Integrative Cancer Therapies
2018, Vol. 17(2) 192–199
© The Author(s) 2018
Reprints and permissions:
sagepub.com/journalsPermissions.nav
DOI: 10.1177/1534735418756193
journals.sagepub.com/home/ict
SAGE

Meta-analysis of Exercise Training on Vascular Endothelial Function in Cancer Survivors

Rhys I. Beaudry, MS[1], Yuanyuan Liang, PhD[2], Steven T. Boyton, MS[1], Wesley J. Tucker, PhD[1], R. Matthew Brothers, PhD[1], Kathryn M. Daniel, PhD[1], Roshni Rao, MD[3], and Mark J. Haykowsky, PhD[1]

Abstract

Cancer and cardiovascular disease (CVD) are leading causes of morbidity and mortality in the United States. Vascular endothelial dysfunction, an important contributor in the development of CVD, improves with exercise training in patients with CVD. However, the role of regular exercise to improve vascular function in cancer survivors remains equivocal. We performed a meta-analysis to determine the effect of exercise training on vascular endothelial function in cancer survivors. We searched PubMed (1975 to 2016), EMBASE CINAHL (1937 to 2016), OVID MEDLINE (1948 to 2016), and Cochrane Central Registry of Controlled Trials (1991 to 2016) using search terms: *vascular function*, *endothelial function*, *flow-mediated dilation* [FMD], *reactive hyperemia*, *exercise*, and *cancer*. Studies selected were randomized controlled trials of exercise training on vascular endothelial function in cancer survivors. We calculated pooled effect sizes and performed a meta-analysis. We identified 4 randomized controlled trials (breast cancer, n=2; prostate cancer, n=2) measuring vascular endothelial function by FMD (n=3) or reactive hyperemia index (n=1), including 163 cancer survivors (exercise training, n=82; control, n=81). Aerobic exercise training improved vascular function (n=4 studies; standardized mean difference [95% CI]=0.65 [0.33, 0.96], I^2=0%; FMD, weighted mean difference [WMD]=1.28 [0.22, 2.34], I^2=23.2%) and peak exercise oxygen uptake (3 trials; WMD [95% CI]=2.22 [0.83, 3.61] mL/kg/min; I^2=0%). Our findings indicate that exercise training improves vascular endothelial function and exercise capacity in breast and prostate cancer survivors.

Keywords

exercise training, vascular endothelial function, cancer, meta-analysis

Submitted August 24, 2017; revised December 9, 2017; accepted December 13, 2017

Introduction

Cancer and cardiovascular disease (CVD) are the leading causes of mortality in the United States.[1] As a result of advances in cancer prevention, early detection, and novel treatment therapies, the cancer mortality rate has decreased by 23% during the past 3 decades.[1] Despite this benefit, cancer survivors are at increased risk for CVD-related mortality.[2,3] Indeed, Armenian *et al.*[3] recently reported that 8-year overall survival is significantly lower among cancer survivors who developed CVD than among cancer survivors without CVD.

In accordance with the "multiple-hit" hypothesis, the increased CVD mortality in cancer survivors is the result of underlying cardiovascular risk factors combined with direct effects of anticancer therapy (eg, cardiotoxicity) and direct effects of a sedentary lifestyle.[5] Cancer survivors' cardiorespiratory fitness, measured objectively as peak aerobic capacity (peak VO_2), is ~25% lower relative to healthy, age- and sex-matched individuals and is an independent predictor of mortality in advanced lung and breast

[1]The University of Texas at Arlington, Arlington, TX, USA
[2]University of Maryland School of Medicine, Baltimore, MD, USA
[3]University of Texas Southwestern Medical Center, Dallas, TX, USA

Corresponding Author:
Mark J. Haykowsky, College of Nursing and Health Innovation, The University of Texas at Arlington, 523 Pickard Hall, 411 South Nedderman Drive, Arlington, TX 76019, USA.
Email: mark.haykowsky@uta.edu

Creative Commons Non Commercial CC BY-NC: This article is distributed under the terms of the Creative Commons Attribution-NonCommercial 4.0 License (http://www.creativecommons.org/licenses/by-nc/4.0/) which permits non-commercial use, reproduction and distribution of the work without further permission provided the original work is attributed as specified on the SAGE and Open Access pages (https://us.sagepub.com/en-us/nam/open-access-at-sage).

cancer.[5-7] The reduced peak VO_2 in breast cancer survivors is partly a result of impaired peripheral vascular function that results in reduced blood flow and oxygen delivery to the active muscles.[7-10] Studies in adult cancer survivors report better,[11-13] not different,[14-16] or impaired[8,10,17] vascular endothelial function relative to age-matched controls.

The endothelium plays a direct role in the balance of tissue oxygen supply and metabolic demand by regulating vessel tone at rest and during exercise.[18] Endothelial dysfunction impairs the endothelium's ability to dilate in response to a variety of vasodilatory stimuli such as intra-arterial infusion of the endothelium-dependent vasodilator acetylcholine or shear stress. As such, endothelial dysfunction can limit blood flow and perfusion of skeletal muscle and organs. Furthermore, endothelial dysfunction has important clinical implications in that it represents an initial, reversible step in the development of atherosclerotic CVD.[19] Endothelial dysfunction leads to upregulation of adhesion molecules (increased leukocyte adherence), chemokine/cytokine secretion, increased vessel permeability, low-density lipoprotein oxidation, platelet activation, and vascular smooth muscle proliferation.[20-22] Flow-mediated dilation (FMD) is currently the standard for noninvasive assessment of large conduit artery endothelial function because of considerable clinical trial experience and validation and its association with cardiovascular events.[18,23,24] In this method, large conduit artery diameter (typically brachial) is measured by Doppler ultrasound before and after an increase in shear stress induced by reactive hyperemia, with vasodilation occurring through local endothelial release of nitric oxide (NO).[25]

In both healthy and diseased populations, exercise training is associated with favorable improvements in endothelial function[26,27] and peak VO_2.[28-30] Moreover, studies in diseased populations found that an increase in peak VO_2 correlated strongly with improvements in vascular endothelial function.[31,32] Functional vascular adaptations (improved ability to accommodate blood flow through vasodilation) elicited with exercise training appear to precede morphological changes (skeletal muscle hypertrophy, vascular and cardiac remodeling) and yield greater oxygen delivery to active muscles.[27,33]

Previous studies have demonstrated the role of exercise training for increasing peak VO_2 in cancer survivors.[28] However, the role of regular exercise to improve vascular endothelial function in cancer survivors remains equivocal. Consequently, we performed a systematic review and meta-analysis to provide pertinent information on CVD risk modulation through exercise training on the primary end point, vascular endothelial function, and the secondary end point, peak VO_2, in cancer survivors.

Methods

Data Sources

The authors (RIB and STB) searched PubMed (1975 to June 2016), EMBASE CINAHL (1937 to June 2016), OVID MEDLINE (1948 to June 2016), and Cochrane Central Registry of Controlled Trials (1991 to June 2016) using the following MESH terms and text words: *vascular function*, *endothelial function*, *reactive hyperemia*, *flow-mediated dilation*, *cancer*, and *exercise*. We also hand searched reference lists of all identified studies.

Study Selection

Two investigators (RIB and STB) independently reviewed the titles and abstracts of all citations to identify studies reporting the effects of exercise training on vascular endothelial function in cancer survivors, defined as any individual with a current or past diagnosis of cancer. Both investigators obtained the full text of potentially relevant articles and independently reviewed those using a pre-standardized data abstraction form and eligibility criteria defined *a priori*. We included randomized controlled trials in cancer survivors with an exercise training intervention (aerobic or resistance training, ≥3 weeks duration) and a measure of vascular endothelial function (FMD, reactive hyperemia).

Data Synthesis and Analysis

Data were analyzed using the change from the preperturbation baseline for both exercise and control groups. Standard deviation of the change was estimated assuming a correlation of 0.5 between baseline and end-of-study measures.[34] Study results were pooled using random effects models. Pooled statistics were calculated using weighted mean differences (WMDs) for outcomes (FMD and peak VO_2) measured using the same methodology and standardized mean differences (SMDs) for vascular endothelial function measured using different scales across studies (ie, FMD and EndoPat). All results were calculated with 95% CIs. Statistical heterogeneity was assed using a χ^2 test that considered a P value of less than .10 to indicate significant heterogeneity. I^2 values were also calculated to quantify variability in effect size; values of 25%, 50%, and 75% described low, moderate, and high heterogeneity, respectively.[35,36]

Results

Study Selection, Evaluation, and Inclusion

We identified 310 citations from electronic databases and by manually scanning references of included studies. After

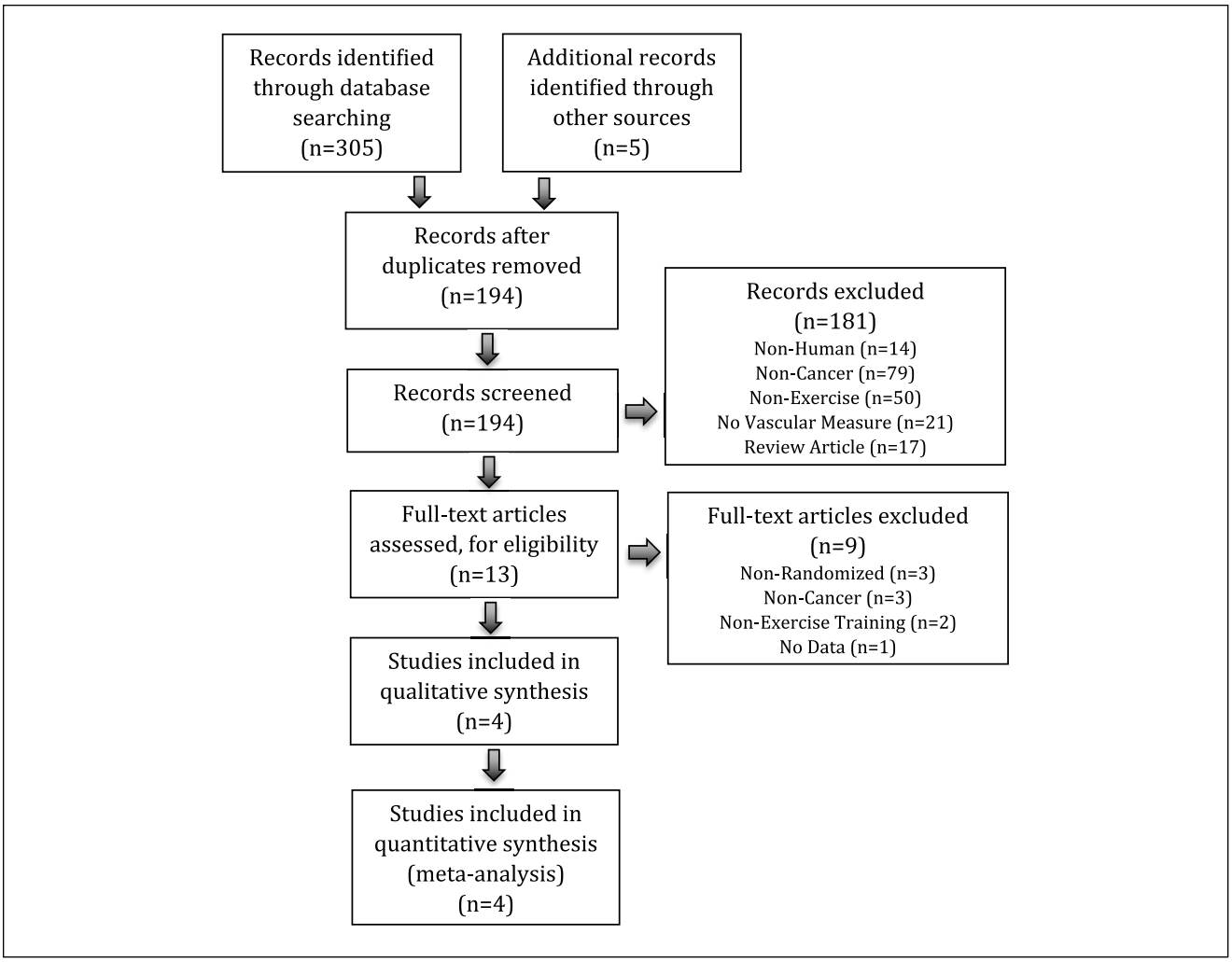

Figure 1. Flow of trials through the selection process.

removal of duplicate publications and initial screening for inclusionary criteria, 13 full articles were reviewed, of which 4 unique randomized controlled trials were identified (exercise training, n = 82; control, n = 81; Figure 1).[17,37-39] The trials included breast (n = 2) and prostate cancer survivors (n = 2) who were middle aged (mean age = 57 ± 7 years). Prostate cancer studies used cohorts of men on long-term androgen deprivation therapy[17] or following surgery (radical prostatectomy).[37] Breast cancer trials used cohorts of women undergoing neoadjuvant doxorubicin-cyclophosphamide therapy[39] or women with a history of invasive breast cancer within the previous 5 years.[38] All trials incorporated aerobic exercise training (n = 82) for 20 to 45 minutes per session at 55% to 75% peak VO_2 (Table 1), 3 days a week, for 3 to 6 months, and one study included a resistance training component.[17] Control groups received usual care. In one study, intervention and control groups received the same dietary intervention,[38] and one study included a dietary education seminar biweekly for the exercise, but not the control group.[17] Risk-of-bias assessment is displayed in Figure 2.

Quantitative Data Synthesis: Exercise Training and Vascular Endothelial Function

Three studies quantified vascular endothelial function by FMD, and 1 study measured reactive hyperemia using the commercially available EndoPAT device to index blood flow response to tissue hypoxia. All studies were pooled, and exercise training was associated with a significant improvement in vascular function (SMD = 0.65 [0.33, 0.96], I^2 = 0%; Figure 3). In the 3 studies measuring FMD, exercise training increased this outcome by approximately 1.3% (WMD = 1.28 [0.22, 2.34]; I^2 = 23.2%) relative to the non–exercise training counterparts.

Table 1. Characteristics of Included Studies.

Study	Cancer Type	Sample Size (n)	Age (years)	BMI (kg/m^2)	Treatment	Exercise Intervention	Vascular Measure
Giallauria et al,[38] 2016	Breast	EXT 25; UC 26	52; 54	27.3 28.2	<5 Years posttherapy	Cycle, 60%-70% VO_{2peak}, 30 minutes, 3 d/wk for 3 months	EndoPAT
Gilbert et al,[17] 2016	Prostate	EXT 22; UC 20	70; 70	30.6 28.8	On ADT	Cycle, rowing, treadmill, 55%-75% HR_{max}, 30 minutes, 3 d/wk for 4 months, plus resistance and balance exercises	FMD
Jones et al,[39] 2013	Breast	EXT 10; UC 10	51; 46	28 27.3	On AC	Cycle, 55%-65% VO_{2peak}, 20-45 minutes, 3 d/wk for 4 months	FMD
Jones et al,[37] 2014	Prostate	EXT 25; UC 25	58; 61	29 28	Postsurgery	Walking, 55%-75% VO_{2peak}, 30-60 minutes, 5 d/wk for 6 months	FMD

Abbreviations: BMI, body mass index; EXT, exercise training; UC, usual care; VO_{2peak}, peak oxygen uptake; ADT, androgen deprivation therapy; HR_{max}, maximal heart rate; FMD, flow-mediated dilation; AC, adriamycin-cyclophosphamide.

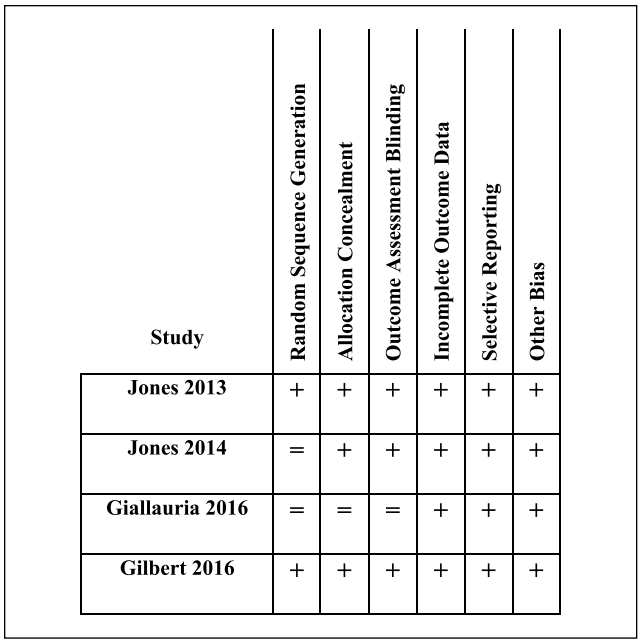

Figure 2. Risk of bias assessment.[a]
[a] +, Low risk of bias; =, unclear risk of bias; -, high risk of bias.

Additional End Points

Three studies examined the effect of exercise training on peak VO_2 with 60 participants in the exercise groups and 61 participants in the control groups. Pooled data indicated that exercise training was associated with a statistically significant increase in peak VO_2 (WMD = 2.22 mL/kg/min [0.83, 3.61], $I^2 = 0\%$; Figure 4).

Discussion

The principal new finding of this meta-analysis is that exercise training is associated with a significant improvement in vascular endothelial function and peak VO_2 in both breast and prostate cancer survivors. The absolute change in FMD that we found (1.3%) is similar in magnitude to that in other publications reporting the effect of exercise training on vascular function in healthy and diseased populations.[40-42] Moreover, a 1% increase in FMD is associated with an 8% to 13% reduction in future cardiovascular events[24]; improvements in FMD are indicative of improved CVD risk independent of changes in traditional risk factors such as BMI, blood pressure, or cholesterol.[27] As such, these improvements in vascular endothelial function and exercise capacity observed following exercise training may contribute to improved clinical outcomes in cancer patients.

There are several plausible mechanisms for this observed improvement in vascular endothelial function following exercise training in cancer patients. Prior studies demonstrate that exercise training has a direct effect on both large conduit and resistance artery endothelium-dependent vasodilatory function in humans.[27,33,43] Specifically, Hambrecht *et al.*[32] reported that 4 weeks of cycle training improved acetylcholine responses and adenosine-mediated blood flow in the left internal mammary artery of coronary artery disease patients.[44] Similarly, in populations without severe vascular disease, improvements in vascular function following exercise training are related to endothelial pathways, particularly NO, with little to no change in endothelial-independent smooth muscle

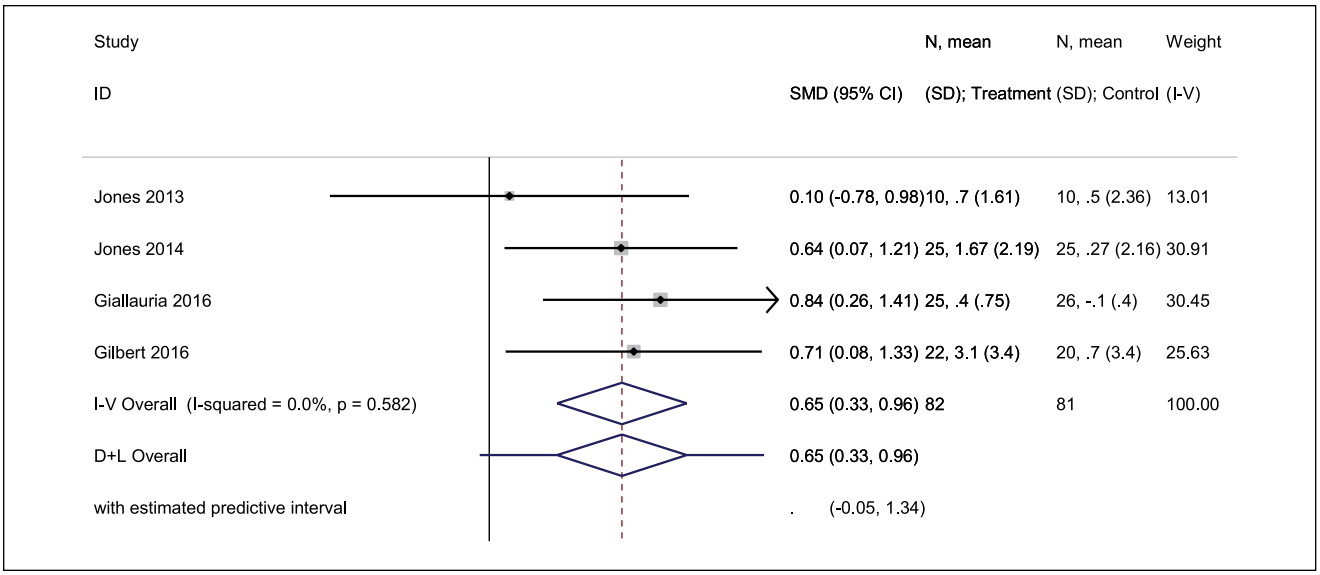

Figure 3. Exercise training and vascular function.
Abbreviations: SMD, standardized mean difference; I-V, inverse variance method (fixed effects model); D+L, DerSimonian and Laird method (random effects model).

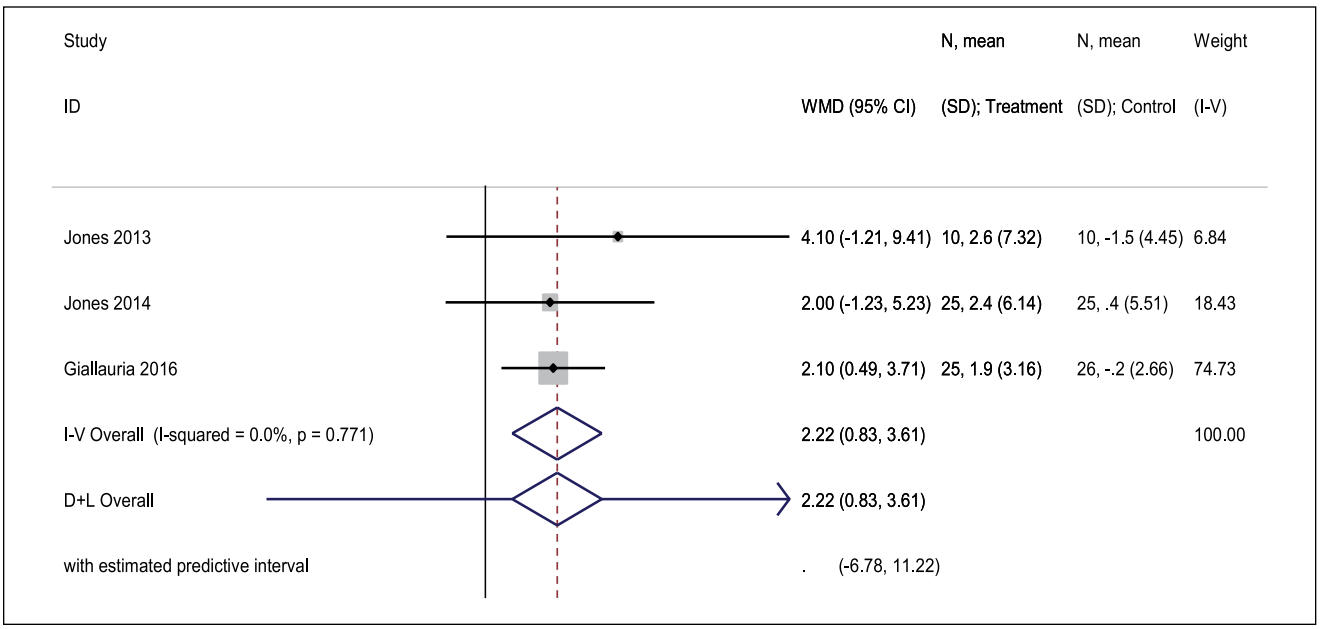

Figure 4. Exercise training and peak VO_2.
Abbreviations: VO_{2peak}, peak oxygen uptake; WMD, weighted mean difference; I-V, inverse variance method (fixed effects model); D+L, DerSimonian and Laird method (random effects model).

function.[43] To date, only 1 study has assessed changes in endothelial-dependent and endothelial-independent vasodilation following exercise training in cancer patients.[17] Gilbert *et al.*[17] showed that 12 weeks of exercise training improved brachial artery FMD (endothelium-dependent vasodilation) by 2.2% in male prostate cancer patients on long-term androgen deprivation therapy, with no change in glyceryl trinitrate–mediated brachial artery vasodilation (endothelium-independent vasodilation). These findings suggest that improvements in peripheral vascular function may be endothelium mediated, with shear stress–mediated enhancements of NO bioactivity.[17]

NO release and magnitude of FMD appears to be dependent on the hyperemic blood flow response.[33,43] Exercise training increases the reactive hyperemia response to ischemia in both healthy and diseased populations.[33,45] In breast

cancer patients, 3 months of cycle exercise training has been shown to improve reactive hyperemia index (RHI) by 19% (measured by peripheral artery tonometry).[38] Furthermore, these favorable improvements in RHI correlated significantly with improvements in VO_{2peak} (ΔVO_{2peak} vs ΔRHI: $r = 0.47$; $P = .017$).

Given that all prior exercise training studies have utilized either FMD or RHI as the measure of changes in vascular function, our mechanistic insights are currently limited to suggesting that exercise training may improve reactive hyperemic and endothelium-dependent pathways in cancer patients.

A consequence of the favorable change in peripheral vascular endothelial function is that it may be associated with increased oxygen delivery to the active muscles and concomitant improvement in peak VO_2.[38,46,47] Indeed, in this meta-analysis, we found that peak VO_2 was significantly higher (WMD = 2.2 mL/kg/min) after exercise training. Several prior meta-analyses found that aerobic training performed during or after adjuvant therapy significantly improved peak VO_2 in cancer survivors, and the magnitude was similar to that in the present meta-analysis.[28,48,49] Importantly, the improvement in vascular endothelial function and peak VO_2 with training may also have prognostic implications because a 3.5 mL/kg/min increase in peak VO_2 is associated with a 12% to 17% decrease in mortality in men and women with and without CVD.[50,51] The mechanisms responsible for increased peak VO_2 are not well known; however, they do not appear to be secondary to improved cardiac function.[9] Specifically, Haykowsky *et al.*[52] found that aerobic training performed during the first 4 months of adjuvant trastuzumab therapy did not improve left-ventricular ejection fraction in response to dobutamine stress in 17 women with HER2+ breast cancer. In a later study, Hornsby *et al.*[53] reported that 12 weeks of moderate- to high-intensity aerobic training did not change resting stroke volume, cardiac output, or left-ventricular ejection fraction in women with operable breast cancer during neoadjuvant chemotherapy. No studies have characterized changes in mitochondrial oxidative capacity or muscle fiber type in breast or prostate cancer, nor changes in autonomic function and blood flow distribution in response to exercise training. Decrements in autonomic function in breast cancer survivors and chemotherapy-treated survivors are reported[54,55]; it is unknown if exercise training can remediate these impairments. The present analysis supports a role of improved vascular endothelial function in improved muscle blood flow and peak VO_2.

Limitations

As with most meta-analyses, our results are constrained by the select diversity of the trial participants, which was limited to breast and prostate cancer survivors. Moreover, our conclusions are drawn from 4 randomized controlled trials and are constrained by the quality of the trials reviewed. Because of the paucity of studies examining the effects of exercise training on vascular endothelial function in cancer survivors, we are unable to analyze modulating factors such as age, cancer type, stage, treatment, gender, time since diagnosis, mode, intensity, and duration of exercise training. Two studies included dietary interventions; it is well established that diet plays a role in vascular endothelial function, and thus, improvements cannot be attributed exclusively to exercise in these studies.[17,38,56,57] However, included studies encompassed diverse groups of survivors, including survivors on neoadjuvant chemotherapy, up to 5 years posttherapy, on hormone therapy, or postsurgery. Finally, the mechanisms responsible for improved vascular endothelial function were not examined. It is also currently unclear whether exercise training may improve other measures of vascular function (such as arterial stiffness) that increase oxygen delivery to the active muscles, potentially enhancing exercise tolerance.

Conclusion

Exercise training improves vascular endothelial function and peak VO_2 in breast and prostate cancer survivors. Future studies are required to examine the biological mechanisms responsible for and the prognostic implications of the favorable improvement in vascular endothelial function in cancer survivors.

Declaration of Conflicting Interests

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

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article. Dr. Haykowsky is supported by the Moritz Chair in Geriatrics at the University of Texas at Arlington.

References

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2017. *CA Cancer J Clin*. 2017;67:7-30.
2. Moslehi J. The cardiovascular perils of cancer survivorship. *N Engl J Med*. 2013;368:1055-1056.
3. Armenian SH, Xu L, Ky B, et al. Cardiovascular disease among survivors of adult-onset cancer: a community-based retrospective cohort study. *J Clin Oncol*. 2016;34:1122-1130.
4. Mele D, Nardozza M, Spallarossa P, et al. Current views on anthracycline cardiotoxicity. *Heart Fail Rev*. 2016;21:621-634.
5. Jones LW, Courneya KS, Mackey JR, et al. Cardiopulmonary function and age-related decline across the breast cancer survivorship continuum. *J Clin Oncol*. 2012;30:2530-2537.
6. Jones LW, Watson D, Herndon JE, et al. Peak oxygen consumption and long-term all-cause mortality in nonsmall cell lung cancer. *Cancer*. 2010;116:4825-4832.

7. Haykowsky M, Pituskin E, Paterson I. Physical health and exercise in cancer [published online August 31, 2016]. *Am Coll Cardiol*. 2016;08:01. Available at: http://www.acc.org/latest-in-cardiology/articles/2016/08/31/08/01/physical-health-and-exercise-in-cancer.
8. Jones LW, Haykowsky M, Pituskin EN, et al. Cardiovascular reserve and risk profile of postmenopausal women after chemoendocrine therapy for hormone receptor: positive operable breast cancer. *Oncologist*. 2007;12:1156-1164.
9. Haykowsky MJ, Beaudry R, Brothers RM, Nelson MD, Sarma S, La Gerche A. Pathophysiology of exercise intolerance in breast cancer survivors with preserved left ventricular ejection fraction. *Clin Sci (Lond)*. 2016;130:2239-2244.
10. Didier KD, Ederer AK, Reiter LK, et al. Altered blood flow response to small muscle mass exercise in cancer survivors treated with adjuvant therapy. *J Am Heart Assoc*. 2017;6:pii: e004784.
11. Stamatelopoulos SF, Stamatelopoulos KS, Lekakis JP, et al. Tamoxifen improves endothelial function and reduces carotid intima-media thickness in postmenopausal women. *Am Heart J*. 2004;147:1093-1099.
12. Herman SM, Robinson JTC, McCredie RJ, Adams MR, Boyer MJ, Celermajer DS. Androgen deprivation is associated with enhanced endothelium-dependent dilatation in adult men. *Arterioscler Thromb Vasc Biol*. 1997;17:2004-2009.
13. Ederer AK, Didier KD, Reiter LK, et al. Influence of adjuvant therapy in cancer survivors on endothelial function and skeletal muscle deoxygenation. *PLoS One*. 2016;11:e0147691.
14. Koelwyn GJ, Lewis NC, Ellard SL, et al. Ventricular-arterial coupling in breast cancer patients after treatment with anthracycline-containing adjuvant chemotherapy. *Oncologist*. 2016;21:141-149.
15. Tesarova P, Kalousova M, Zima T, et al. Endotelial activation and flow-mediated vasodilation in young patients with breast cancer. *Neoplasma*. 2013;60:690-697.
16. Dardano A, Ghiadoni L, Plantinga Y, et al. Recombinant human thyrotropin reduces endothelium-dependent vasodilation in patients monitored for differentiated thyroid carcinoma. *J Clin Endocrinol Metab*. 2006;91:4175-4178.
17. Gilbert SE, Tew GA, Fairhurst C, et al. Effects of a lifestyle intervention on endothelial function in men on long-term androgen deprivation therapy for prostate cancer. *Br J Cancer*. 2016;114:401-408.
18. Deanfield JE, Halcox JP, Rabelink TJ. Endothelial function and dysfunction: testing and clinical relevance. *Circulation*. 2007;115:1285-1295.
19. Bonetti PO, Lerman LO, Lerman A. Endothelial dysfunction: a marker of atherosclerotic risk. *Arterioscler Thromb Vasc Biol*. 2003;23:168-175.
20. Hadi HAR, Carr CS, Al Suwaidi J. Endothelial dysfunction: cardiovascular risk factors, therapy, and outcome. *Vasc Health Risk Manag*. 2005;1:183-198.
21. Widmer RJ, Lerman A. Endothelial dysfunction and cardiovascular disease. *Glob Cardiol Sci Pract*. 2014;2014:291-308.
22. Naseem KM. The role of nitric oxide in cardiovascular diseases. *Mol Aspects Med*. 2005;26:33-65.
23. Gokce N, Vita JA, Bader DS, et al. Effect of exercise on upper and lower extremity endothelial function in patients with coronary artery disease. *Am J Cardiol*. 2002;90:124-127.
24. Inaba Y, Chen JA, Bergmann SR. Prediction of future cardiovascular outcomes by flow-mediated vasodilatation of brachial artery: a meta-analysis. *Int J Cardiovasc Imaging*. 2010;26:631-640.
25. Joannides R, Haefeli WE, Linder L, et al. Nitric-oxide is responsible for flow-dependent dilatation of human peripheral conduit arteries in-vivo. *Circulation*. 1995;91:1314-1319.
26. Green DJ, Maiorana A, O'Driscoll G, Taylor R. Effect of exercise training on endothelium-derived nitric oxide function in humans. *J Physiol Sci*. 2004;561:1-25.
27. Green DJ. Exercise training as vascular medicine: direct impacts on the vasculature in humans. *Exerc Sport Sci Rev*. 2009;37:196-202.
28. Jones LW, Liang YY, Pituskin EN, et al. Effect of exercise training on peak oxygen consumption in patients with cancer: a meta-analysis. *Oncologist*. 2011;16:112-120.
29. Boulé NG, Kenny GP, Haddad E, Wells GA, Sigal RJ. Meta-analysis of the effect of structured exercise training on cardiorespiratory fitness in type 2 diabetes mellitus. *Diabetologia*. 2003;46:1071-1081.
30. Weston M, Taylor KL, Batterham AM, Hopkins WG. Effects of low-volume high-intensity interval training (HIT) on fitness in adults: a meta-analysis of controlled and non-controlled trials. *Sports Med*. 2014;44:1005-1017.
31. Wisloff U, Stoylen A, Loennechen JP, et al. Superior cardiovascular effect of aerobic interval training versus moderate continuous training in heart failure patients: a randomized study. *Circulation*. 2007;115:3086-3094.
32. Hambrecht R, Fiehn E, Weigl C, et al. Regular physical exercise corrects endothelial dysfunction and improves exercise capacity in patients with chronic heart failure. *Circulation*. 1998;98:2709-2715.
33. Thijssen DHJ, Maiorana AJ, O'Scoll G, Cable NT, Hopman MTE, Green DJ. Impact of inactivity and exercise on the vasculature in humans. *Eur J Appl Physiol*. 2010;108:845-875.
34. Follmann D, Elliott P, Suh I, Cutler J. Variance imputation for overviews of clinical trials with continuous response. *J Clin Epidemiol*. 1992;45:769-773.
35. Cohen J. A power primer. *Psychol Bull*. 1992;112:155-159.
36. Julian PTH, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ*. 2003;327:557-560.
37. Jones LW, Hornsby WE, Freedland SJ, et al. Effects of nonlinear aerobic training on erectile dysfunction and cardiovascular function following radical prostatectomy for clinically localized prostate cancer. *Eur Urol*. 2014;65:852-855.
38. Giallauria F, Vitelli A, Maresca L, et al. Exercise training improves cardiopulmonary and endothelial function in women with breast cancer: findings from the Diana-5 dietary intervention study. *Intern Emerg Med*. 2016;11:183-189.
39. Jones LW, Fels DR, West M, et al. Modulation of circulating angiogenic factors and tumor biology by aerobic training in breast cancer patients receiving neoadjuvant chemotherapy. *Cancer Prev Res*. 2013;6:925-937.

40. Green DJ, Eijsvogels TM, Bouts YM, et al. Exercise training and artery function in humans: nonresponse and its relationship to cardiovascular risk factors. *J Appl Physiol*. 2014;117:345-352.
41. Early KS, Stewart A, Johannsen N, Lavie CJ, Thomas JR, Welsch M. The effects of exercise training on brachial artery flow-mediated dilation: a meta-analysis. *J Cardiopulm Rehabil Prev*. 2017;37:77-89.
42. Ashor AW, Lara J, Siervo M, et al. Exercise modalities and endothelial function: a systematic review and dose–response meta-analysis of randomized controlled trials. *Sports Med*. 2015;45:279-296.
43. Green DJ, Spence A, Halliwill JR, Cable NT, Thijssen DHJ. Exercise and vascular adaptation in asymptomatic humans. *Exp Physiol*. 2011;96:57-70.
44. Hambrecht R, Adams V, Erbs S, et al. Regular physical activity improves endothelial function in patients with coronary artery disease by increasing phosphorylation of endothelial nitric oxide synthase. *Circulation*. 2003;107:3152-3158.
45. Olver TD, Ferguson BS, Laughlin MH. Molecular mechanisms for exercise training-induced changes in vascular structure and function: skeletal muscle, cardiac muscle, and the brain. *Prog Mol Biol Transl Sci*. 2015;135:227-257.
46. Kasikcioglu E, Oflaz H, Kasikcioglu HA, Kayserilioglu A, Umman S, Meric M. Endothelial flow-mediated dilatation and exercise capacity in highly trained endurance athletes. *Tohoku J Exp Med*. 2005;205:45-51.
47. Andreassen AK, Kvernebo K, Jørgensen B, Simonsen S, Kjekshus J, Gullestad L. Exercise capacity in heart transplant recipients: relation to impaired endothelium-dependent vasodilation of the peripheral microcirculation. *Am Heart J*. 1998;136:320-328.
48. McNeely ML, Campbell KL, Rowe BH, Klassen TP, Mackey JR, Courneya KS. Effects of exercise on breast cancer patients and survivors: a systematic review and meta-analysis. *Can Med Assoc J*. 2006;175:34-41.
49. Beaudry R, Kruger C, Liang YY, Parliament M, Haykowsky M, McNeely M. Effect of supervised exercise on aerobic capacity in cancer survivors: adherence and workload predict variance in effect. *World J Meta-Anal*. 2015;3:43-53.
50. Myers J, Prakash M, Froelicher V, Do D, Partington S, Atwood JE. Exercise capacity and mortality among men referred for exercise testing. *N Engl J Med*. 2002;346:793-801.
51. Gulati M, Pandey DK, Arnsdorf MF, et al. Exercise capacity and the risk of death in women: The St James Women Take Heart Project. *Circulation*. 2003;108:1554-1559.
52. Haykowsky MJ, Mackey JR, Thompson RB, Jones LW, Paterson DI. Adjuvant trastuzumab induces ventricular remodeling despite aerobic exercise training. *Clin Cancer Res*. 2009;15:4963-4967.
53. Hornsby WE, Douglas PS, West MJ, et al. Safety and efficacy of aerobic training in operable breast cancer patients receiving neoadjuvant chemotherapy: a phase II randomized trial. *Acta Oncol*. 2014;53:65-74.
54. Adams SC, Schondorf R, Benoit J, Kilgour RD. Impact of cancer and chemotherapy on autonomic nervous system function and cardiovascular reactivity in young adults with cancer: a case-controlled feasibility study. *BMC Cancer*. 2015;15:414.
55. Lakoski SG, Jones LW, Krone RJ, Stein PK, Scott JM. Autonomic dysfunction in early breast cancer: incidence, clinical importance, and underlying mechanisms. *Am Heart J*. 2015;170:231-241.
56. Macready AL, George TW, Chong MF, et al. Flavonoid-rich fruit and vegetables improve microvascular reactivity and inflammatory status in men at risk of cardiovascular disease—FLAVURS: a randomized controlled trial. *Am J Clin Nutr*. 2014;99:479-489.
57. Lopez-Garcia E, Schulze MB, Meigs JB, et al. Consumption of trans fatty acids is related to plasma biomarkers of inflammation and endothelial dysfunction. *J Nutr*. 2005;135:562-566.