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Exercise and Cardio-Oncology Rehab

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Abstract

Purpose of Review To evaluate the evidence supporting the use of exercise training as a treatment strategy to reduce risk of cardiovascular disease (CVD) in cancer populations and to provide an overview of the use of cardiac rehabilitation (CR) in cancer patients and survivors.

Recent Findings A recent scoping review suggests that CR-style interventions are feasible in cancer patients, but more evidence is needed to establish the benefits of this approach.

Summary Cancer survivors are at increased risk of CVD as a result of side effects of cancer treatment, shared risk factors for cancer and CVD, and effects from the cancer itself. Aerobic exercise training improves peak VO_2, but few models exist to support widespread incorporation of exercise training into cancer care. CR could provide infrastructure to support the incorporation of exercise in cancer populations, but data are limited regarding the feasibility or benefits of CR in cancer patients.

Introduction

As advancements are made in early detection of cancer and therapeutic options improve, life expectancy after a cancer diagnosis has risen, and the number of cancer survivors continues to grow [1]. The growth in this segment of the population has highlighted the adverse effects of cancer and associated cancer therapeutics on the cardiovascular system and the need for cardioprotective interventions that help to mitigate these effects. Exercise training has been identified as an appealing intervention to reduce the risk of cardiovascular (CV) disease in patients with cancer, as it is relatively safe and well-tolerated, and its effects are systemic and target multiple organ systems. Exercise training is a type of physical activity that is defined as planned, purposeful, repetitive movement with the purpose of improving physical fitness [2]. Observational studies show that higher levels of physical activity are associated with lower cancer risk and improved cancer outcomes, and interventional studies have demonstrated that exercise improves cardiorespiratory fitness and other end points in cancer patients during and after cancer treatment [3, 4, 5•]. Here, we provide a focused review of the evidence supporting the use of exercise training as a treatment strategy to reduce the morbidity of cancer and cancer treatment, as well as to mitigate CV risk in cancer populations. In addition, we review the use of cardiac rehabilitation (CR) to help deliver a multidisciplinary exercise intervention to cancer patients and survivors.

Adverse Effects of Cancer/cancer Therapeutics On the Cardiovascular System

Cancer survivors are at increased risk of adverse CV events during their treatment course and in the years following [6, 7]. This elevated risk stems from cardiotoxic and metabolic effects of therapies (such as radiation, chemotherapy, and targeted therapies), weight gain and physical deconditioning due to inactivity during and after treatment, shared risk factors for cancer and cardiovascular disease (e.g., obesity and inactivity), and effects from the cancer itself such as malnutrition, cachexia, and sarcopenia [6, 8–12]. The data indicate that cancer survivors living at least 5 years beyond their diagnosis have a 1.3- to 3.6-fold increased risk of CV-specific mortality and a 1.7- to 18.5-fold increased incidence of CV risk factors such as hypertension, diabetes mellitus, and dyslipidemia compared with cancer-free age-matched controls [4, 13, 14]. Additionally, while decreases in cardiac function and the development of heart failure symptoms are important sequelae of cancer therapies and should be appropriately screened for, it is also important to recognize that there is damage to the entire cardiovascular-skeletal muscle axis [6, 7, 9, 10].

Cardiorespiratory fitness (CRF), as measured by peak oxygen uptake (VO_2), is an integrated measurement of cardiovascular, respiratory, and skeletal muscle capacity and function [15]. Cancer therapy is associated with a decline in CRF of 5–26%, depending on the cancer type and therapeutic exposure [16, 17•]. This drop in CRF is associated with worse patient outcomes, both in terms of patient reported metrics (such as fatigue, anxiety, depression, function, and quality of life) and subsequent CV disease incidence and overall survival [8, 18]. For example, a meta-analysis of 71,654 cancer patients and

2002 cases of cancer mortality found that patients with an intermediate or high level of CRF had a lower risk of overall cancer mortality as compared to patients with lower CRF (relative risk [RR] 0.80 95% confidence interval [CI] 0.67–0.97, and RR 0.55, 95% CI 0.47–0.65, respectively) [19].

Observational Evidence of Physical Activity and Cancer

Observational evidence increasingly demonstrates an association between higher levels of physical activity (PA), one of the few lifestyle behaviors known to improve CRF, and lower levels of developing and dying from cancer. Hundreds of epidemiologic studies have found strong evidence of an association between higher levels of PA and lower incidence of cancer. For example, a pooled study including the data from 12 cohorts consisting of more than 1.44 million individuals in the USA and Europe found that higher levels of leisure time PA were associated with decreased rates of 13 cancers, with most relationships remaining significant in multivariate analyses adjusted for body mass index [20]. The US Department of Health and Human Services (HHS) 2018 Physical Activity Guidelines Advisory Committee (PAGAC) systematically reviewed the literature evaluating the relationship between PA and cancer risk and identified 45 systematic reviews, meta-analyses, and pooled analyses on this topic, in aggregate including several million participants (https://health.gov/sites/default/files/2019-09/PAG_Advisory_Committee_Report.pdf). A systematic review and meta-analysis by McTiernan et al. summarizing these data demonstrated a significant association between highest versus lowest physical activity levels and reduced risks of bladder, breast, colon, endometrial, esophageal adenocarcinoma, renal, and gastric cancers, with relative risk reductions ranging from 10 to 20% [20]. In several cases, the relationship was dose-dependent relationship. The analysis found insufficient evidence to establish a relationship between physical activity and other cancers including hematologic, head and neck, ovarian, pancreatic, and prostate.

Physical Activity and Cancer Recurrence and Mortality

While epidemiologic evidence showing the inverse relationship between PA and cancer risk is long-standing and expansive, the relationship between PA and cancer outcomes like recurrence and mortality has only been recognized more recently. Breast, colorectal, and prostate cancers are the most widely studied in this setting. In these cancers, higher levels of PA after cancer diagnosis are associated with a 37–48% lower risk of all-cause mortality [21•]. A meta-analysis by Friedenreich et al. compiled 136 studies across cancer types and examined cancer-specific mortality in patients with highest levels of PA levels versus those with lowest [22]. Most of the studies focused on mixed cancers (38 studies), breast cancer (39 studies), colorectal cancer (19 studies), or prostate cancer (9 studies). Cancer-specific mortality was lower in individuals who engaged in

the highest vs lowest amount of PA before diagnosis (HR 0.82, 95% CI 0.79 to 0.86) and after diagnosis (HR 0.63, 95% CI 0.53–0.75). The authors found evidence that higher physical activity levels before cancer diagnosis were protective against cancer-specific mortality in patients with breast (HR = 0.86, 95% CI 0.78 to 0.94), colorectal (HR = 0.80, 95% CI 0.74 to 0.87), hematologic (HR = 0.82, 95% CI 0.76 to 0.90), liver (HR = 0.78, 95% CI 0.66 to 0.92), lung (HR = 0.81, 95% CI 0.75 to 0.87), and stomach cancer (HR = 0.74, 95% CI 0.58 to 0.95), and higher levels of PA after cancer diagnosis were associated with lower cancer-specific mortality in patients with breast (HR = 0.63, 95% CI 0.53 to 0.75), colorectal (HR = 0.62, 95% CI 0.44 to 0.86), and prostate cancer (HR = 0.70, 95% CI 0.55 to 0.90) [22].

Randomized Trials Using Exercise Training As an Intervention in Cancer Populations

Despite the large body of observational evidence linking higher levels of PA to lower cancer risk and better cancer outcomes, to date, there are no data from randomized clinical trials (RCTs) testing the benefit of exercise training on cancer related mortality or overall survival. However, hundreds of interventional trials have tested the effect of exercise training on other endpoints such as patient-reported outcomes and CRF [5•, 23]. Notably, there is significant heterogeneity in the type, frequency, and intensity of exercise training that has been studied in the cancer populations, with some evidence that benefits may be strongest in trials that have incorporated supervised exercise training [22, 24, 25]. Exercise training during and after cancer treatment improves patient-reported outcomes such as fatigue, mood, and quality of life [26–28]. For example, a meta-analysis of 113 studies found that exercise and psychological interventions (both independently and in conjunction with one another) improved cancer-related fatigue during and after treatment ($P < 0.001$), whereas pharmacologic intervention did not [29]. Similarly, meta-analyses demonstrate that exercise interventions during and after cancer treatment lead to improvements in self-reported physical function in mixed cancers (SMD 0.22, 95% CI 0.13 to 0.32), as well as in patients with breast (SMD 0.14, 95% CI 0.01 to 0.27) and colorectal (SMD 0.26, 95% CI 0.04 to 0.48) cancers [30, 31].

Randomized Trials Testing the Impact of Exercise Training On Cancer Recurrence and Mortality

Although there are currently no data from RCTs testing the impact of an exercise intervention on cancer recurrence or mortality, a number of ongoing or recently completed trials will test the impact of exercise interventions, with or without a dietary component, on disease-free and overall survival in individuals with cancer (Table 2). Two of these studies, the Colon Health and Life-Long Exercise Change (CHALLENGE) trial and the INTERVAL GAP-4 trial, focus specifically on the impact of exercise training on cancer outcomes

(Table 1). CHALLENGE will randomize 962 patients with high-risk stage II or III colon cancer who recently completed adjuvant chemotherapy to a 36-month exercise program or to a health education control group, with the primary goal of evaluating the impact of the exercise intervention on disease-free survival. One-year feasibility results of the CHALLENGE trial were published after 273 participants had completed the first year of the exercise or control program, demonstrating that individuals randomized to the exercise program increased weekly exercise by 15.6 MET (metabolic equivalents of task)-hours vs 5.1 MET-hours in the health education group [mean difference 10.5 MET-hours/week; 95% CI 3.1–17.9; $P = 0.002$]. Exercise participants (vs controls) also experienced improvements in peak VO_2 ($P = 0.068$), 6-min walk ($P < 0.001$), 30-s chair stand ($P < 0.001$), 8-foot get up-and-go ($P = 0.004$), and sit-and-reach ($P = 0.08$) tests [32]. The INTERVAL GAP-4 trial focuses on individuals with advanced cancer and will randomize 866 men with castration-resistant metastatic prostate cancer to high-intensity aerobic and resistance training versus self-directed training, with a primary endpoint of the overall survival. Enrollment is currently ongoing [33]. There are also a number of phase III RCTs testing the impact of exercise within a multicomponent lifestyle intervention on cancer recurrence and morality in individuals with breast and ovarian cancer (Table 2) [32–37]. These studies will better define the role of exercise training, by itself and as a part of broader lifestyle change, in cancer treatment over the coming years.

Exercise and Cardiovascular Outcomes in Cancer Patients

Several RCTs have tested the impact of exercise training on CRF during and after cancer treatment [17•, 38, 39, 40]. Studies have tested aerobic training interventions, with or without a resistance training component, in patients with a variety of cancer types. Notably, several trials specifically enrolled patients to exercise training interventions during treatment with anthracyclines and other potentially cardiotoxic chemotherapy agents [41]. Overall, these studies have demonstrated that exercise training is a safe and effective strategy to improve CRF in cancer patients [41]. The largest meta-analysis on this topic included 48 RCTs, accounting for 3632 cancer patients randomized to exercise training during and after cancer treatment [17•]. The results demonstrated that aerobic exercise training interventions led to a significant increase in CRF ($+2.80$ mL·kg^{-1}·min^{-1}) as compared with no change ($+0.02$ mL·kg^{-1}·min^{-1}) in controls (weighted mean differences, $+2.13$ mL·kg^{-1}·min^{-1}; 95% CI, 1.58 to 2.67; I2, 20.6; $P < 0.001$) [17•].

There is less evidence regarding the role of exercise in the prevention of treatment-associated cardiotoxicities such as congestive heart failure and myocardial infarction. One preclinical mouse model found that the initiation of exercise after the administration of doxorubicin therapy promoted recovery of left ventricular ejection fraction and fractional shortening [42], but a similar study showed no effect [43]. A few small human studies have also evaluated the impact of exercise training during cardiotoxic chemotherapy on markers

Table 1 Ongoing randomized control trials examining the effects of lifestyle interventions on various cancer/overall survival endpoints

	Patient population	Size (n)	Intervention	Outcome
CHALLENGE trial [63]	Stage II or III colorectal cancer s/p adjuvant chemotherapy	$N = 962$	36-month physical activity program	Overall survival, disease-free survival
INTERVAL GAP-4 trial [33]	Metastatic castrate-resistant prostate cancer	$N = 866$	High intensity aerobic and resistance training	Overall survival
SUCCESS-C trial [34]	Stage II-III HER2/neu negative breast cancer, BMI 24-40 kg/m2	$N = 3547$	Lifestyle intervention program aimed at moderate weight loss	Disease-free survival
DIANA-5 trial [35]	Stage I-III breast cancer; unfavorable metabolic factors or triple negative cancer	$N = 1208$	Lifestyle intervention program (macrobiotic, mediterranean diet + exercise)	Breast cancer recurrence
BWEL trial [36]	Stage II-III HER2/negative breast cancer, BMI > 27kg/m2	$N = 3136$	Supervised weight loss program	Disease-free survival
LIVES trial [37]	Stage II–IV ovarian cancer	$N = 1070$	Diet + moderate-low intensity exercise intervention	Progression-free survival

Table 2 Interventional studies of cardiac rehabilitation in cancer patients

Author/year	*N*	Cancer type	Study design	Intervention type	Intervention duration	Results
Young-McCaughan et al. [64]	62	Cancer survivors w/ mixed primary malignancy site (22% breast, 19% prostate, 8% colorectal, 3% lung, 8% hematologic, 39% other), diagnosed within 2 years of study start	Single arm feasibility study	Modified CR	12 weeks 2 sessions/week	Significant improvements: - CRF (7.4±2.1METs to 8.4±2.1 METs, $P<0.001$) - QOL (46.8±8.62 to 44.3±10.12, $P=0.03$) No significant change in minutes of PA
Dittus et al. [65]	280	Cancer survivors w/ mixed primary malignancy site (68% breast, 2% prostate, 2% colorectal, 3% lung, 3% hematological, 22% other)	Single arm study	Modified CR	12 weeks 2 sessions/week	Significant improvements: - 6MWT (534.2±171 m to 582.7±157.2 m, $P=0.03$) - Strength: chest press and leg press (each $P<0.0001$) - Fatigue (15.7±12.2 to 10.0±11.8, $P<0.0001$) - Depression (5.34±4.0, to 3.7±3.5, $P<0.0001$) - Anxiety (2.87±3.5 to 2.34±3.2, $P<0.042$) No significant change in CRF
Hubbard et al. [60]	41	Post-surgical colorectal cancer survivors	RCT	Standard CR	6–12 weeks 1–3 sessions/ week	Study met primary feasibility endpoint (62% of participants completed program per protocol)
De Jesus et al. [66]	20	Breast cancer patient with fatigue post adjuvant chemotherapy	Single arm study	Standard CR	16 weeks 3 sessions/week	No significant differences in body composition, CRF, fatigue, minutes of PA, anxiety, depression, or QOL
Rothe et al. [67]	30	Lymphoma patients post autologous HSCT	Single arm study	Standard CR	8 weeks 1 session/week	Significant improvements: - Grip strength (38 kg±13 to 40 kg±12, $P<0.005$) - Gait speed (1.35 m/s±0.22 to 1.47 m/s±0.22, $P=0.02$) - 6MWT (484 m±95 to 532 m±98, $P=0.001$)

Table 2 (continued)

Author/year	*N*	Cancer type	Study design	Intervention type	Intervention duration	Results
Dolan et al. [61]	152	Early-stage breast cancer survivors	Single arm study	Modified CR	22 weeks 1 session/week	Significant improvements: - CRF (21 mL/kg/min ± 6 to 24 mL/kg/min ± 7, $P < .001$) - QOL (101.5 ± 23.9 to 110.6 ± 20, $P < .001$) - Depression (13.3 ± 9.4 to 11.8 ± 8.7, $P = 0.019$) No significant change in pain
Hubbard et al. [68]	20	Early-stage breast cancer patients post-surgery	Single arm feasibility study	Modified CR	12 weeks	Patients who were provided with options for post-treatment exercise programs were more likely to choose telephone-based PA consultations or referral to a leisure center over in-person CR programs
Zvinovski et al. [69]	25	Breast cancer survivors	Single arm feasibility study	Standard CR	14 weeks	Significant improvements: - PA (mean Δ13.2; $P < 0.001$) - Fatigue (mean Δ − 1.7, $P = 0.007$) - QOL (Δ5.66, $P = 0.008$) Study did not meet primary feasibility goal of 80% of participants completing at least 30/36 sessions No significant change in CRF

Standard CR, program in which oncology patients participated alongside cardiac patients in traditional CR structure

Modified CR, program in which oncology patients participated in a separate modified CR/exercise program

CRF cardiorespiratory fitness, *PA* physical activity, *QOL* quality of life, *6MWT* 6-min walk test, *CR* cardiac rehabilitation

of subclinical cardiac damage. A secondary analysis of the OPTiTrain Trial included 88 women with breast cancer who were undergoing treatment with an anthracycline and were randomized to 16 weeks of high-intensity interval training, plus either aerobic or resistance training, or to usual care. The results demonstrated that exercise did not impact levels of troponin immediately following the completion of chemotherapy but did result in lower levels of natriuretic peptides (BNP), used to diagnose heart failure, at 1-year follow-up [44]. Another trial randomized 24 women receiving doxorubicin for early breast cancer to an acute bout of aerobic exercise immediately before chemotherapy infusion or to usual care [45]. Exercise did not impact doxorubicin-related change in left ventricular mechanics (longitudinal strain or twist), or cardiac troponin, but women randomized to exercise were less likely to experience decreased cardiac output, increased resting heart rate, or decreased systemic vascular resistance as compared with controls (all $P < 0.01$) [45].

A number of ongoing studies are also examining the ability of exercise training to prevent cancer therapy-associated cardiotoxicity. The caloric restriction and exercise protection from anthracycline toxic effects (CREATE) trial will evaluate the impact of exercise and caloric restriction on MRI-derived left ventricular ejection fraction reserve (peak exercise LVEF-resting LVEF), as well MRI-derived measures of cardiac, aortic, and skeletal muscle structure and function, circulating NT-proBNP, CRF, and patient-reported outcomes [46]. The trial will randomize 56 women with early breast cancer scheduled to receive an anthracycline to one of the 3 groups: [1] exercise, participants will complete a single, 30-min, vigorous-intensity, aerobic exercise session 24 h before each chemotherapy cycle; [2] caloric restriction, participants will consume a diet that includes 50% of their caloric needs for 48 h prior to each chemotherapy cycle; or [3] usual care [46]. A second study, the Tailored Therapeutic Exercise and Recovery Strategies (ATOPE) trial, will randomize 120 women undergoing cardiotoxic treatment for early breast cancer to a tailored exercise training program delivered before and during cancer treatment or to usual care and will evaluate the impact of the exercise training on left ventricular ejection fraction, as well as other biomarkers and patient-reported outcomes [47]. These trials will further define the role of exercise training in preventing chemotherapy-induced cardiotoxicity.

Cardiac Rehabilitation and its Application in the Cancer Population

Cardiac rehabilitation (CR) is an early outpatient (often called phase II) secondary prevention program recognized as integral to the comprehensive care of patients with CVD [48–51]. The model of CR has evolved over the past four decades, as the role of exercise as an integral part of secondary CVD prevention has been better studied and understood. The CR model places aerobic exercise at its core, while also incorporating multidisciplinary CVD risk modification strategies including medication management, nutrition and weight loss, smoking cessation, and psychosocial counseling.

The benefits of CR for patients with coronary artery disease—including those with acute coronary syndrome, recent coronary revascularization, or stable angina pectoris—are broad and well-established [51–55]. The data from RCTs demonstrate that CR leads to a 10–25% reduction in mortality over 1–3 years and an almost 30% reduction in rates of rehospitalization over 1 year, in addition to increasing CRF and patient quality of life in individuals with coronary artery disease and in those with congestive heart failure [56–58]. Much of this benefit is thought to stem from the 15–30% increase in CRF that results from participation in the supervised program, as well as the associated favorable physiologic effects that such a regimen has on coronary and peripheral endothelial function, insulin resistance, blood pressure, and systemic inflammation [55, 57].

Given the effectiveness of CR and the significant infrastructure that has been built around it, CR has been advanced as a potential framework for delivering multidisciplinary rehabilitation care to cancer patients and survivors [59]. However, only a few small trials have evaluated the feasibility or benefits of applying the CR model to cancer populations (Table 2), and only one of these studies, a pilot trial of CR in patients with colorectal cancer, employed a randomized design. In that study, 41 patients who had undergone surgery for stage I–III colorectal cancer were randomized to referral to a CR program or to usual care [60]. The CR program met the protocol-specified definition of acceptability, with 62% of participants completing the intervention as per protocol, and no adverse events were reported. The remaining studies of CR in cancer patients have used quasi-experimental designs, evaluating changes in outcomes before and after participation in CR programs or comparing effects of CR to historical controls. For example, Dolan et al. retrospectively reviewed medical records from 152 breast cancer survivors taking part in a tailored exercise program, including both aerobic and resistance training exercise performed once weekly in a group setting supervised by CR staff, and found that patients who took part in the program experienced significant improvements in CRF ($P < 0.01$) and patient-reported outcomes (PROs; $P < 0.05$ for all) [61]. Although these preliminary data are promising, larger-scale trials employing randomized designs are needed to provide more robust evidence on the efficacy of utilizing CR in cancer patients.

Cardio-oncology Rehabilitation (CORE) Model and Future Directions

A 2019 American Heart Association scientific statement endorsed by the American Cancer Society laid out the framework for a cardio-oncology model of rehabilitation (CORE) based on the CR model [4]. As in the cardiac patient population, CORE would serve as a structured way to incorporate exercise training to increase CRF in patients who are undergoing or who have previously undergone cancer treatment, while also incorporating comprehensive risk factor

modification, behavioral/lifestyle intervention, and psychological and community support.

The application of a standardized exercise intervention model in cancer populations would require significant work to identify the most efficacious and practical exercise training model or models. It is notable that some of the trials described above testing the feasibility and benefits of CR or CR-like interventions in cancer patients have delivered a standard CR program to cancer patients alongside cardiac patients, while others have used the CR infrastructure but have created tailored stand-alone oncology programs. Both approaches have advantages and disadvantages. Utilizing existing CR programs provides greater potential for dissemination, given that these programs exist throughout the USA, while building an oncology-specific program provides the opportunity to customize the program to fit the unique medical and psychosocial needs of cancer patients.

More broadly, the implementation of a CR model in cancer patients will present a unique set of challenges, despite the existing framework of this program for the CVD population and the evidence supporting the value of exercise in patients with cancer. Widespread, systematic adoption will require buy-in from both the multidisciplinary care team and the patient. While significant progress has been made in the recognition of exercise as an important part of survivorship care and CVD risk factor modification, education and proper pipelines for referral will be imperative for ensuring broad uptake of CR. Evidence-based discussions between the care team and patients regarding the benefits of exercise will be an important aspect of widespread adoption, and the education of providers will help catalyze meaningful discussions with patients. In addition, patients may be hesitant to participate in a structured exercise program due to a variety of factors including time constraints, side effects from therapy, and struggles with transportation and funding. Finally, policy barriers such as lack of insurance reimbursement need to be addressed [62]. Looking forward, critical data from high-quality randomized controlled trials testing the efficacy and acceptability of CR in cancer populations will be needed to support widespread dissemination.

Conclusions

Cancer patients are at increased risk of CVD, due to the effects of cancer treatment and to shared risk factors for malignancy and CVD. Higher levels of physical activity have been linked to lower cancer risk and better outcomes in patients diagnosed with early-stage malignancies, and RCTs have demonstrated that exercise training during and after cancer treatment reduces treatment-related side effects and improves quality of life in cancer patients. Exercise training also improves CRF in cancer patients, but less is known regarding the efficacy of exercise in preventing cardiac toxicity of cancer treatment. Structured exercise training programs are needed to better disseminate exercise to cancer patients. Though data to support optimization is still needed, the CORE model provides a promising approach to delivering a bundled, interdisciplinary intervention with a focus on supervised rigorous

aerobic exercise training to cancer patients using the well-established framework of traditional CR, with long-term goals of decreasing cardiovascular events and enhancing survivorship in cancer patients.

Declarations

Conflict of Interest

A Nohria has received research support from Amgen, Inc. and is a consultant for AstraZeneca, Bantam Pharmaceuticals, Boehringer Ingelheim, and Takeda Oncology. J Ligibel has received in-kind product support (to Dana-Farber) from Fitbit and Nestle Health Science in support of the Breast Cancer Weight Loss Study. S Gilchrist reports no conflicts of interest. Of note, after manuscript completion, Dr. Gilchrist started full-time employment with LabCorp. Her employment at LabCorp did not create any new conflicts related to the manuscript. The authors Newman, Basen-Engquist, Kerrigan, Keteyian, and Schmitz report no financial conflict of interest.

Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

References

Papers of particular interest, published recently, have been highlighted as:
• Of importance

1. Miller KD, Siegel RL, Lin CC, Mariotto AB, Kramer JL, Rowland JH, et al. Cancer treatment and survivorship statistics, 2016. CA Cancer J Clin. 2016;66(4):271–89.
2. Caspersen CJ, Powell KE, Christenson GM. Physical activity, exercise, and physical fitness: definitions and distinctions for health-related research. Public Health Rep Wash DC 1974. 1985 Apr;100(2):126–31.
3. Scott JM, Nilsen TS, Gupta D, Jones LW. Exercise therapy and cardiovascular toxicity in cancer. Circulation. 2018;137(11):1176–91.
4. Gilchrist SC, Barac A, Ades PA, Alfano CM, Franklin BA, Jones LW, et al. Cardio-oncology rehabilitation to manage cardiovascular outcomes in cancer patients and survivors: a scientific statement from the American Heart Association. Circulation [Internet]. 2019 May 21 [cited 2021 Sep 19];139(21). Available from: https://www.ahajournals.org/doi/10.1161/CIR.0000000000000679.
5. • Campbell KL, Winters-Stone KM, Wiskemann J, May AM, Schwartz AL, Courneya KS, et al. Exercise guidelines for cancer survivors: consensus statement from International Multidisciplinary Roundtable. Med Sci Sports Exerc. 2019 Nov;51(11):2375–90.
This consensus statement from the American College of Sports Medicine provides recommendations for the prescription of exercise to reduce common side effects of cancer treatment.
6. Chang H-M, Moudgil R, Scarabelli T, Okwuosa TM, Yeh ETH. Cardiovascular complications of cancer therapy: best practices in diagnosis, prevention, and management: part 1. J Am Coll Cardiol. 2017 Nov 14;70(20):2536–51.
7. Chang H-M, Okwuosa TM, Scarabelli T, Moudgil R, Yeh ETH. Cardiovascular complications of cancer therapy: best practices in diagnosis, prevention, and management: part 2. J Am Coll Cardiol. 2017;70(20):2552–65.
8. Jones LW, Courneya KS, Mackey JR, Muss HB, Pituskin EN, Scott JM, et al. Cardiopulmonary function and age-related decline across the breast cancer survivorship continuum. J Clin Oncol. 2012;30(20):2530–7.
9. Alexandre J, Cautela J, Ederhy S, Damaj GL, Salem J-E, Barlesi F, et al. Cardiovascular toxicity related

to cancer treatment: a pragmatic approach to the American and European cardio-oncology guidelines. J Am Heart Assoc. 2020;9(18): e018403.
10. Lenneman CG, Sawyer DB. Cardio-oncology: an update on cardiotoxicity of cancer-related treatment. Circ Res. 2016;118(6):1008–20.
11. Herrmann J. Adverse cardiac effects of cancer therapies: cardiotoxicity and arrhythmia. Nat Rev Cardiol. 2020;17(8):474–502.
12. Yu AF, Flynn JR, Moskowitz CS, Scott JM, Oeffinger KC, Dang CT, et al. Long-term cardiopulmonary consequences of treatment-induced cardiotoxicity in survivors of ERBB2-positive breast cancer. JAMA Cardiol. 2020;5(3):309–17.
13. Hooning MJ, Botma A, Aleman BMP, Baaijens MHA, Bartelink H, Klijn JGM, et al. Long-term risk of cardiovascular disease in 10-year survivors of breast cancer. J Natl Cancer Inst. 2007;99(5):365–75.
14. Chow EJ, Mueller BA, Baker KS, Cushing-Haugen KL, Flowers MED, Martin PJ, et al. Cardiovascular hospitalizations and mortality among recipients of hematopoietic stem cell transplantation. Ann Intern Med. 2011;155(1):21–32.
15. Jones LW, Courneya KS, Mackey JR, Muss HB, Pituskin EN, Scott JM, et al. Cardiopulmonary function and age-related decline across the breast cancer survivorship continuum. J Clin Oncol. 2012;30(20):2530–7.
16. Hurria A, Jones L, Muss HB. Cancer treatment as an accelerated aging process: assessment, biomarkers, and interventions. Am Soc Clin Oncol Educ Book Am Soc Clin Oncol Annu Meet. 2016;35:e516-522.
17. • Scott JM, Zabor EC, Schwitzer E, Koelwyn GJ, Adams SC, Nilsen TS, et al. Efficacy of exercise therapy on cardiorespiratory fitness in patients with cancer: a systematic review and meta-analysis. J Clin Oncol. 2018 Aug 1;36(22):2297–305.
This systematic review summarizes data from randomized trials showing that exercise interventions improve cardiorespiratory fitness in cancer patients during and after treatment.
18. Mehta LS, Watson KE, Barac A, Beckie TM, Bittner V, Cruz-Flores S, et al. Cardiovascular disease and breast cancer: where these entities intersect: a scientific statement from the American Heart Association. Circulation. 2018 Feb 20;137(8):e30–66.
19. Schmid D, Leitzmann MF. Cardiorespiratory fitness as predictor of cancer mortality: a systematic review and meta-analysis. Ann Oncol Off J Eur Soc Med Oncol. 2015;26(2):272–8.
20. Moore SC, Lee I-M, Weiderpass E, Campbell PT, Sampson JN, Kitahara CM, et al. Association of leisure-time physical activity with risk of 26 types of cancer in 1.44 million adults. JAMA Intern Med. 2016 Jun 1;176(6):816–25.
21. • Mctiernan A, Friedenreich CM, Katzmarzyk PT, Powell KE, Macko R, Buchner D, et al. Physical activity in cancer prevention and survival: a systematic review. Med Sci Sports Exerc. 2019 Jun;51(6):1252–61.
This systematic review summarizes the observational evidence showing an association between higher levels of physical activity and lower risk of developing and dying from cancer.
22. Friedenreich CM, Stone CR, Cheung WY, Hayes SC. Physical activity and mortality in cancer survivors: a systematic review and meta-analysis. JNCI Cancer Spectr. 2020 Feb;4(1):pkz080.
23. Patel AV, Friedenreich CM, Moore SC, Hayes SC, Silver JK, Campbell KL, et al. American College of Sports Medicine roundtable report on physical activity, sedentary behavior, and cancer prevention and control. Med Sci Sports Exerc. 2019;51(11):2391–402.
24. Chipperfield K, Brooker J, Fletcher J, Burney S. The impact of physical activity on psychosocial outcomes in men receiving androgen deprivation therapy for prostate cancer: a systematic review. Health Psychol Off J Div Health Psychol Am Psychol Assoc. 2014;33(11):1288–97.
25. van Vulpen JK, Peeters PHM, Velthuis MJ, van der Wall E, May AM. Effects of physical exercise during adjuvant breast cancer treatment on physical and psychosocial dimensions of cancer-related fatigue: a meta-analysis. Maturitas. 2016;85:104–11.
26. Galvão DA, Newton RU, Chambers SK, Spry N, Joseph D, Gardiner RA, et al. Psychological distress in men with prostate cancer undertaking androgen deprivation therapy: modifying effects of exercise from a year-long randomized controlled trial. Prostate Cancer Prostatic Dis. 2021;24(3):758–66.
27. Singh F, Newton RU, Galvão DA, Spry N, Baker MK. A systematic review of pre-surgical exercise intervention studies with cancer patients. Surg Oncol. 2013;22(2):92–104.
28. Cheema B, Gaul CA, Lane K, Fiatarone Singh MA. Progressive resistance training in breast cancer: a systematic review of clinical trials. Breast Cancer Res Treat. 2008;109(1):9–26.
29. Mustian KM, Alfano CM, Heckler C, Kleckner AS, Kleckner IR, Leach CR, et al. Comparison of pharmaceutical, psychological, and exercise treatments for cancer-related fatigue: a meta-analysis. JAMA Oncol. 2017;3(7):961–8.
30. Sweegers MG, Altenburg TM, Chinapaw MJ, Kalter J, Verdonck-de Leeuw IM, Courneya KS, et al. Which exercise prescriptions improve quality of life and physical function in patients with cancer during and following treatment? A systematic review and meta-analysis of randomised controlled trials. Br J Sports Med. 2018;52(8):505–13.
31. Lund CM, Dolin TG, Mikkelsen MK, Juhl CB, Vinther A, Nielsen DL. Effect of exercise on physical function and psychological well-being in older patients with colorectal cancer receiving chemotherapy-a systematic review. Clin Colorectal Cancer. 2020;19(4):e243–57.
32. Courneya KS, Vardy JL, O'Callaghan CJ, Friedenreich CM, Campbell KL, Prapavessis H, et al. Effects of a structured exercise program on physical activity and

fitness in colon cancer survivors: one year feasibility results from the CHALLENGE trial. Cancer Epidemiol Biomark Prev Publ Am Assoc Cancer Res Cosponsored Am Soc Prev Oncol. 2016;25(6):969–77.
33. Newton RU, Kenfield SA, Hart NH, Chan JM, Courneya KS, Catto J, et al. Intense exercise for survival among men with metastatic castrate-resistant prostate cancer (INTERVAL-GAP4): a multicentre, randomised, controlled phase III study protocol. BMJ Open. 2018;8(5): e022899.
34. Rack B, Andergassen U, Neugebauer J, Salmen J, Hepp P, Sommer H, et al. The German SUCCESS C study-the first European lifestyle study on breast cancer. Breast Care Basel Switz. 2010;5(6):395–400.
35. Villarini A, Pasanisi P, Traina A, Mano MP, Bonanni B, Panico S, et al. Lifestyle and breast cancer recurrences: the DIANA-5 trial. Tumori. 2012;98(1):1–18.
36. Ligibel JA, Barry WT, Alfano CM, Hershman DL, Irwin ML, Neuhouser M, et al. The breast cancer weight loss (BWEL) trial: randomized phase III trial evaluating the role of weight loss in adjuvant treatment of overweight and obese women with early-stage breast cancer (Alliance A011401). J Clin Oncol. 2018 May 20;36(15_suppl):TPS598–TPS598.
37. Thomson CA, Crane TE, Miller A, Garcia DO, Basen-Engquist K, Alberts DS. A randomized trial of diet and physical activity in women treated for stage II-IV ovarian cancer: rationale and design of the lifestyle intervention for ovarian cancer enhanced survival (LIVES): an NRG Oncology/Gynecologic Oncology Group (GOG-225) Study. Contemp Clin Trials. 2016;49:181–9.
38. Bjørke ACH, Sweegers MG, Buffart LM, Raastad T, Nygren P, Berntsen S. Which exercise prescriptions optimize VO2 max during cancer treatment? A systematic review and meta-analysis. Scand J Med Sci Sports. 2019;29(9):1274–87.
39. Maginador G, Lixandrão ME, Bortolozo HI, Vechin FC, Sarian LO, Derchain S, et al. Aerobic exercise-induced changes in cardiorespiratory fitness in breast cancer patients receiving chemotherapy: a systematic review and meta-analysis. Cancers. 2020;12(8):E2240.
40. Singh B, Spence RR, Steele ML, Sandler CX, Peake JM, Hayes SC. A systematic review and meta-analysis of the safety, feasibility, and effect of exercise in women with stage II+ breast cancer. Arch Phys Med Rehabil. 2018;99(12):2621–36.
41. Hornsby WE, Douglas PS, West MJ, Kenjale AA, Lane AR, Schwitzer ER, et al. Safety and efficacy of aerobic training in operable breast cancer patients receiving neoadjuvant chemotherapy: a phase II randomized trial. Acta Oncol Stockh Swed. 2014;53(1):65–74.
42. Wang F, Chandra J, Kleinerman ES. Exercise intervention decreases acute and late doxorubicin-induced cardiotoxicity. Cancer Med. 2021;10(21):7572–84.
43. Sturgeon K, Schadler K, Muthukumaran G, Ding D, Bajulaiye A, Thomas NJ, et al. Concomitant low-dose doxorubicin treatment and exercise. Am J Physiol Regul Integr Comp Physiol. 2014;307(6):R685-692.
44. Ansund J, Mijwel S, Bolam KA, Altena R, Wengström Y, Rullman E, et al. High intensity exercise during breast cancer chemotherapy - effects on long-term myocardial damage and physical capacity - data from the OptiTrain RCT. Cardio-Oncol Lond Engl. 2021;7(1):7.
45. Kirkham AA, Eves ND, Shave RE, Bland KA, Bovard J, Gelmon KA, et al. The effect of an aerobic exercise bout 24 h prior to each doxorubicin treatment for breast cancer on markers of cardiotoxicity and treatment symptoms: a RCT. Breast Cancer Res Treat. 2018;167(3):719–29.
46. Kirkham AA, Paterson DI, Prado CM, Mackey JR, Courneya KS, Pituskin E, et al. Rationale and design of the caloric restriction and exercise protection from anthracycline toxic effects (CREATE) study: a 3-arm parallel group phase II randomized controlled trial in early breast cancer. BMC Cancer. 2018;18(1):864.
47. Postigo-Martin P, Peñafiel-Burkhardt R, Gallart-Aragón T, Alcaide-Lucena M, Artacho-Cordón F, Galiano-Castillo N, et al. Attenuating treatment-related cardiotoxicity in women recently diagnosed with breast cancer via a tailored therapeutic exercise program: protocol of the ATOPE trial. Phys Ther. 2021 Mar 3;101(3):pzab014.
48. Balady GJ, Williams MA, Ades PA, Bittner V, Comoss P, Foody JM, et al. Core components of cardiac rehabilitation/secondary prevention programs: 2007 update: a scientific statement from the American Heart Association Exercise, Cardiac Rehabilitation, and Prevention Committee, the Council on Clinical Cardiology; the Councils on Cardiovascular Nursing, Epidemiology and Prevention, and Nutrition, Physical Activity, and Metabolism; and the American Association of Cardiovascular and Pulmonary Rehabilitation. Circulation. 2007;115(20):2675–82.
49. Ades PA, Keteyian SJ, Wright JS, Hamm LF, Lui K, Newlin K, et al. Increasing cardiac rehabilitation participation from 20% to 70%: a road map from the million hearts cardiac rehabilitation collaborative. Mayo Clin Proc. 2017;92(2):234–42.
50. Smith SC, Benjamin EJ, Bonow RO, Braun LT, Creager MA, Franklin BA, et al. AHA/ACCF secondary prevention and risk reduction therapy for patients with coronary and other atherosclerotic vascular disease: 2011 update: a guideline from the American Heart Association and American College of Cardiology Foundation. Circulation. 2011;124(22):2458–73.
51. Thomas RJ, Beatty AL, Beckie TM, Brewer LC, Brown TM, Forman DE, et al. Home-based cardiac rehabilitation: a scientific statement from the American Association of Cardiovascular and Pulmonary Rehabilitation, the American Heart Association, and the American College of Cardiology. J Am Coll Cardiol. 2019;74(1):133–53.
52. Anderson L, Oldridge N, Thompson DR, Zwisler A-D, Rees K, Martin N, et al. Exercise-based cardiac

rehabilitation for coronary heart disease: Cochrane systematic review and meta-analysis. J Am Coll Cardiol. 2016;67(1):1–12.
53. Powell R, McGregor G, Ennis S, Kimani PK, Underwood M. Is exercise-based cardiac rehabilitation effective? A systematic review and meta-analysis to re-examine the evidence. BMJ Open. 2018;8(3): e019656.
54. Long L, Anderson L, Dewhirst AM, He J, Bridges C, Gandhi M, et al. Exercise-based cardiac rehabilitation for adults with stable angina. Cochrane Database Syst Rev. 2018 Feb 2;2:CD012786.
55. Lavie CJ, Milani RV. Cardiac rehabilitation and exercise training in secondary coronary heart disease prevention. Prog Cardiovasc Dis. 2011;53(6):397–403.
56. Long L, Mordi IR, Bridges C, Sagar VA, Davies EJ, Coats AJ, et al. Exercise-based cardiac rehabilitation for adults with heart failure. Cochrane Database Syst Rev. 2019 Jan 29;1:CD003331.
57. Anderson L, Thompson DR, Oldridge N, Zwisler A-D, Rees K, Martin N, et al. Exercise-based cardiac rehabilitation for coronary heart disease. Cochrane Database Syst Rev. 2016 Jan 5;(1):CD001800.
58. Ji H, Fang L, Yuan L, Zhang Q. Effects of exercise-based cardiac rehabilitation in patients with acute coronary syndrome: a meta-analysis. Med Sci Monit Int Med J Exp Clin Res. 2019;7(25):5015–27.
59. Jones LW, Courneya KS, Mackey JR, Muss HB, Pituskin EN, Scott JM, et al. Cardiopulmonary function and age-related decline across the breast cancer survivorship continuum. J Clin Oncol Off J Am Soc Clin Oncol. 2012;30(20):2530–7.
60. Hubbard G, Adams R, Campbell A, Kidd L, Leslie SJ, Munro J, et al. Is referral of postsurgical colorectal cancer survivors to cardiac rehabilitation feasible and acceptable? A pragmatic pilot randomised controlled trial with embedded qualitative study. BMJ Open. 2016;6(1): e009284.
61. Dolan LB, Barry D, Petrella T, Davey L, Minnes A, Yantzi A, et al. The cardiac rehabilitation model improves fitness, quality of life, and depression in breast cancer survivors. J Cardiopulm Rehabil Prev. 2018;38(4):246–52.
62. Basen-Engquist K, Alfano CM, Maitin-Shepard M, Thomson CA, Schmitz KH, Pinto BM, et al. Agenda for translating physical activity, nutrition, and weight management interventions for cancer survivors into clinical and community practice. Obes Silver Spring Md. 2017;25(Suppl 2):S9-22.
63. Courneya KS, Booth CM, Gill S, O'Brien P, Vardy J, Friedenreich CM, et al. The colon health and life-long exercise change trial: a randomized trial of the National Cancer Institute of Canada Clinical Trials Group. Curr Oncol Tor Ont. 2008;15(6):279–85.
64. Young-McCaughan S, Mays MZ, Arzola SM, Yoder LH, Dramiga SA, Leclerc KM, et al. Research and commentary: change in exercise tolerance, activity and sleep patterns, and quality of life in patients with cancer participating in a structured exercise program. Oncol Nurs Forum. 2003 Jun;30(3):441–54; discussion 441–454.
65. Dittus KL, Lakoski SG, Savage PD, Kokinda N, Toth M, Stevens D, et al. Exercise-based oncology rehabilitation: leveraging the cardiac rehabilitation model. J Cardiopulm Rehabil Prev. 2015;35(2):130–9.
66. De Jesus S, Fitzgeorge L, Unsworth K, Massel D, Suskin N, Prapavessis H, et al. Feasibility of an exercise intervention for fatigued breast cancer patients at a community-based cardiac rehabilitation program. Cancer Manag Res. 2017;9:29–39.
67. Rothe D, Cox-Kennett N, Buijs DM, Venner CP, Paterson DI, Gyenes GT, et al. Cardiac rehabilitation in patients with lymphoma undergoing autologous hematopoietic stem cell transplantation: a cardio-oncology pilot project. Can J Cardiol. 2018;34(10):S263–9.
68. Hubbard G, Campbell A, Fisher A, Harvie M, Maltinsky W, Mullen R, et al. Physical activity referral to cardiac rehabilitation, leisure centre or telephone-delivered consultations in post-surgical people with breast cancer: a mixed methods process evaluation. Pilot Feasibility Stud. 2018;4:108.
69. Zvinovski F, Stephens JA, Ramaswamy B, Reinbolt RE, Noonan AM, VanDeusen JB, et al. A cardiac rehabilitation program for breast cancer survivors: a feasibility study. J Oncol. 2021;2021:9965583.

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