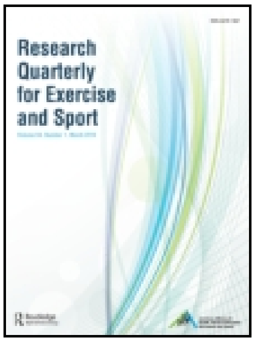

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Kerry S. Courneya, Laura Q. Rogers, Kristin L. Campbell, Jeff K. Vallance & Christine M. Friedenreich

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SPECIAL TOPICS: Top 10 Research Questions

Top 10 Research Questions Related to Physical Activity and Cancer Survivorship

Kerry S. Courneya
University of Alberta

Laura Q. Rogers
University of Alabama at Birmingham

Kristin L. Campbell
University of British Columbia

Jeff K. Vallance
Athabasca University

Christine M. Friedenreich
Alberta Health Services

In the United States, there are more than 14 million cancer survivors. Many of these survivors have been treated with multimodal therapy including surgery, radiation therapy, chemotherapy, and targeted therapies. These therapies improve survival; however, they also cause acute and chronic side effects that can undermine health and quality of life. Physical activity (PA) and cancer survivorship is a rapidly growing field of inquiry that studies the role of PA in people diagnosed with cancer. In this article, we propose the following top 10 research questions for the field of PA and cancer survivorship: (1) Does PA reduce the risk for cancer recurrence and/or improve survival? (2) Does PA influence cancer treatment decisions, completion rates, and/or response? (3) What is the optimal PA prescription for cancer survivors? (4) What is the role of sedentary behavior in cancer survivorship? (5) What are the most effective PA behavior change interventions for cancer survivors? (6) Which cancer variables modify the PA response? (7) What are the safety issues concerning PA in cancer survivors? (8) Which specific cancer symptoms can be managed by PA? (9) Is there a role for PA in advanced cancer? And (10) How do we translate PA research into clinical and community oncology practice? The answers to these questions are critical not only for advancing the field of PA and cancer survivorship, but for improving the lives of the millions of cancer survivors every year who are diagnosed with cancer, going through treatments, recovering after treatments, or coping with advanced disease.

Keywords: cancer patients, exercise, oncology, sedentary behavior

Cancer is a large group of diseases characterized by uncontrolled growth of abnormal cells that are able to invade other tissues and spread to other parts of the body. In 2014, an estimated 1.7 million Americans were diagnosed with cancer and 585,000 died from the disease

Correspondence should be addressed to Kerry S. Courneya, Faculty of Physical Education and Recreation, University of Alberta, E-488 Van Vliet Center, Edmonton, AB T6G 2H9, Canada. E-mail: kerry.courneya@ualberta.ca

(American Cancer Society, 2014). About 44% of men and 38% of women in the United States will develop cancer at some point in their lifetime (American Cancer Society, 2014). The 5-year relative survival rate has increased significantly during the past few decades and now stands at 68% for all cancers combined (American Cancer Society, 2014). This survival rate varies, however, by the type of cancer, stage of disease, and other factors. The increased incidence and survival rates have resulted in more than 14 million American cancer survivors (i.e., a person with a previous diagnosis of cancer; DeSantis et al., 2014).

Surviving cancer often requires treatment with multimodal therapy that can last many months or years. The major cancer treatments include surgery, radiation therapy, chemotherapy, hormone or endocrine therapy, biologic or immunotherapy, targeted therapies, and stem cell transplantation. These treatments dramatically improve survival rates; however, they also produce numerous acute, chronic, and late-appearing side effects that undermine the health and quality of life of cancer survivors (Aziz, 2007). The American College of Sports Medicine (ACSM; Schmitz et al., 2010) and the American Cancer Society (Rock et al., 2012) have recommended physical activity (PA) as an intervention strategy to help cancer survivors manage symptoms, improve quality of life, and possibly even extend survival.

PA and cancer survivorship—or exercise oncology—is the field that studies the connections between cancer variables (i.e., disease and treatment variables) and PA in people who have been diagnosed with cancer. Courneya (2014) proposed a simple framework for organizing research on PA and cancer survivorship. The framework highlights four overarching research themes involving PA and cancer variables. Specifically, cancer variables may be studied as outcomes of PA (i.e., they are causally affected by PA), moderators of other PA outcomes (i.e., they alter the typical response to PA observed in other populations), determinants of PA (i.e., they influence exercise adherence or PA participation rates), and moderators of other PA determinants (i.e., they alter the typical determinants of PA observed in other populations).

PA and cancer survivorship research can also be organized along the postdiagnosis cancer continuum from diagnosis to death. Courneya and Friedenreich (2007) proposed the Physical Activity and Cancer Control framework, which highlights four distinct postdiagnosis time periods in which PA and cancer variables may be studied: pretreatment, treatment, survivorship, and end of life. Pretreatment includes the time period after a definitive cancer diagnosis until treatment is initiated, which may range from weeks to several years for some cancers. The treatment time period usually includes the "primary" cancer treatments such as surgery, radiation therapy, chemotherapy, and biologic therapies, and this time period may last months or years. The survivorship time period is the period following first diagnosis and treatment and is prior to the development of a recurrence of cancer or death. It includes an early recovery/rehabilitation phase that may last from treatment completion until 6 months to 12 months and a longer-term survivorship phase that focuses on disease prevention and health promotion and can extend for the entire normal life expectancy. The "end of life" time period is meant to capture the time period of advanced cancer and progressive disease that may last from several weeks to several months. Cancer survivors may cycle through these time periods multiple times if they experience multimodal treatments, disease recurrence, progression, or a second cancer. During each of these phases of the cancer continuum, the links between PA and cancer variables may be quite different. Consequently, research is needed into the four overarching research themes across the four main postdiagnosis time periods.

TOP 10 RESEARCH QUESTIONS

In this article, we use these two frameworks to inform our proposed top 10 research questions in the field of PA and cancer survivorship. Our process for generating the top 10 research questions was to ask each coauthor to create their own list of the top 10 questions independently. Based on commonalities across the lists—as well as our desire to address all four research themes and the entire postdiagnosis time period—the first author distilled the five independent lists into one list of 14 questions. All coauthors then reviewed this list to reach a consensus on the top 10 questions. Given that our small group of coauthors did not achieve a full consensus on the top 10 questions, we recognize that there would likely be differences in the content and order of these questions among our colleagues. Nevertheless, we believe that many of these questions will be viewed as critical to the field of PA and cancer survivorship by other investigators, clinicians, cancer survivors, and their families. Our top 10 questions in the field of PA and cancer survivorship are presented in Table 1. The ranking of the 10 questions reflects some indication of their relative importance, although it is not precise. In the following sections, we provide a brief background and rationale for each of our top 10 selected research questions. Our primary goal is to highlight why these questions are important rather than to provide a comprehensive systematic review of the literature for each question.

1. Does PA Reduce the Risk for Cancer Recurrence and/or Improve Survival?

Perhaps the most compelling question for any cancer survivor is whether PA can alter the course of their disease. Numerous observational studies have shown that higher PA levels after a cancer diagnosis are associated with reduced

TABLE 1
Top 10 Research Questions Related to Physical Activity and Cancer Survivorship

1. Does physical activity reduce the risk for cancer recurrence and/or improve survival?
2. Does physical activity influence cancer treatment decisions, completion rates, and/or response?
3. What is the optimal physical activity prescription for cancer survivors?
4. What is the role of sedentary behavior in cancer survivorship?
5. What are the most effective physical activity behavior change interventions for cancer survivors?
6. Which cancer variables modify the response to physical activity?
7. What are the safety issues concerning physical activity in cancer survivors?
8. Which specific cancer symptoms can be managed by physical activity?
9. Is there a role for physical activity in cancer survivors with advanced disease?
10. How do we translate physical activity research into clinical and community oncology practice?

overall mortality and cancer-specific mortality (Ballard-Barbash et al., 2012). The magnitude of the risk reduction is 30% to 40% when comparing the most active to least active breast and colorectal cancer survivors. There is consistent evidence for an association from more than 20 breast cancer studies and 15 colorectal cancer studies that have examined either prediagnosis or postdiagnosis PA. Relatively few studies have been conducted for other cancer sites, although preliminary evidence for a protective effect of PA for prostate cancer outcomes also exists (Ballard-Barbash et al., 2012). There is some indication of a dose–response association in breast cancer survivors (Zhong et al., 2014). Most of the observational studies have been limited by self-reported PA in cohort studies not designed to examine PA and cancer survival. Perhaps most importantly, there have been no adequately powered randomized controlled trials (RCTs) that have examined the effects of a PA intervention on cancer survival. The World Cancer Research Fund (WCRF) recently classified the evidence regarding the role of PA on breast cancer survival as “limited” based on the lack of RCT evidence, the relatively few studies that have been conducted, and the lack of objective measures (WCRF International, 2014).

Since the WCRF International (2014) report, there has been one published follow-up of cancer outcomes from an RCT called the Supervised Trial of Aerobic versus Resistance Training (START; Courneya, Segal, et al., 2014). Researchers of the START trial randomly assigned 242 patients with breast cancer receiving adjuvant chemotherapy to aerobic exercise, resistance exercise, or usual care. The results showed that the exercise groups achieved a nonsignificantly improved 8-year disease-free survival (hazard ratio [HR] = 0.68, 95% confidence interval [CI] [0.37, 1.24]) and overall survival (HR = 0.60, 95% CI [0.27, 1.33]; Courneya, Segal, et al., 2014). These results are promising and warrant confirmation in a larger exercise trial that is adequately powered to study the effects of exercise during chemotherapy on breast cancer outcomes.

One Phase III trial designed to examine the effects of exercise on cancer survival is currently ongoing. The Colon Health And Life-Long Exercise ChaNGE (CHALLENGE) trial is examining the effects of a 3-year structured exercise program on disease-free survival in 962 high-risk Stage II and III colon cancer survivors (Courneya, Vardy, et al., 2014). Additional RCTs are needed to examine the effects of different types and doses of PA on cancer outcomes in different cancer survivor groups. In the absence of RCTs, better quality observational studies are needed. For example, the ongoing Alberta Moving Beyond Breast Cancer (AMBER) study is the first prospective cohort designed specifically to examine the role of PA and health-related fitness (HRF) in breast cancer survival (Courneya, Vallance, et al., 2012). The AMBER study will recruit 1,500 patients with newly diagnosed breast cancer and collect objective measures of PA and HRF soon after diagnosis, at 1 year, and at a 3-year follow-up. Recurrence and mortality outcomes will be assessed up to 10 years postdiagnosis (Courneya, Vallance, et al., 2012). This large cohort study is also collecting biologic data to examine how biomarkers associated with PA may influence survival after breast cancer. Studies like the CHALLENGE trial and AMBER cohort will provide strong evidence on the role of PA in cancer survival.

2. Does PA Influence Cancer Treatment Decisions, Completion Rates, and/or Response?

Next to improving survival, perhaps the most compelling clinical question for cancer survivors and oncology providers is whether PA can influence treatments. Any effects of PA on treatments may indirectly influence the risk for cancer recurrence and overall survival. PA may influence treatment decisions because almost all cancer treatment guidelines suggest that oncologists should take into account the overall health and physical condition of the patient in making treatment decisions. This implies that cancer survivors who are in poor physical condition may not be offered more intensive treatments such as major surgical procedures, extensive radiotherapy protocols, or cardiotoxic chemotherapies even though such treatments may improve survival. PA interventions after diagnosis could influence these treatment decisions if there is a time delay between diagnosis and the first-line treatment or if there are second- and third-line therapies available after initial treatment. Moreover, PA interventions could influence treatment completion rates by improving the overall health of patients or by managing specific symptoms that may cause treatment delays, dose reductions, or discontinuation (e.g., bone marrow recovery, febrile neutropenia, peripheral neuropathy, arthralgias, fatigue). Finally, PA interventions could influence treatment response through influences on drug distribution, metabolism, or tumor physiology.

Limited research has examined the effects of PA on cancer treatments. The START trial described earlier reported that the weight-training group completed more of their chemotherapy than the usual-care group (Courneya et al., 2007). Another study, the Healthy Exercise for Lymphoma Patients (HELP) trial, compared aerobic exercise to usual care in 122 patients with lymphoma who were receiving chemotherapy or no treatment (Courneya et al., 2009). In the 54 patients who were receiving chemotherapy, it was reported that the exercise group completed 94% of its planned maximum number of cycles compared with 89% for the control group. Moreover, 46.4% of patients with lymphoma in the exercise group had a complete response to their chemotherapy compared with just 30.8% in the usual-care group. In neither of these studies, however, was a cancer treatment variable the primary outcome. Consequently, these data are only suggestive of PA treatment effects and are hypothesis-generating. What are needed are large Phase III trials with treatment variables as the primary outcome. If PA interventions are shown to influence cancer treatment decisions, completion rates, and/or response, this indeed would be compelling evidence for clinical benefit in cancer survivors.

3. What Is the Optimal PA Prescription for Cancer Survivors?

Although many PA programs have been demonstrated to be safe and efficacious in many cancer survivor groups, the optimal PA prescription for cancer survivors is unknown. To date, the majority of studies have compared a single PA prescription to no exercise at all (i.e., usual care, attention control, or education only). As a result, the current ACSM (Schmitz et al., 2010) Exercise Guidelines for Cancer Survivors provide a general recommendation that cancer survivors should avoid inactivity, return to normal daily activities as soon as possible following diagnosis, and follow the general PA guidelines for aerobic and strength exercise (Schmitz et al., 2010).

To determine the optimal PA prescription for cancer survivors, second-generation studies are needed that directly compare exercise prescriptions. The main components of an exercise prescription are *frequency, intensity, type, and time*, or the FITT principle. Each of these components can be manipulated to determine its effects on a given outcome in a given cancer survivor group. To date, however, few studies have directly compared two or more PA prescriptions in a cancer survivor group.

The *intensity* of PA is one important component. Because the safety of low- and moderate-intensity activity has been demonstrated in many cancer survivor groups, there is some interest in examining the role of vigorous-intensity activity or higher-intensity interval training. A comparison of a prescription of vigorous or high-intensity versus low-to-moderate intensity aerobic and resistance exercise is planned in an ongoing Dutch trial in a mixed cancer group following adjuvant treatment (Chinapaw et al., 2012). The safety and efficacy of high-intensity interval training compared to a standard continuous aerobic exercise prescription or comparing difference exercise *intensities* using a fixed exercise volume (i.e., time to achieve the same energy expenditure) has not been reported in cancer survivors.

In terms of exercise *type*, several studies have compared aerobic and strength exercise. For example, Segal et al. (2009) compared 24 weeks of aerobic exercise to resistance exercise and usual care in men receiving radiotherapy (with or without androgen deprivation therapy) for prostate cancer. Although both aerobic and resistance exercise improved fatigue at 12 weeks, only the resistance exercise group had improved fatigue levels compared with usual-care controls at 24 weeks. With increased interest in other types of PA, such as yoga, tai chi, Qigong, extreme sports, and adventure activities, additional exercise *type* studies are warranted.

Time or *duration* can also be manipulated in exercise trials. In women undergoing chemotherapy treatment for breast cancer, Courneya et al. (2013) tested the impact of duration of aerobic exercise in a three-arm trial that used the same exercise *frequency* (three times per week) and *intensity* (55% to 75% peak oxygen consumption), but they compared a *standard duration* of aerobic exercise (25 min–30 min) to a *higher duration* of aerobic exercise (50 min–60 min) as well as a combined aerobic and resistance group (Courneya et al., 2013). For the primary outcome of patient-reported physical functioning, there was no additional benefit with the higher-duration or combined aerobic and resistance interventions. There were differences, however, for several important secondary outcomes such as endocrine symptoms, bodily pain, and physical health. Additional studies manipulating different components of an exercise prescription to determine their effects on specific outcomes in defined cancer survivor populations as well as improved reporting of adherence to each exercise prescription component (Campbell, Neil, & Winters-Stone, 2012) will help refine the exercise guidelines for cancer survivors.

4. What Is the Role of Sedentary Behavior in Cancer Survivorship?

Sedentary behaviors are activities low in energy expenditure. They have been conceptualized as sitting or reclining and are in the energy-expenditure range of 1.0 to 1.5 metabolic equivalents. Sedentary behavior is emerging as an important and distinct field of scientific inquiry for cancer survivorship research (Lynch, 2010). Sitting time has been associated with mechanisms operative in carcinogenesis (adiposity, metabolic dysfunction, inflammation, and vitamin D deficiency) and could therefore plausibly contribute to adverse disease outcomes in cancer survivors. Recent objective estimates (using accelerometers) of sedentary time suggest that cancer survivors spend 60% to 70% of their waking hours in sedentary pursuits. In the only study to assess sitting time objectively (previous studies included sitting and standing combined), Lowe and colleagues (2014) reported that patients with cancer and brain metastases were sitting/supine for an average of 20.2 hr per day and were standing for an average 2.0 hr per day. Taken collectively, cancer survivors spend the overwhelming majority of their waking hours in sedentary pursuits, the consequences of which are largely unknown.

Given the limited number of published studies to date and the mixed and conflicting results, it is difficult to draw conclusions regarding associations of sedentary time and health outcomes among cancer survivors. Using objectively assessed sedentary time, Vallance, Boyle, Courneya, and Lynch (2014) found no associations with quality of life, fatigue, depression, anxiety, or satisfaction with life among colon cancer survivors. Conversely, among patients with brain metastases, those who were sitting/supine for at least 20.7 hr per day reported higher depression, anxiety, and drowsiness, as well as poor well-being compared with patients who were supine for less than 20.7 hr per day (Lowe et al., 2014). Interestingly, these patients also reported better physical functioning, which suggests that among patients with advanced cancer, perhaps sitting has a protective effect on physical function. Finally, patients who stood for 1.6 hr or more per day had better quality of life compared with patients who stood for less than 1.6 hr per day.

Many key questions remain regarding the study of sedentary behavior in cancer survivors. Although limited in number, current studies indicate the association between sedentary time (not necessarily sitting) and quality of life, fatigue, and other psychosocial health outcomes may differ among survivors of different cancers. These inconsistent relationships between sedentary time and patient-reported outcomes, however, might be due to the self-reported sedentary time assessments (e.g., highly variable responses) and the heterogeneous samples recruited into several of these studies. With the exception of one study (Lowe et al., 2014), all studies objectively assessing sedentary time have not considered posture-specific behaviors (i.e., sitting). Future studies should obtain objective assessments of both total sedentary time (accelerometers) as well as the specific behavior of sitting (inclinometers). Along with objective measures, an understanding of how sedentary time changes across the cancer trajectory (i.e., from diagnosis to death) is currently lacking. Unknown are the associations between sedentary time and physical health outcomes (e.g., body mass index, functional well-being), HRF outcomes (e.g., cardiorespiratory fitness, muscular strength), and cancer-related outcomes (e.g., recurrence, mortality). Determining the unique contribution of sedentary time to these health outcomes is an important undertaking in PA and cancer survivorship research.

5. What Are the Most Effective PA Behavior Change Interventions for Cancer Survivors?

Given the proven benefits of PA in cancer survivors and the low PA participation rates, it is essential to determine the most effective interventions for helping cancer survivors increase PA. Several behavior change RCTs (i.e., the primary outcome was PA) have demonstrated significant effects on aerobic exercise. These interventions have ranged from less intensive interventions using print materials with pedometers (Vallance, Courneya, Plotnikoff, Yasui, & Mackey, 2007) to more intensive contact using telephone-delivered (Pinto et al., 2008) or multicomponent behavioral support (individual and group combined with supervised and home-based exercise; Rogers et al., 2009). Nevertheless, the percent of cancer survivors meeting recommendations after the interventions has not exceeded 65%, and most have not documented increased PA with an objective measure (Bourke et al., 2013). Therefore, a better understanding of the most effective PA behavior change interventions for cancer survivors is crucial for increasing the number of survivors experiencing PA benefits.

In addition to increasing PA behavior in the short term, methods for achieving long-term maintenance of PA are needed. Moreover, identifying which behavior change intervention components are most effective is also critical (Kampshoff et al., 2014). Similarly, there are insufficient published data regarding moderating factors that could be used to individualize behavior change interventions. Therefore, larger RCTs of PA behavior change interventions are needed to determine mediating and moderating factors.

It is also noteworthy that most behavior change interventions have focused on common cancer types and increasing aerobic PA (as opposed to resistance exercise). Moreover, these interventions have almost exclusively been studied in healthy cancer survivors without advanced disease or significant medical comorbidities. Interventions for understudied groups (e.g., advanced disease, less prevalent cancer types, significant noncancer medical comorbidities) should be developed and tested, as should interventions that increase both aerobic and resistance exercise. Lastly, the most effective technologies for changing PA behavior in cancer survivors are understudied and warrant further research. One pilot study using an e-mail intervention demonstrated promising results for increasing PA behavior in breast cancer survivors (Hatchett, Hallam, & Ford, 2013). As research in this area grows, strategies for overcoming barriers related to suboptimal user engagement, privacy concerns, and limited Internet access for certain subgroups should be tested (Cavallo, Chou, McQueen, Ramirez, & Riley, 2014).

6. Which Cancer Variables Modify the Response to PA?

As noted by Courneya (2014), the proposition that cancer variables may moderate the response to PA is fundamental to the field of PA and cancer survivorship because it suggests that research on other populations cannot be generalized to cancer survivors. Moreover, even research within the cancer setting cannot be generalized across cancer settings (e.g., from patients with breast cancer receiving chemotherapy to patients with prostate cancer receiving hormone therapy). Identifying which cancer variables modify which PA outcomes is critical for improving clinical practice in exercise oncology.

Most of the research in the field of PA and cancer survivorship has treated cancer variables as implied moderators of the exercise response (Courneya, 2014). That is, the rationale for the study implies a potentially different exercise response based on some cancer variable, but the moderator counterpart is not actually included in the study. There are a number of important conceptual and methodological issues to consider when examining cancer moderators in randomized exercise trials (Courneya, 2014). Some of the most important design and analytical features include a direct test of the moderator within the randomized trial design, a statistical test of the interaction, and adequate power to test the interaction effect (Courneya, 2014). Few exercise oncology trials have provided strong tests of cancer moderators, in large part because of inadequate sample sizes.

The START trial was the first trial to report that the chemotherapy protocol might moderate the PA response (Courneya et al., 2008). Specifically, weight training resulted in a larger improvement in muscular strength in patients with breast cancer who were receiving non-taxane-based chemotherapies compared with patients with breast cancer receiving taxane-based chemotherapies. Moreover, patients with breast cancer with more advanced disease stage experienced improvements in body composition, whereas no such benefits were observed for patients with breast cancer who had local disease. The HELP trial also revealed that the effects of aerobic exercise on lean body mass were moderated by disease stage (Courneya et al., 2009). Specifically, aerobic exercise training resulted in a significant increase in lean body mass for patients with Stage III/IV lymphoma but not for patients with Stage I/II disease or those with no evidence of disease. However, neither the START trial nor the HELP trial was powered to test for moderator effects.

Uncovering the most important cancer moderators of the exercise response is a critical undertaking for the field of PA and cancer survivorship. Based on current research, there is some suggestion that cancer type, disease stage, and treatments may moderate the exercise response, but the relative importance of these moderators is unknown. Moreover, the relative importance of cancer variables as moderators of PA outcomes may depend on the PA intervention and the health outcome. Large Phase III trials with adequate power to test for a-priori hypothesized cancer moderators are needed to determine which cancer variables should drive the exercise prescription for cancer survivors.

7. What Are the Safety Issues Concerning PA in Cancer Survivors?

Questions about the safety of PA are a critical issue in any chronic disease populations including cancer survivors. There is now an accumulating research literature from RCTs demonstrating the benefits of PA for cancer survivors with a variety of cancer diagnosis and treatment approaches. Unfortunately, this literature may have led to the general impression that exercise is safe for all cancer survivors without considering that legitimate safety concerns do remain. The Exercise Guidelines for Cancer Survivors from the ACSM (Schmitz et al., 2010) provide some exercise contraindications by cancer site, and the PA guidelines from the American Cancer Society (Rock et al., 2012) provide additional general precautions. Nevertheless, establishing the safety of exercise for all cancer survivors has been limited by several factors.

First, most trials to date have been very selective in the recruitment of participants, which likely excludes many “high-risk” survivors. Second, the majority of research has been focused on the more common cancers—namely breast, prostate, and colon cancers. Finally, comprehensive adverse event reporting has been limited in the published literature (Mishra, Scherer, Snyder, et al., 2012). The select populations and limited information on adverse events pose a challenge to documenting the safety of exercise for many cancer survivor groups.

Although issues such as bone health, risk, and management of lymphedema and the prevalence of cardiotoxicity related to specific treatment modalities are important safety concerns, three prominent safety issues that are either unique to cancer or relevant across many cancer sites are: (a) immune compromise, (b) advanced disease, and (c) appropriate safety screening for engagement in exercise. Specific to chemotherapy and hematopoietic stem cell transplant, immune compromise and altered blood counts, including low hemoglobin, low white blood cells, and low platelets, are an important safety consideration. Although specific guidelines and safety cut points for exercise have been published (McNeely & Campbell, in press), there is limited research on the potential of exercise to improve immune parameters in cancer survivors (Kruijsen-Jaarsma, Revesz, Bierings, Buffart, & Takken, 2013). The impact of exercise in patients with advanced disease, particularly those with bone metastases, has not been adequately researched. To date, the majority of studies have focused on individuals with early-stage cancer (Albrecht & Taylor, 2012).

Finally, the appropriate safety screening and approach to medical clearance for exercise for cancer survivors remains unclear. The main objective is to eliminate unnecessary barriers to exercise while ensuring that key safety issues are identified and addressed. A 2014 survey asked experts in the field of exercise physiology, rehabilitation medicine, and cancer survivorship which individuals should undergo a pre-exercise evaluation prior to engaging in unsupervised moderate- to vigorous-intensity exercise (Brown, Ko, & Schmitz, 2014). Despite a consensus that pre-exercise evaluation was indicated based on specific comorbidities, use of medications related to cardiovascular disease, and presence of some acute symptoms, 38% of respondents noted it was difficult to provide absolute answers because no two patients are alike (Brown et al., 2014). Studies are needed that systematically report adverse events and target higher-risk cancer survivors rather than exclude them.

8. Which Specific Cancer Symptoms Can Be Managed by PA?

Exercise has been shown to have modest but significant positive effects on several symptoms including fatigue, sleep disturbance, depression, and anxiety in patients with cancer (Mishra, Scherer, Snyder, et al., 2012) and cancer survivors (Mishra, Scherer, Geigle, et al., 2012), but few studies have targeted patients with these symptoms. For example, Speck, Courneya, Masse, Duval, and Schmitz (2010) reviewed more than 80 exercise trials involving almost 7,000 cancer survivors and noted that few exercise trials targeted participants based on their need for improvement in the symptom (e.g., fatigued, depressed, poor sleep). Consequently, most exercise trials and subsequent meta-analyses have likely underestimated the benefit of exercise for a given symptom because of a ceiling or floor effect. The lack of targeted trials means that the effect of exercise on these symptoms is likely under-appreciated and there are insufficient data to develop clinical practice guidelines for managing symptoms with exercise. Exercise trials are needed that target patients with cancer with existing symptoms (i.e., symptom control exercise trials) to provide a clear clinical indication to support exercise interventions in patients with cancer in the absence of data for a survival benefit.

For example, in the HELP trial (Courneya, Sellar, et al., 2012), there was no overall benefit of exercise on sleep quality in 122 patients with lymphoma who were receiving chemotherapy or no treatments. In a planned subgroup analysis, however, there was a statistically significant interaction between group assignment and baseline sleep quality (p for interaction $= .041$). Specifically, exercise compared with usual care improved sleep quality by -1.95 points in patients who were poor sleepers at baseline ($p = .007$, $d = -0.74$), but it had no effect in patients who were good sleepers at baseline ($p = .92$, $d = 0.06$). A similar interaction was reported in the Combined Aerobic and Resistance Exercise trial of 301 patients with breast cancer receiving chemotherapy (Courneya, McKenzie, et al., 2014). There was no overall effect of high-dose versus standard-dose exercise on depression, but there was a statistically significant interaction between group assignment and baseline level of depressive symptoms (p for interaction $= .027$). In subgroup analyses of patients with clinical levels of depressive symptoms at baseline ($n = 93$), high-dose exercise was superior to standard-dose exercise (mean group difference $= -2.2$, 95% CI $[-0.1, -4.3]$, $p = .039$, $d = -0.47$). Conversely, there was no difference for patients with low depressive symptoms at baseline. These data suggest that exercise interventions targeted to patients with cancer who have sleep problems or depression may yield clinically important benefits.

Moreover, symptom control studies are needed for some other common but understudied symptoms such as nausea/vomiting, pain, peripheral neuropathy, arthralgia, hot flashes, bowel function, sexual function, and cognitive dysfunction. More robust research is starting to emerge exploring specific cancer symptoms and side effects and the potential role of PA in alleviating these outcomes. For example, one recent study of patients with lymphoma with chemotherapy-induced peripheral neuropathy showed that the intervention group reported an 87.5% reduction in reduced deep sensitivity compared with a 0% reduction observed in the control group (Streckmann et al., 2014).

9. Is There a Role for PA in Cancer Survivors With Advanced Disease?

To date, relatively few studies have examined how PA can improve outcomes for cancer survivors with advanced disease because of the challenges in studying this population. Some limited evidence exists that PA in survivors with advanced cancer can decrease anxiety, stress, depression, pain, fatigue, shortness of breath, constipation, and insomnia (Albrecht & Taylor, 2012). Cancer survivors with advanced disease often have decreased physical functioning and multiple concurrent symptoms (including pain, fatigue, nausea, and dyspnea) that are a direct consequence of their cancer treatment and disease progression; hence, optimizing the functional abilities that remain and controlling these symptoms are key objectives of a PA intervention in this group (Albrecht & Taylor, 2012; Lowe et al., 2014).

The studies that have been conducted are generally small-scale and are hampered by methodological limitations. For example, recruitment into intervention studies in advanced cancer is often low and attrition-high.

Eligibility criteria may exclude patients who have the characteristics that have not yet been adequately studied such as patients who have experienced a large weight loss or who are very weak and deconditioned. The possibility of selection bias exists in these studies because the participants who drop out of the intervention trials are likely those who have not benefitted from the intervention because of poor health. Given the lack of available data from well-controlled intervention trials or even from large prospective observational studies, no guidelines have yet been developed for this patient population because it remains unknown if exercise is safe and efficacious for cancer survivors with advanced disease. Patients diagnosed with advanced cancer often experience severe declines in functional status with difficulties performing even activities of daily living that are a consequence of their late-stage disease and the more extensive and aggressive treatments they often receive. It has been recognized that these patients are rarely referred to rehabilitation to improve their functional status despite the emerging evidence that they may experience some benefits from PA and are willing to participate (Lowe, Watanabe, Baracos, & Courneya, 2009).

Several methodological issues that are specific to this patient group need to be considered in the design and reporting of results from observational studies and intervention trials in advanced cancer. Outcomes measures specific for participants with advanced cancer are needed because progressive functional decline is inevitable in this group. Future research should ascertain the optimal PA interventions in advanced cancers to include the safety, feasibility, and efficacy of different types, doses, and timing of these interventions. Intervention studies will need to address the methodological issues specific to this population including the need for appropriately timed and individually tailored interventions.

10. How Do We Translate PA Research Into Clinical and Community Oncology Practice?

The efficacy of PA interventions in many cancer survivor groups is well established when tested in scientific settings with trained research staff. This step in the translational continuum has led to evidence-based PA guidelines (Rock et al., 2012; Schmitz et al., 2010). There have been few effectiveness trials of exercise in cancer survivors; hence, less is known about how to translate this information into "real-world" settings and few disseminable interventions for increasing PA in cancer survivors exist (Phillips & McAuley, 2015). Dissemination and implementation (D&I) science develops and tests strategies that increase dissemination (e.g., distributing knowledge, spreading interventions) and implementation (e.g., process of integrating and adopting new interventions) and that are used in translation of interventions to nonresearch settings (Brownson, Jacobs, Tabak, Hoehner, & Stamatakis, 2013). Two D&I goals of particular importance to the PA and cancer survivorship field include: (a) increase intervention uptake to boost the number of individuals benefiting from scientific research, and (b) minimize the loss in efficacy that often occurs when an intervention is implemented in a nonresearch setting (Brownson et al., 2013).

An important step in increasing D&I in cancer practice is dissemination of information to oncology health care professionals regarding exercise benefits and PA behavior change interventions. The inclusion of an exercise intervention algorithm in the National Comprehensive Cancer Network (NCCN, 2014) survivorship guidelines suggests that exercise efficacy information is reaching oncology health care professionals (NCCN, 2014). This education should be ongoing as new data become available regarding the optimal exercise type, dose, timing, and moderators of response. What is not known is how to best reach and educate the health care professional so that practice patterns change. Although scientific presentations at national and international oncology meetings are important, other potential methods for educating health care professionals using phone apps, online resources, and credentialing organizations have not been well studied.

Likewise, very little is known about how to improve implementation of PA and cancer interventions in "real-world" settings (e.g., carried out within a health care infrastructure using nonresearch staff and resources). For example, PA and cancer survivorship D&I trials are needed to determine the following: (a) optimal strategies for obtaining stakeholder buy-in within the clinical organizations, (b) effects of integrating PA counseling and referral into the survivorship care plan and/or the electronic health record on prompting and changing clinical practice, (c) ideal methods for maintaining intervention fidelity when training nonresearch staff to implement an intervention, and (d) implementation approaches for integrating exercise professionals into the health care setting and referral pathways.

One excellent example of an exercise oncology implementation study has been recently published (Beidas et al., 2014). This study tested the effectiveness and implementation of a strength-training program that had previously been demonstrated to be safe and efficacious for breast cancer survivors in a well-controlled randomized trial. The "Strength After Breast Cancer" program was delivered to 84 breast cancer survivors in a community-based physical therapy setting and showed similar safety and health benefits to those of the original efficacy trial. The one exception was the smaller improvements in muscular strength in the implementation study than in the original efficacy trial. Moreover, the study identified challenges to implementation that could be addressed to further improve the implementation of this evidence-based intervention.

A major factor in broader intervention implementation is cost. Few studies have performed an economic analysis of PA interventions, and additional research determining cost-effectiveness and return on investment is needed (Phillips & McAuley, 2015). Such information can then be used to lobby third-party payers to cover the cost of PA interventions and, in so doing, increase sustainability of intervention implementation in the longer term. D&I research in PA and cancer survivorship is crucial to the field and will require collaborations among exercise oncology, D&I, and health economics experts.

SUMMARY AND CONCLUSIONS

The number of cancer survivors in the United States and around the world will continue to increase. Many of these survivors will experience side effects and symptoms from their cancer and its treatments that may be improved with PA. In this article, we proposed our top 10 research questions for the field of PA and cancer survivorship. We believe that the answers to these questions are critical not only for advancing the field of PA and cancer survivorship, but for improving the lives of the millions of cancer survivors every year who are newly diagnosed, receiving treatments, recovering from cancer, or coping with advanced disease.

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