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RESEARCH UPDATES 2020 VOLUME 1

FOR THE LATEST IN WORLDWIDE SUPPORTIVE CANCER CARE

IN THIS ISSUE:

This issue is dedicated to exploring the role of exercise as a specific adjunct to cancer treatment. In particular, exercise has been shown to mitigate many of the common side effects of cancer treatment. Research supporting exercise's many benefits is consistent and robust and includes both molecular and human studies. We are pleased to share some of it with you.

PHYSICAL ACTIVITY IN PREVENTION & SURVIVAL

McTiernan, A., Friedenreich, C.M., Katzmarzyk, P.T., et al.

Physical activity in cancer prevention and survival: A systematic review

Medicine in Science, Sports, & Exercise (2019), 51(6), 1252-1261.

ABSTRACT | Purpose: This article reviews and updates the evidence on the associations between physical activity and risk for cancer, and for mortality in persons with cancer, as presented in the 2018 Physical Activity Guidelines Advisory Committee Scientific Report. **Methods:** Systematic reviews of meta-analyses, systematic reviews, and pooled analyses were conducted through December 2016. An updated systematic review of such reports plus original research through February 2018 was conducted. This article also identifies future research needs. **Results:** In reviewing 45 reports comprising hundreds of epidemiologic studies with several million study participants, the report found strong evidence for an association between highest versus lowest physical activity levels and reduced risks of bladder, breast, colon, endometrial, esophageal adenocarcinoma, renal, and gastric cancers. Relative risk reductions ranged from approximately 10% to 20%. Based on 18 systematic reviews and meta-analyses, the report also found moderate or limited associations between greater amounts of physical activity and decreased all-cause and cancer-specific mortality in individuals with a diagnosis of breast, colorectal, or prostate cancer, with relative risk reductions ranging almost up to 40% to 50%. The updated search, with five meta-analyses and 25 source articles reviewed, confirmed these findings. **Conclusions:** Levels of physical activity recommended in the 2018 Guidelines are associated with reduced risk and improved survival for several cancers. More research is needed to determine the associations between physical activity and incidence for less common cancers and associations with survival for other cancers. Future studies of cancer incidence and mortality should consider these associations for population subgroups, to determine dose-response relationships between physical activity and cancer risk and prognosis, and to establish mechanisms to explain these associations.

INSPIREHEALTH'S INTERPRETATION: In 2019 an estimated 220,400 new cancers will be diagnosed among Canadians and 82,000 Canadian cancer-related deaths will occur. An estimated 63% of Canadians diagnosed with cancer in 2019 will survive for at least five years. For many, cancer is a manageable chronic illness. It is imperative, therefore, to develop strategies to optimize cancer survival. Most cancers are caused by a complex interaction of genetic, environmental and lifestyle factors. While much research has been done to identify lifestyle factors which may reduce the development of cancer in the first place, researchers are now concentrating on the lifestyle factors associated with increased cancer survival. In particular, the role of exercise is studied. The authors of this review examined the relationship between exercise and cancer incidence (new cancer diagnoses), and also investigated the following questions: "Among cancer survivors, what is the relationship between physical activity and 1) all cause mortality, 2) cancer-specific mortality, or 3) risk of cancer recurrence or second primary [new] cancer?" This systematic review included the results of 68 previously summarized reviews, meta-analyses, or pooled analyses (with several million participants) addressing physical activity and cancer risk/survival. For cancer prevention, strong evidence was found for physical activity reducing risk for bladder, breast, colon, endometrial, esophagus, gastric and renal cancers,

and moderate evidence for preventing lung cancer (overall reducing risk by 10%-20%). For many other cancers, evidence was either limited or insufficient. For cancer survival, moderate evidence suggested that greater physical activity levels were associated with decreased all-cause and cancer-specific mortality (overall reducing risk by 40%-50%), especially in those with breast, colorectal, or prostate cancers. Interestingly only post-diagnosis physical activity was included in the review of cancer survival and importantly, "…there did not appear to be a lower threshold below which no benefit was evident…almost any level of physical activity confers some benefit.". This finding is especially important for those who have been more sedentary prior to a diagnosis of cancer and illustrates the facts that it's "never to late to start", and "some activity is better than none".

EXERCISE IN ADVANCED SOLID TUMORS

Nadler MB, Desnoyers A, Langelier, DM, Amir E.

The effect of exercise on quality of life, fatigue, physical function, and safety in advanced solid tumor cancers: A meta-analysis of randomized control trials

Journal of Pain and Symptom Management (2019), 58(5):899-908.e7

ABSTRACT | Background: People with metastatic cancers experience poor quality of life (QoL), fatigue, and decreased physical function. Exercise improves these symptoms in the curative setting, but the efficacy and safety of exercise in the metastatic setting is uncertain. **Methods:** Prospective, randomized trials of moderate/high-intensity aerobic exercise or resistance training vs. control in patients with advanced/metastatic solid cancers were identified from prior reviews and updated using a search of PubMed. The mean and SD for validated outcome measures (QoL, physical function, and fatigue) were extracted for intervention and control groups at baseline and postintervention. The Mann-Whitney test was used to evaluate the effect of exercise on the pooled change between baseline and postintervention. Safety was evaluated qualitatively. **Results:** Sixteen trials were analyzed. Among patients with scores at the mean or 2SD above, exercise was not associated with significant or clinical difference in QoL or fatigue. In patients with baseline scores 2SD below mean, exercise was associated with nonsignificant difference meeting minimal clinical important difference in QoL (-2.8 vs. 4.6, P = 0.28). For function, patients at the mean had nonstatistically significant, but clinically meaningful difference in the six-minute walk test (6-MWT) (14.7 vs. 29.0 m, P = 0.44). In patients 2 SD below the mean, there was a clinically meaningful difference in two patient-reported functional subscales (0.1 vs. 5.3, P = 0.076 and 0.44 vs. 8.5, P = 0.465) and a clinically meaningful improvement in the 6-MWT (-7.5 vs. 27.0 m, P = 0.34), although none of these associations met statistical significance. There were no differences in falls, fractures, or pain. **Discussion:** Exercise is associated with clinically meaningful improvements in QoL, function, and 6-MWT in some patients with metastatic cancer. Despite poor reporting of safety, there was no signal of increased harm from exercise in this setting.

INSPIREHEALTH'S INTERPRETATION: It is well known that exercise can improve symptoms and quality of life for cancer patients, and many international guidelines recognize these benefits. However, there is a group of patients for whom the evidence on exercise is not as straightforward: patients with advanced cancers. For a patient with metastases or locally advanced cancer, the combination of the disease and the treatment can lead to many side effects including fatigue and decline in physical function, which in turn can decrease quality of life. Some clinicians have been hesitant to recommend exercise for these patients, mostly due to safety concerns. Recent publications suggest that exercising is feasible and safe, and may in turn improve quality of life.

This meta-analysis reviewed 16 studies measuring fatigue, physical function and overall quality of life, to understand the role of exercise for patients with advanced cancer. Exercise intensity ranged from moderate to vigorous, and the type of cancers varied among studies. Although not statistically significant, there were benefits for quality of life and physical function markers especially for those with limited exercise exposure/practice and reduced quality of life at baseline. Trials lasted between two and 16 weeks, suggesting that exercise effects were evident early on. Although the meta-analysis did not see improvements in fatigue, it is speculated that longer follow-up times could show better results, and exercise could protect from further decline in energy levels. Reported side effects such as muscular pain tended to be minor. The exercise in these trials happened under supervision of healthcare professionals, which could explain the positive safety results. At InspireHealth, our qualified exercise therapists tailor personalized exercise programs and supervise our many exercise class offerings. This approach ensures safety and has the potential for symptom management for everybody, including those with advanced cancers.

EXERCISE AND THE IMMUNE SYSTEM

Khosravi, N., Stoner, L., Farajivafa, V., et al.

Exercise training, circulating cytokine levels and immune function in cancer survivors: A meta-analysis

Brain, Behavior, and Immunity (2019), 81, 92-104, doi: 10.1016/j.bbi.2019.08.187. Epub 2019 Aug 24.

ABSTRACT | Background: Anti-cancer therapies lead to chronic non-resolving inflammation and reduced immune function. One potential therapy is exercise training, but the effectiveness of these interventions to improve immune-related outcomes, the gaps in the literature, and recommendations to progress the field need to be determined. **Objectives:** (1) to conduct

separate meta-analyses in cancer survivors to determine the effects of exercise training on pro- and anti-inflammatory markers, and immune cell proportions and function; and (2) to perform subgroup analyses to determine whether exercise modality, cancer type, and specific markers help to explain heterogeneity in each meta-analysis. **Data Sources:** Electronic databases (PubMed/MEDLINE, EMBASE, CENTRAL, and CINAHL) from inception to March 2018. The reference lists of eligible articles and relevant reviews were also checked. **Study Selection:** Inclusion criteria were adult cancer survivors from randomized controlled trials performing structured exercise intervention (aerobic, resistance or combined training or Tai Chi/yoga) compared to usual care control group and included pro-inflammatory, anti-inflammatory, and/or immune cell outcomes. **Appraisal and Synthesis Methods:** A total of 5349 potentially eligible articles were identified, of which 26 articles (27 trials) met the inclusion criteria. Effect sizes were calculated as standardized mean differences (SMD), where <0.2 was defined as trivial, 0.2-0.3 as small, 0.4-0.8 as moderate, and >0.8 as a large effect. **Results:** Exercise training decreased pro-inflammatory markers (SMD: -0.2, 95% CI: -0.4, -0.1, $p < 0.001$). Sub-group analysis for the pro-inflammatory markers indicated that combined aerobic and resistance training had the greatest effect (SMD: -0.3, 95% CI: -0.5, -1.9, $p < 0.001$), that prostate (SMD: -0.5, 95% CI: -0.8, 0.1, $p = 0.004$) and breast cancer populations were most responsive (SMD: -0.2, 95% CI: -0.3, -0.1, $p = 0.001$), and that C-reactive protein (SMD: -0.5, 95% CI: -0.9, -0.06, $p = 0.025$) and tumor necrosis factor (SMD: -0.3, 95% CI: -0.5, -0.06, $p = 0.004$) were the most sensitive to change. Exercise training tended to decrease anti-inflammatory markers ($p = 0.072$) but had no effect on natural killer or natural killer T cell proportions or cytotoxic activity. **Conclusions:** Exercise training reduces pro-inflammatory markers in cancer survivors, with the strongest evidence for combined training and for prostate and breast cancer survivors. Further research is warranted to determine if these changes are clinically relevant or are associated with improvements in symptoms. To strengthen future research, focusing on novel immune populations that include functional parameters and standardized reporting of key immune outcomes is recommended.

INSPIREHEALTH'S INTERPRETATION: Chronic inflammation and compromised immunity may play crucial roles in cancer development and progression. This meta-analysis reveals that higher levels of specific inflammatory markers have been observed in cancer patients and are also associated with higher mortality rates. Cytokines are a group of small protein messenger molecules secreted by some immune cells to regulate immunity, inflammation and red and white blood cell formation. Immune function is important since properly functioning immune cells recognize and eliminate tumours. Evidence shows that exercise can optimize immunity by increasing the total number of certain types of helpful immune cells such as natural killer cells and lymphocytes. As regulators of inflammation, cytokines can have either anti- or pro-inflammatory functions. Because cancer treatment itself can promote some inflammation and reduce immunity, it is critical to find ways to manage these negative effects. One of those ways, we now know, is exercise.

The authors conclude that exercise training reduces pro-inflammatory markers, and that combination training (aerobic and resistance training) is the most effective mode for reducing inflammation. The greatest decrease in pro-inflammatory markers is seen in prostate and breast cancer patients. While exercise also tends to reduce some anti-inflammatory cytokines, its overall effect is to reduce inflammation and optimize immune function. The authors conclude that oncology guidelines should consider reduced inflammation as an evidence-based outcome of exercise.

EXERCISE & CANCER POSITION STAND

Cormie P, Atkinson M, Bucci L, Cust A, Eakin E, Hayes S, et al.

Clinical Oncology Society of Australia position statement on exercise in cancer care

Medical Journal of Australia (2018), 209 (4): 1-4. doi: 10.5694/mja18.00199

ABSTRACT | Introduction: Clinical research has established exercise as a safe and effective intervention to counteract the adverse physical and psychological effects of cancer and its treatment. This article summarises the position of the Clinical Oncology Society of Australia (COSA) on the role of exercise in cancer care, taking into account the strengths and limitations of the evidence base. It provides guidance for all health professionals involved in the care of people with cancer about integrating exercise into routine cancer care. **Main recommendations:** COSA calls for: exercise to be embedded as part of standard practice in cancer care and to be viewed as an adjunct therapy that helps counteract the adverse effects of cancer and its treatment; all members of the multidisciplinary cancer team to promote physical activity and recommend that people with cancer adhere to exercise guidelines; and best practice cancer care to include referral to an accredited exercise physiologist or physiotherapist with experience in cancer care. **Changes in management as a result of the guideline:** COSA encourages all health professionals involved in the care of people with cancer to: discuss the role of exercise in cancer recovery; recommend their patients adhere to exercise guidelines (avoid inactivity and progress towards at least 150 minutes of moderate intensity aerobic exercise and two to three moderate intensity resistance exercise sessions each week); and refer their patients to a health professional who specialises in the prescription and delivery of exercise (ie, accredited exercise physiologist or physiotherapist with experience in cancer care).

INSPIREHEALTH'S INTERPRETATION: At InspireHealth, we have a collaborative environment where physicians, counsellors, dietitians, and exercise therapists work together to provide cancer care. We also work with other healthcare professionals including oncologists, general practitioners, nurse practitioners, pharmacists and more. Canada is still working on a national strategy to align all multidisciplinary cancer care professionals with the common goal of improving cancer care. Healthcare

professionals all want the best outcomes for their patients but may not always be working cohesively to make it happen. Australia, however, has an organization that represents all cancer care professionals called the Clinical Oncology Society of Australia (COSA). Through COSA, clinicians collaborate to determine how they will provide Australia's best cancer care.

This article outlines COSA's position on the importance of exercise in cancer care. In short, it recommends that people who have cancer be as active as their conditions will allow, and ideally work up to 150 minutes per week of aerobic exercise plus 2-3 weekly strengthening sessions. These recommendations are expected to be individualized for each patient depending on abilities, and it is recognized that abilities may change with treatments, side effects and overall health status. COSA also recommends specific training for exercise professionals who work with people who have cancer. Importantly, all healthcare professionals are encouraged to promote exercise in cancer care.

The article noted that most people who have cancer do not meet the recommendations for exercise despite their intentions to be active. Thus, guidance from healthcare professionals is essential to help people with cancer become more active. Impressively, this article emphasizes the importance of exercise in cancer care from a multitude of disciplines in healthcare. Not only do exercise specialists discuss the positive impact of exercise in cancer care; exercise is now formally recognized as a standard practice for cancer care by medical oncologists in Australia. This approach is part of a larger movement to officially integrate exercise into cancer care worldwide.

EXERCISE IS MEDICINE

Schmitz KH, Campbell A, Stuiver MM, et al.

Exercise is medicine in oncology: engaging clinicians to help patients move through cancer

A Cancer Journal for Clinicians (2019), 69:468-484

ABSTRACT: Multiple organizations around the world have issued evidence-based exercise guidance for patients with cancer and cancer survivors. Recently, the American College of Sports Medicine has updated its exercise guidance for cancer prevention as well as for the prevention and treatment of a variety of cancer health-related outcomes (eg, fatigue, anxiety, depression, function, and quality of life). Despite these guidelines, the majority of people living with and beyond cancer are not regularly physically active. Among the reasons for this is a lack of clarity on the part of those who work in oncology clinical settings of their role in assessing, advising, and referring patients to exercise.

The authors propose using the American College of Sports Medicine's Exercise Is Medicine initiative to address this practice gap. The simple proposal is for clinicians to assess, advise, and refer patients to either home-based or community-based exercise or for further evaluation and intervention in outpatient rehabilitation. To do this will require care coordination with appropriate professionals as well as change in the behaviors of clinicians, patients, and those who deliver the rehabilitation and exercise programming. Behavior change is one of many challenges to enacting the proposed practice changes. Other implementation challenges include capacity for triage and referral, the need for a program registry, costs and compensation, and workforce development. In conclusion, there is a call to action for key stakeholders to create the infrastructure and cultural adaptations needed so that all people living with and beyond cancer can be as active as is possible for them.

INSPIREHEALTH'S INTERPRETATION: Many people with cancer diagnoses would like to receive exercise advice directly from their medical oncologists, yet a limited number of oncologists prescribe exercise. Oncologists may lack awareness of the value of exercise, lack clarity on how to prescribe exercise, lack knowledge of available community programming, or believe that prescribing exercise falls outside of their scope of practice. This is unfortunate, because individuals with cancer are more likely to exercise if they are advised to do so by their oncologists, and many people do not learn about the cancer-specific exercise services from which they could benefit.

The American College of Sports Medicine (ACSM) is one of the leading organizations in sport science worldwide. In 2010 they created exercise recommendations for people who have cancer, knowing that the recommendations would need to be updated as new research arose. Recently, these updates have been published, and the ACSM has specific exercise prescriptions for cancer-related fatigue, quality of life, physical function, anxiety and depression. Yet, how do these recommendations make their way to people with cancer? How do people with cancer get the resources they need to follow the prescriptions? This article proposes using the ASCM's Exercise is Medicine program to assist with referrals by oncologists.

The Exercise is Medicine program integrates exercise prescriptions into the existing healthcare system by asking healthcare providers to refer patients to exercise services. In cancer care, the Exercise is Medicine approach would require oncologists to conduct regular physical activity assessments, advise patients to follow exercise guidelines, and refer patients to appropriate exercise programming. Ideally, oncologists would also recommend moving more and sitting less. InspireHealth fully supports this model, and we value referrals from oncologists, general practitioners and nurse practitioners. We are establishing partnerships with local physicians, including the gastric cancer pilot program, in which surgical oncologists directly refer patients to our dietitians, and thereby also learn about our exercise programming. We are looking to grow these formalized relationships to strengthen referrals from oncologists to InspireHealth for exercise services amongst all of our valuable offerings.

EXERCISE GUIDELINES

Campbell, K.L., Winters-Stone, K.M., Wiskemann, J., et al.

Exercise guidelines for cancer survivors: Consensus statement from International Multidisciplinary Roundtable

Medicine in Science, Sport, and Exercise (2019), 51(11), 2375-2390

ABSTRACT | Purpose: The number of cancer survivors worldwide is growing, with over 15.5 million cancer survivors in the United States alone-a figure expected to double in the coming decades. Cancer survivors face unique health challenges as a result of their cancer diagnosis and the impact of treatments on their physical and mental well-being. For example, cancer survivors often experience declines in physical functioning and quality of life while facing an increased risk of cancer recurrence and all-cause mortality compared with persons without cancer. The 2010 American College of Sports Medicine Roundtable was among the first reports to conclude that cancer survivors could safely engage in enough exercise training to improve physical fitness and restore physical functioning, enhance quality of life, and mitigate cancer-related fatigue. **Methods:** A second Roundtable was convened in 2018 to advance exercise recommendations beyond public health guidelines and toward prescriptive programs specific to cancer type, treatments, and/or outcomes. **Results:** Overall findings retained the conclusions that exercise training and testing were generally safe for cancer survivors and that every survivor should "avoid inactivity." Enough evidence was available to conclude that specific doses of aerobic, combined aerobic plus resistance training, and/or resistance training could improve common cancer-related health outcomes, including anxiety, depressive symptoms, fatigue, physical functioning, and health-related quality of life. Implications for other outcomes, such as peripheral neuropathy and cognitive functioning, remain uncertain. **Conclusions:** The proposed recommendations should serve as a guide for the fitness and healthcare professional working with cancer survivors. More research is needed to fill remaining gaps in knowledge to better serve cancer survivors, as well as fitness and healthcare professionals, to improve clinical practice.

INSPIREHEALTH'S INTERPRETATION: As noted above, in 2010, a consensus statement, based on the then available scientific data regarding exercise and cancer, was published. It concluded that cancer patients could safely engage in regular exercise in order to support physical functioning, quality of life, and cancer-related fatigue. Since that time, the number of published randomized controlled trials in the field of exercise and cancer has increased by approximately 281%. This substantial (and growing) body of research allows experts to develop more specific guidelines and recommendations. The authors of this paper held a follow-up roundtable discussion to review the updated relevant literature.

Overall, the researchers suggest that cancer survivors avoid inactivity. For overall health benefits, the recommendations echo those of 2010 to aim for 150 minutes of moderate intensity aerobic exercise and two resistance (strength) training sessions each week. They were also able to provide specific recommendations on the amount and type of exercise to help mitigate a number of common cancer-related and cancer-treatment-related symptoms. Strong evidence exists for exercise to reduce cancer-related fatigue, anxiety, depression, improve physical function, and quality of life. Strong evidence suggests that exercise will not exacerbate lymphedema. Moderate level evidence exists for exercise to support bone health (resistance training 2-3 times per week) and sleep (aerobic training 3-4 times per week for 30-40 minutes). Although insufficient evidence exists for exercise's effects on cardiotoxicity, chemotherapy-induced peripheral neuropathy, cognitive function, fall risk, nausea, pain, sexual function, and treatment tolerance, the current research is promising.

As always, it is important to seek support from an exercise professional who has training in exercise for cancer patients in order to tailor these recommendations to you and your current condition.