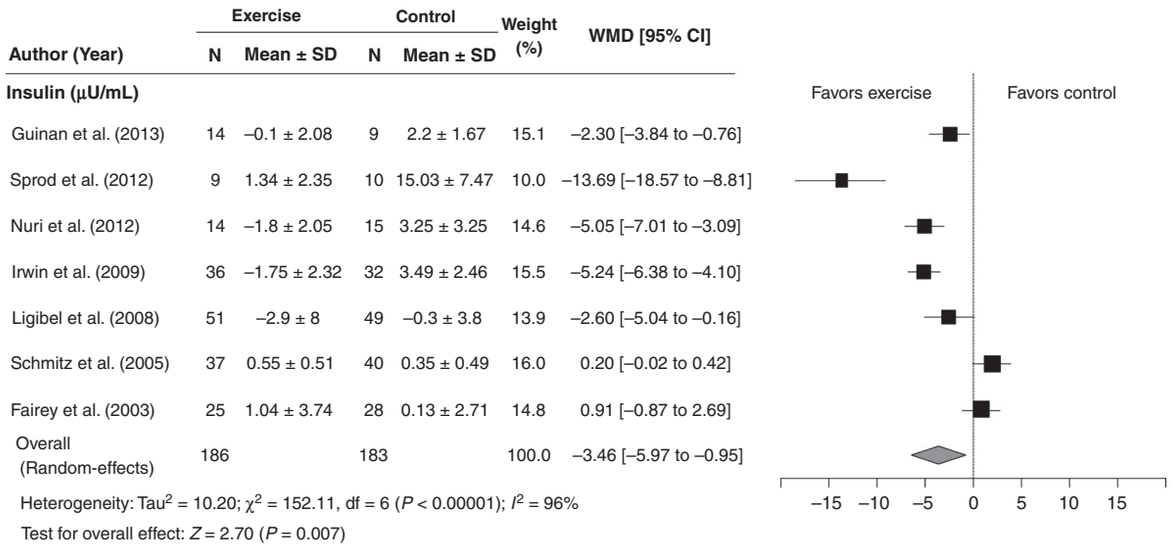

Figure 2.

Pooled effect of exercise on insulin in breast cancer survivors. Studies were ordered according to the publication year. Heterogeneity among studies was determined using Higgin I^2 statistics, and a random-effects model was used for insulin ($I^2 > 50\%$, heterogeneous). There was a significant effect of exercise on insulin reduction. SMD, standardized mean difference.

cancer (63, 64). Increased IL6 (65) and TNFα (66) have been suggested to promote angiogenesis, resulting in breast tumor proliferation. In addition, CRP, as an indicator of acute infection or inflammation, may not only be a diagnostic and prognostic marker (67) but also plays a role in promoting carcinogenesis and angiogenesis (68, 69). In our meta-analysis, we did not find significant changes in IL6 and TNFα, although CRP showed an insignificant but potentially meaningful reduction in response to the exercise interventions. Similar to adiponectin, the effects of exercise on IL6, TNFα, and CRP do not appear to be consistent among studies, implying that further large RCTs are needed.

We have provided the evidence from the meta-analyses for the first time that exercise intervention has a significant effect on insulin reduction in patients with breast cancer, which may be a key mechanism between exercise and better prognosis in breast cancer. In our subgroup analyses, weight change appeared as a potential mediating factor in insulin reduction, emphasizing the importance of weight control for patients with breast cancer. Furthermore, we examined the effects of exercise on IGF-axis and inflammatory markers that have been known to be related to breast cancer prognosis. However, it should be acknowledged that various other molecular parameters may interfere with the outcome, which has not been analyzed in this study.

However, there are important points to be addressed in understanding the lasting effect of exercise and its relationship with cytokines. Although the positive effects of exercise on several biomarkers in breast cancer survivors are promising, we should note that a several-week exercise intervention would not result in permanent changes in biomarkers. For example, the effects of not only a single bout of exercise but also weeks of exercise training on fasting insulin are lost after cessation of exercise (70). However, this does not imply that there is no lasting effect of exercise; studies have shown that insulin reduction during and immediately after exercise is greater in the exercise training group. This suggests that although there may be little effect of exercise on sustained insulin reduction, a several-week of exercise intervention could lastingly increase insulin sensitivity using glucose transporter type 4 mechanisms (38), which may further cause greater insulin reduction in response to exercise. However, these mechanisms are in conjunction with a broad range of cells releasing cytokines, including adipose cells, B and T lymphocytes, and macrophages (71, 72). The short- and long-term effects of exercise on these cells and the cytokines have not been well-understood and may not identically apply to insulin, IGF axis, cytokines, and inflammatory markers; future studies should investigate the long-lasting effect of exercise on the biomarkers.

There are several limitations to this study. First, only a small number of RCTs examined the effects of exercise on any specific biomarker in patients with breast cancer, so the effects of exercise may not be definitive. RCTs with larger sample sizes are needed to better understand the effects and mechanisms of exercise on biomarkers in breast cancer survivors. Second, lack of available data from selected studies restricted potentially important analysis such as menopause or hormone receptor status (73). Larger numbers of RCTs are needed to analyze the effects of different types of exercise and subgroup analyses according to menopausal status and hormonal receptor status. Third, given that the characteristics of exercise intervention, including exercise type, setting, frequency, intensity, time, and intervention period, were varied across the studies, the effects of exercise on the biomarkers may be controversial. Subgroup analysis based on the features of exercise intervention seems necessary for future studies, which is currently limited due to lack of the number of studies. Last, this meta-analysis did not adjust potential confounding factors, including sex, age, and BMI, that might influence outcome variables. To better understand the independent effect of exercise on biomarkers in patients with breast cancer, future studies may use a meta-regression model to adjust potential confounding factors.

Improving cancer survivorship has been one of our primary concerns and participating in physical activity is a promising

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Author (Year)	Exercise N	Exercise Mean ± SD	Control N	Control Mean ± SD	Weight (%)	WMD [95% CI]
Glucose (mg/dL)						
Thomas et al. (2013)	35	−1.31 ± 7.16	30	0.6 ± 7.12	17.4	−1.91 [−5.39 to −1.57]
Guinan et al. (2013)	15	0.6 ± 2.91	10	−0.4 ± 2.76	22.4	1.00 [−1.26 to 3.26]
Sprod et al. (2012)	9	5.78 ± 2.86	10	3.5 ± 7.1	12.9	2.28 [−2.50 to 7.06]
Nuri et al. (2012)	14	−9.4 ± 11.37	15	8.9 ± 13.96	5.2	−18.30 [−27.54 to −9.06]
Ligibel et al. (2008)	40	−3.1 ± 19.4	42	−0.4 ± 12.8	7.7	−2.70 [−9.85 to 4.45]
Schmitz et al. (2005)	39	−3.7 ± 1.71	41	−3.38 ± 1.66	27.7	−0.32 [−1.06 to 0.42]
Fairey et al. (2003)	25	−1.26 ± 18.02	28	−2.9 ± 9.01	6.8	1.64 [−6.17 to 9.45]
Overall (Random-effects)	177		176		100.0	−0.95 [−3.27 to 1.38]
Heterogeneity: Tau^2 = 4.94; χ^2 = 18.46, df = 6 (P = 0.005); I^2 = 68%						
Test for overall effect: Z = 0.80 (P = 0.42)						
Insulin Resistance						
Guinan et al. (2013)	14	0.1 ± 0.36	9	0.5 ± 0.29	29.5	−0.40 [−0.67 to −0.13]
Nuri et al. (2012)	14	−0.4 ± 0.96	15	0.4 ± 1.78	8.2	−0.80 [−1.83 to 0.23]
Ligibel et al. (2008)	40	−0.8 ± 2.5	42	−0.04 ± 1.1	11.0	−0.76 [−1.60 to 0.08]
Schmitz et al. (2005)	38	0.05 ± 0.15	41	0.05 ± 0.14	35.8	0.00 [−0.06 to 0.06]
Fairey et al. (2003)	25	0.4 ± 1.4	28	0 ± 0.9	15.5	0.40 [−0.24 to 1.04]
Overall (Random-effects)	131		135		100.0	−0.20 [−0.54 to 0.13]
Heterogeneity: Tau^2 = 0.08; χ^2 = 14.91, df = 4 (P = 0.005); I^2 = 73%						
Test for overall effect: Z = 1.20 (P = 0.23)						
IGF-1 [ng/mL]						
Sprod et al. (2012)	9	−27.32 ± 15.02	10	−16.64 ± 21.03	22.4	−10.68 [−27.00 to 5.64]
Irwin et al. (2009)	36	−7.36 ± 6.02	32	12.7 ± 6.39	26.1	−20.06 [−23.02 to −17.10]
Schmitz et al. (2005)	39	8.29 ± 6.26	40	−3.97 ± 6.1	26.1	12.26 [9.53 to 14.99]
Fairey et al. (2003)	25	−4.9 ± 10.7	28	2.5 ± 14.8	25.4	−7.40 [−14.30 to −0.50]
Overall (Random-effects)	109		110		100.0	−6.31 [−26.57 to 13.96]
Heterogeneity: Tau^2 = 457.99; χ^2 = 250.25, df = 3 (P < 0.00001); I^2 = 99%						
Test for overall effect: Z = 0.61 (P = 0.54)						
IGFBP-3 [ng/mL]						
Sprod et al. (2012)	9	89.0 ± 104.0	10	−70.0 ± 119.0	23.8	159.0 [58.7 to 259.3]
Irwin et al. (2009)	36	−190.0 ± 80.0	32	−150.0 ± 100.0	28.1	−40.0 [−83.4 to 3.4]
Schmitz et al. (2005)	38	16.6 ± 85.9	40	135.3 ± 83.8	28.3	−118.8 [−156.5 to −81.1]
Fairey et al. (2003)	25	103.4 ± 224.7	28	−77.1 ± 313.5	19.8	180.5 [34.8 to 326.3]
Overall (Random-effects)	108		110		100.0	28.7 [−85.2 to 142.6]
Heterogeneity: Tau^2 = 11,548.07; χ^2 = 38.93, df = 3 (P < 0.00001); I^2 = 92%						
Test for overall effect: Z = 0.49 (P = 0.62)						

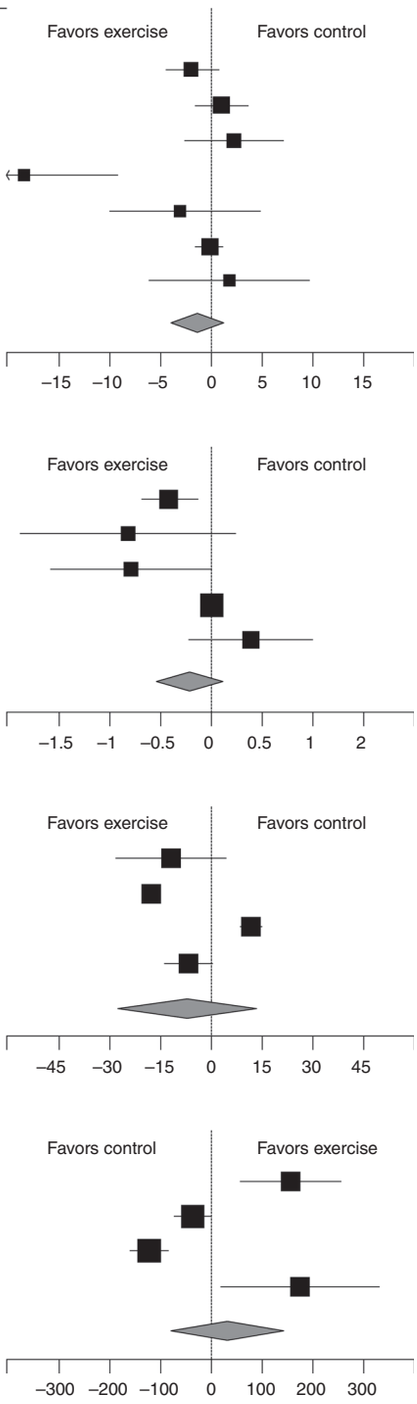

Figure 3.

Pooled effect of exercise on glucose, IR, IGF1, and IGFBP3 in breast cancer survivors. Studies were ordered according to the publication year. Heterogeneity among studies was determined using Higgin I^2 statistics, and a random-effects model was used for glucose, IR, IGF1, and IGFBP3 (I^2 > 50%, heterogeneous). There was no significant effect of exercise on glucose, IR, IGF1, and IGFBP3. SMD, standardized mean difference.

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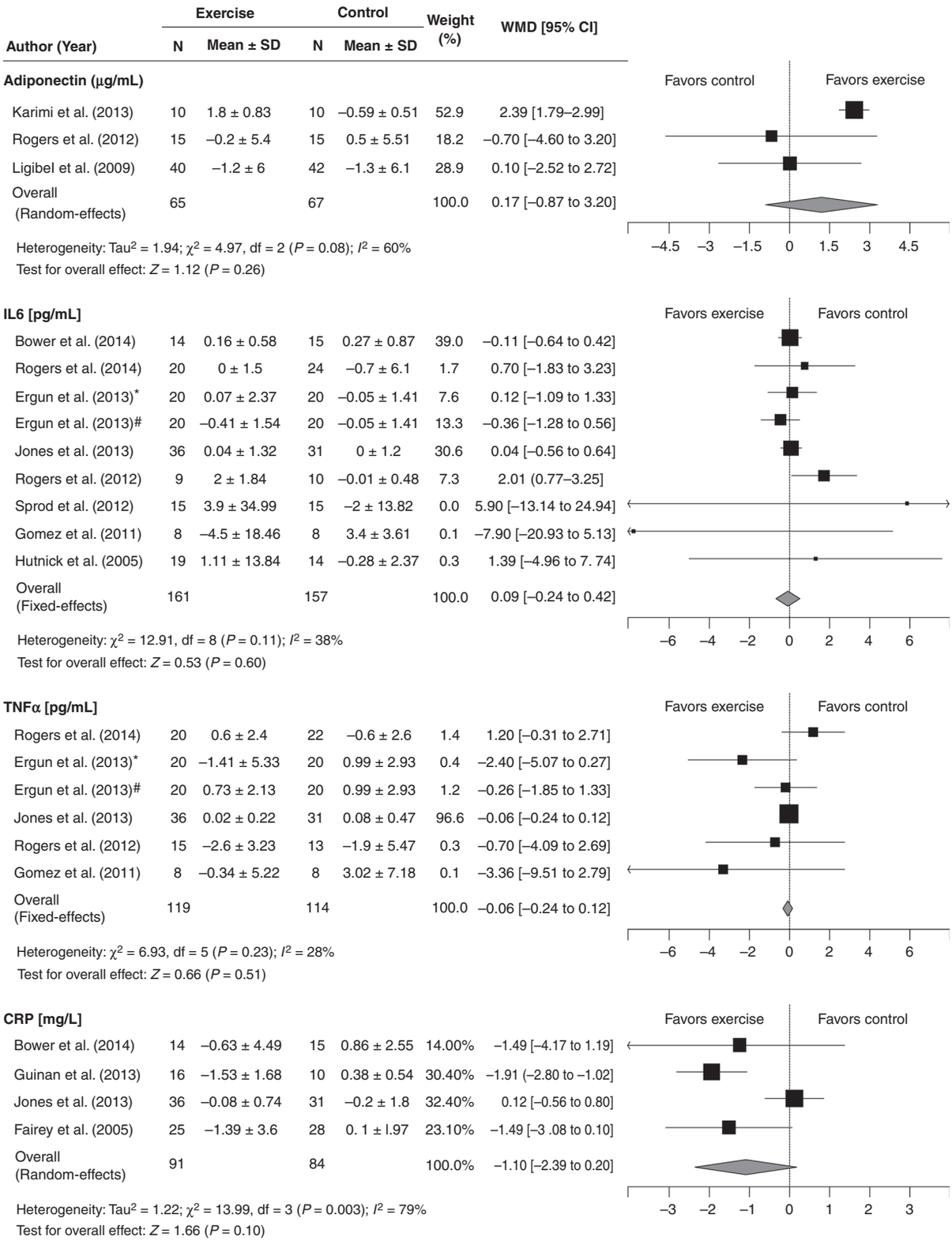

Figure 4.

Pooled effect of exercise on adiponectin, IL6, TNFα, and CRP in breast cancer survivors. Studies were ordered according to the publication year. Heterogeneity among studies was determined using Higgin I^2 statistics. A random-effects model was used (I^2 > 50%, heterogeneous) for adiponectin and CRP, and a fixed-effects model was used for IL6 and TNFα ($I^2 \leq 50\%$, nonheterogeneous). There was no significant effect of exercise on adiponectin, IL6, TNFα, and CRP. SMD, standardized mean difference; *, supervised exercise intervention; #, home-based exercise intervention.

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therapy for better survivorship. It has been well-established that exercise is feasible and beneficial for breast cancer survivors regarding managements of side effects including depression, poor quality of life, fatigue, and loss of physical function and fitness. However, in terms of minimizing risks of recurrence and mortality, the optimal frequency, intensity, time, and type (FITT) of exercise, as well as mechanisms between exercise and cancer, are relatively uncertain. Furthermore, this benefit may be more substantial when accompanied by weight reduction. However, there is still lack of evidence. Future studies should be large RCTs concentrating on cancer-related biomarkers, as surrogate markers for long-term survivorship, and different modalities of exercise such as resistance exercise or high-intensity exercise. Therefore, practitioners and clinicians may better help breast cancer prognosis be improved through exercise, anticipating physiological effects on cancer.

In conclusion, this was the first meta-analysis to our knowledge which found a significant reduction in fasting insulin levels after exercise intervention. In addition, we suggest that concurrent weight reduction is needed to have greater decrease in circulating insulin levels in breast cancer survivors. However, RCTs with larger sample sizes and different subgroups of breast cancer survivors according to medical and hormonal status are needed to confirm the effect of exercise on other biomarkers.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Authors' Contributions

Conception and design: D.-W. Kang, J. Lee, S.-H. Suh, J.A. Ligibel, K.S. Courneya, J.Y. Jeon
Development of methodology: D.-W. Kang, J. Lee, K.S. Courneya
Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): D.-W. Kang, J. Lee
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): D.-W. Kang, J. Lee, J.A. Ligibel, K.S. Courneya
Writing, review, and/or revision of the manuscript: D.-W. Kang, J. Lee, J.A. Ligibel, K.S. Courneya, J.Y. Jeon
Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): D.-W. Kang
Study supervision: J.Y. Jeon

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Effects of Exercise on Insulin, IGF Axis, Adipocytokines, and Inflammatory Markers in Breast Cancer Survivors: A Systematic Review and Meta-analysis

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