



RESEARCH UPDATES FALL 2016

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THE EXERCISE EDITION

IN THIS ISSUE: The scientific literature pertaining to regular exercise participation among cancer survivors has grown exponentially throughout the last decade and researchers continue to look at new ways in which exercise may be beneficial throughout a cancer diagnosis. Because of this growing body of literature, this issue of Research Updates is dedicated entirely to research on the topic of exercise and cancer. Papers interpreted examine exercise across the cancer spectrum in areas such as sleep, treatment- and cancer-related side-effects, immune support, and quality of life.

INSOMNIA

Bernard, P., Ivers, M.H., & Savard, J.

Temporal relationships between sleep and physical activity among breast cancer patients with insomnia

Health Psychology (2016), DOI: 10.1037/hea0000408

ABSTRACT | Objective: The present study prospectively investigated the day-to-day bidirectional relationships between objective measures of sleep parameters and physical activity among breast cancer patients with insomnia symptoms. **Method:** A subgroup of participants (N= 66) enrolled in a randomized controlled trial for insomnia comorbid with cancer wore an actigraphic recorder for seven 24-hr periods before the intervention. Multilevel models examined whether sleep parameters (sleep onset latency, wake after sleep onset [WASO], total wake time [TWT], sleep efficiency [SE], and total sleep time [TST]) on a given night predicted the levels of physical activity (daily activity counts and minutes of moderate to vigorous physical activity [MVPA]) the following day and vice versa. **Results:** Adjusted models revealed that a lower WASO ($\beta = -.12$, SE = .07, $p < .05$), TWT ($\beta = -.14$, SE = .05, $p < .05$), and TST ($\beta = -.14$, SE = .06, $p < .05$) were significantly associated with a greater daily activity count fluctuation the next day. Conversely, greater total daily count fluctuations were significantly associated with a higher WASO ($\beta = .18$, SE = .08, $p < .05$), TWT ($\beta = .12$, SE = .04, $p < .05$), and TST ($\beta = .22$, SE = .08, $p < .05$) the following night. **Conclusions:** These findings support a reciprocal and complex relationship between sleep parameters and physical activity. While they do not confirm a possible beneficial effect of physical activity on objective sleep parameters, they suggest that successful insomnia treatment could increase daily physical activity in patients with cancer.

INSPIREHEALTH'S INTERPRETATION: There is a well-documented body of literature examining the dynamic relationship between physical activity (PA) and sleep. Among cancer survivors, the importance of sleep in the body's healing and recovery process is well-known, however, insomnia is highly prevalent among breast cancer survivors currently undergoing chemotherapy, and can be as high as 69%. Physical activity rates among breast cancer survivors currently in treatment are also low, with often fewer than 30% meeting the recommended PA guidelines (i.e. 150 minutes of moderate intensity PA per week). There are known negative effects of both poor sleep and inactivity, including increased levels of pain, fatigue, cognitive impairment, anxiety, and decreased daytime functioning. Previous studies have shown that there is a bi-directional relationship between PA and sleep, where regular PA may improve sleep, and poor sleep may result in lower PA. It has been suggested that regular PA may help sleep quality by improving thermoregulation (thereby regulating temperature while sleeping), hormone function, immune function, circadian rhythms, and mood.

On the flip side, poor sleep quality has been associated with elevated levels of stress hormones (fight or flight response), increased fatigue and worsening mood, all of which may decrease PA levels. This study examined the relationship between sleep and PA levels using objective measures (actigraphic recorders) among 79 breast cancer patients who were diagnosed with insomnia and had had cancer treatment within the last 18 months. They objectively measured specific components of

sleep quality, including sleep onset latency (the amount of time between getting in bed and falling asleep (SOL)), wake after sleep onset (periods of wakefulness following sleep onset (WASO)), total wake time (TWT), sleep efficiency (total sleep time as a proportion of total time in bed (SE)), and total sleep time (TST), as well as total daily activity counts and total minutes of moderate to vigorous intensity PA (MVPA) per day. Participants were instructed to wear the actigraphic recorder for seven days (consecutive 24 hour periods). Results indicated that decreased WASO, TWT, and TST were associated with greater fluctuations in PA counts on the following day. That is, decreased WASO and TWT led to increased PA, and decreased TST led to decreased PA. It was also found that greater fluctuations in daily PA led to increased WASO, TWT, and TST the following night. That is, decreased PA led to increased WASO and TWT during the following night and increased PA led to greater TST. These results are complicated and do not necessarily indicate a clear relationship between increased PA leading to better sleep and better sleep leading to increased PA. Most interestingly, the results were only significant for within-person analyses and not between-person analyses, meaning that relationships were only significant when there were deviations from a person's normal sleep and PA patterns. Therefore, maintaining a regular sleep schedule as well as regular daily PA is likely to be most helpful. While the results indicate a complex relationship between PA and sleep, it may be postulated that improving sleep quality may lead to increased PA. Focusing on activities that aid in promoting sleep, including meditation, yoga, deep breathing, and proper sleep hygiene (e.g. sleeping in a dark and cool room and limiting electronics before bed) may be helpful.

TREATMENT-RELATED SIDE EFFECTS AND QUALITY OF LIFE

Streckmann, F., Kneis, S., Leifert, J.A., et al.

Exercise program improves therapy-related side-effects and quality of life in lymphoma patients undergoing therapy

Annals of Oncology (2014), 25: 493–499.

ABSTRACT | Background: Lymphoma patients undergoing therapy must cope with the side-effects of the disease itself, therapy and associated immobility. Peripheral neuropathy (PNP), loss of balance control and weakness not only diminishes patients' quality of life (QOL), it can also affect planning and the dosage of therapy. Exercise may enable patients to reverse these declines, improving their performance level and QOL. **Patients and methods:** We carried out a randomized, controlled trial, assigning 61 Lymphoma patients either to a control group (CG; N = 31) or to a 36-week intervention (IG; N = 30), consisting of sensorimotor-, endurance- and strength training twice a week. Primary end point was QOL; secondary end points included movement coordination, endurance, strength and therapy-induced side-effects. **Results:** Intergroup comparison revealed improved QOL- ($\Delta T1-T0$; $P=0.03$) and PNP-related deep sensitivity in the IG: 87.5% were able to reduce the symptom, compared with 0% in the CG ($P<0.001$). Significant differences in the change of balance control could be found between the groups, with the IG improving while the CG steadily declined (monopedal static $\Delta T3-T0$; $P=0.03$; dynamic $\Delta T3-T0$; $P=0.007$; perturbed mono- $\Delta T3-T0$; $P=0.009$ and bipedal $\Delta T3-T0$; $P=0.006$), failed attempts (monopedal static $\Delta T3-T0$; $P=0.02$, dynamic $\Delta T3-T0$; $P<0.001$ and perturbed $\Delta T3-T0$; $P=0.006$) and improved time to regain balance ($\Delta T3-T0$; $P=0.04$). Moreover, the change in the aerobic performance level ($\Delta T3-T0$; $P=0.05$) and additional amount of exercise carried out per week [metabolic equivalent (MET); $P=0.02$] differed significantly across groups.

INSPIREHEALTH'S INTERPRETATION: This randomized controlled trial was designed in Germany to evaluate the effects of exercise on improving cancer treatment side effects and overall quality of life (QOL) in patients with lymphoma. Patients with a diagnosis of Hodgkin's disease, B- and T-cell Non-Hodgkin's disease, and Multiple Myeloma were recruited for the study. Patients underwent heart and lung testing to ensure fitness prior to participation. Thirty patients were randomly assigned to the intervention (exercise) group (IG) and 31 patients were randomly assigned to the control group (CG). The CG received usual care including physiotherapy. The IG trained for one hour, two times each week for 36 weeks with a combination of aerobic, sensorimotor (balance and coordination training), and strength training. Sensorimotor training was deemed particularly important as a way to potentially ameliorate therapy-induced peripheral neuropathy (PNP) which up to 50% of lymphoma patients experience. PNP causes numbness and tingling in hands and feet, impaired balance control and increased risk of falls, and is a common side effect of several chemotherapeutic agents. Sensorimotor training involved postural stabilization exercises such as standing (feet together, then one foot at a time) on a hard surface, on a soft foam-padded surface, and on a surface which unexpectedly shifted. Failed attempts were counted whenever patients needed support to maintain balance. Unfortunately, the researchers were unable to recruit sufficient numbers of patients and the study was stopped early, possibly limiting the robustness of the findings. The researchers did not find overall differences between the groups after the 36 week intervention with respect to QOL, however, the IG did show significant improvements in balance control and reductions in PNP. The IG also reported improved QOL throughout all phases of therapy, whereas the control group did not. The benefit to PNP appeared to be specifically related to the sensorimotor exercises.

Though this study used very formal postural stabilization exercises, it is possible to include balance training into everyday life. Standing on one leg at a time while doing typical activities such as brushing your teeth or taking off your shoes, as well as walking as if on a tightrope can improve balance over time. The authors summarize that their trial was the first randomized controlled trial assessing balance control and PNP in lymphoma patients, and that their findings were both statistically and clinically meaningful. In addition, no adverse effects were noted for the type of low intensity exercise training employed. Peripheral neuropathy is a side effect of many common chemotherapy protocols, so these findings may be applicable to any cancer patient who is at risk of therapy-induced PNP.

IMMUNE SYSTEM FUNCTION

Idorn, M., & Hojman, P.

Exercise-dependent regulation of NK Cells in cancer protection

Trends in Molecular Medicine (2016), 22(7), 565-577.

ABSTRACT | Natural killer (NK) cells are the most responsive immune cells to exercise, displaying an acute mobilization to the circulation during physical exertion. Recently, exercise-dependent mobilization of NK cells was found to play a central role in exercise-mediated protection against cancer. Here, we review the link between exercise and NK cell function, focusing on circulating exercise factors and additional effects, including vascularization, hypoxia, and body temperature in mediating the effects on NK cell functionality. Exercise dependent mobilization and activation of NK cells provides a mechanistic explanation for the protective effect of exercise on cancer, and we propose that exercise represents a potential strategy as adjuvant therapy.

INSPIREHEALTH'S INTERPRETATION: The underlying mechanism by which exercise protects against cancer has long fascinated scientists. These Danish authors reviewed the link between exercise and natural killer (NK) cells. Natural killer cells are a type of lymphocyte (which is a type of white blood cell or leukocyte) and have the ability to toxically kill harmful cells such as viruses or cancer cells. NK cells are part of the innate (in-born or non-specific) immune system and do not need to be activated by antibodies, so can respond quickly to harmful cells without requiring a previous exposure. Circulating immune cells such as lymphocytes were first shown to be regulated by exercise in the 1890s and over the past few decades more interest has developed in the role that exercise may play in actual cancer treatment. In population-based studies exercise has been associated with reduced risk of developing cancer in the first place. Additionally, over 100 studies have shown that exercise can benefit cancer patients both in terms of quality of life (e.g. less depression, fewer adverse treatment effects) and improved physical functioning. Growing evidence also suggests that exercise may help reduce the risk of recurrence in colorectal, prostate, and breast cancer patients. That is, it appears that exercise has a direct anti-tumour effect. It is believed that exercise may facilitate the accumulation of NK cells in solid tumours. Exercise can increase blood flow (perfusion) in the tumour and while this had been thought of as unfavourable (by increasing nutrients and oxygen to facilitate tumour growth), current research suggests that increased perfusion actually increases the access of several healthy immune cells to the tumour, so overall benefits outweigh potential risks. Furthermore, increased blood perfusion can limit low oxygen levels (hypoxia) in tumours which have been associated with a reduced ability of human immune cells to recognize tumours. Exercise also increases body temperature which may make the tumour's blood vessels more permeable to immune cell migration. It is also believed that epinephrine (adrenaline) released during exercise helps to mobilize NK cells. This epinephrine-dependent mobilization of NK cells also seems to encourage the release of muscle-messenger cells called myokines which can modulate other important immune cells. In other words, there seems to be a muscle-to-immune cell crosstalk linking exercise to immune cell regulation.

In addition to directly killing tumour cells, NK cells may also activate other important immune cells such as the anti-tumour M1 macrophages (another type of white blood cell). Mobilization of NK cells occurs within minutes of exercise when done at a moderate intensity associated with slight breathlessness and increased heart rate. Maximal mobilization of NK cells occurs at about 30 minutes and elevated levels are maintained for up to three hours of training. After three hours of endurance exercise, NK levels start to fall. Recommendations to achieve 30 minutes of moderate exercise three to five times per week are consistent with what is needed for optimal NK cell mobilization into tumours. The authors conclude that in addition to improving QOL and reducing treatment-related side effects, exercise may actually represent a "complementary anti-cancer therapeutic approach", by facilitating tumour cell death.

HEALTH-RELATED QUALITY OF LIFE

Mishra, S.I., Schere, R.W., Snyder, C., et al.

Are exercise programs effective for improving health-related quality of life among cancer survivors? A systematic review and meta-analysis

Oncology Nursing Forum (2014), 41(6), E326-E342.

ABSTRACT | Objectives: To evaluate the effectiveness of exercise interventions on overall health-related quality of life (HRQOL) and its domains among cancer survivors who have completed primary treatment. **Data Sources:** 11 electronic databases were searched from inception (dates varied) to October 2011. The authors also identified eligible trials through a search of additional sources. **Data Synthesis:** 40 trials with 3,694 participants met the inclusion criteria. At 12 weeks, cancer survivors exposed to exercise interventions had greater positive improvement in overall HRQOL (standardized mean difference [SMD] 0.48; 95% confidence interval [CI] [0.16, 0.81]), emotional wellbeing (SMD 0.33; 95% CI [0.05, 0.61]), and social functioning (SMD 0.45; 95% CI [0.02, 0.87]); and had a significant reduction in anxiety (SMD -0.26; 95% CI [-0.44, -0.07]) and fatigue (SMD -0.82; 95% CI [-1.5, -0.14]). **Conclusions:** Exercise programs have a beneficial effect on HRQOL and most of its domains and can be integrated into the management plans for cancer survivors who have completed treatment. Future research is needed to help understand specific attributes of exercise programs that are beneficial for improving HRQOL within and across cancer types. **Implications for Nursing:** Evidence presented in this review supports the inclusion of exercise programs in clinical guidelines for the management of cancer survivors who have completed treatment, such as the Oncology Nursing Society's Putting Evidence Into Practice resource.

INSPIREHEALTH'S INTERPRETATION: The authors of this paper examined the effect of exercise participation on health-related quality of life (HRQOL) among cancer patients who had completed treatments. This article used extensive search criteria so that as many relevant randomized controlled trials were included as possible. Randomized controlled trials are important in research because they can provide support for cause and effect. Twenty four studies were included in a meta-analysis that pooled all the data from these studies together and 40 studies were included for overall analysis. Positive effects were found on a number of HRQOL factors including anxiety, body image, depression, sexuality, sleep disturbance, emotional well-being, fatigue, physical functioning, social functioning, pain, and overall quality of life. While the statistical significance of these effects varied at 12 weeks and six months post-baseline, the take-home message is that exercise can improve many aspects of psychological, emotional, and physical health among cancer survivors who have finished treatment. The greatest effects were seen when individuals engaged in moderate to vigorous intensity exercise. Moderate to vigorous intensity exercise can vary greatly and includes options such as walking, cycling, resistance training, yoga, Tai Chi, Qi Gong, or various combinations. The authors recommend that regular exercise should be incorporated into the self-care routines of cancer survivors following treatment.

EXERCISE DURING CHEMOTHERAPY

Van Vulpen, J.K., Velthuis, M.J., Steins Bisschop, C.N., et al.

Effects of an exercise program in colon cancer patients undergoing chemotherapy

Medicine & Science in Sports & Exercise (2016), 48 (5), 767–775.

ABSTRACT | Purpose: Fatigue is a common problem among colon cancer patients and typically increases during chemotherapy. Exercise during chemotherapy might have beneficial effects on fatigue. To investigate the short- and long-term effects of an exercise program in colon cancer patients during adjuvant treatment, the Physical Activity During Cancer Treatment study was conducted. **Methods:** In this multicenter randomized controlled trial, 33 colon cancer patients undergoing chemotherapy (21 men and 12 women) were randomly assigned to either a group receiving an 18-wk supervised exercise program (n = 17) or to usual care (n = 16). The primary outcome was fatigue as measured by the Multidimensional Fatigue Inventory and the Fatigue Quality List. Secondary outcomes were quality of life, physical fitness, anxiety, depression, body weight, and chemotherapy completion rate. Outcome assessment took place at baseline, postintervention (18 wk) and at 36 wk. **Results:** Intention-to-treat mixed linear model analyses showed that patients in the intervention group experienced significantly less physical fatigue at 18 wk and general fatigue at 36 wk (mean between group differences, -3.2; 95% confidence interval [CI], -6.2 to -0.2; effect size [ES], -0.9 and -2.7; 95% CI, 5.2 to -0.1; ES, -0.8, respectively), and reported higher physical functioning (12.3; 95% CI, 3.3–21.4; ES, 1.0) compared with patients in the usual care group. **Conclusion:** The Physical Activity During Cancer Treatment trial shows that an 18-wk supervised exercise program in colon cancer patients during chemotherapy is safe and feasible. The intervention significantly reduced physical fatigue at 18 wk and general fatigue at 36 wk. Considering the number of patients included in the present study, replication in a larger study population is required.

INSPIREHEALTH'S INTERPRETATION: This is one of the first randomized controlled trials to investigate the effects of a supervised exercise program among a group of colorectal cancer patients undergoing chemotherapy. The primary outcome of this study was fatigue and the secondary outcomes were quality of life, anxiety, and depression. Between the years 2010 and 2013, 33 participants were randomized to either an 18 week supervised exercise program or to usual care (control). The exercise program consisted of workouts twice each week that included a ten minute warm-up, 40 minutes of aerobic (cardio) exercise and muscle strengthening, and a ten minute cool down. The aerobic portion included interval training (alternating between higher and lower intensities) for approximately 20 minutes. The strength portion consisted of one or two sets of 10-20 repetitions focusing on all major muscle groups. At the end of the 18 weeks, the exercise group experienced significantly less physical fatigue than the control group. At the end of 36 weeks, the exercise group experienced less general fatigue (overall feelings of fatigue including both physical and mental-emotional fatigue). Physical functioning was significantly higher in the exercise group compared to the control. No significant differences were found with anxiety, depression, or other quality of life factors. Women who were part of the exercise program had significantly higher aerobic fitness than women in the control group after the 18 week program and at 36 weeks. Interestingly, there were no significant differences between the exercisers and control group among men when measuring physical fitness at 18 weeks. Due to the small sample size of the study, further exploration in this area is required. As a pilot study, the exercise intervention was feasible without adverse effects and yielded benefit with regards to fatigue levels. Given that fatigue is one of the most commonly noted side effects during chemotherapy treatment, exercise may be a viable means of maintaining energy levels.

INTO THE VAULT:

Courneya, K.S., & Friedenreich, C.M.

Physical activity and cancer control

Seminars in Oncology Nursing (2007), 23(4), 242-252.

ABSTRACT | Objectives: To provide an overview and update of physical activity (PA) research across the entire cancer control continuum. **Data Sources:** Previous cancer control frameworks and selected PA and cancer research that has been published over the past 5 years. **Conclusion:** There have been major scientific advances in PA research across many, but not all, of the

cancer control categories over the past 5 years. **Implications For Nursing Practice:** Nurses should have a comprehensive understanding of the potential role of PA across the entire cancer control continuum.

INSPIREHEALTH'S INTERPRETATION: This 2007 literature review was designed to update the (then) current state of knowledge with respect to cancer and physical activity (PA). Although this is an older paper, it outlines a framework, still relevant today, pertaining to the utility and benefit of PA throughout the stages of a cancer journey. This framework, titled 'Physical Exercise Across the Cancer Experience' (PEACE), was first developed in 2001, and was updated for this paper. The authors divide the cancer experience into six cancer-related time periods: two prior to a diagnosis (pre-screening and screening), and four after a diagnosis (pre-treatment, treatment, survivorship, and end of life). Within these six time periods are eight cancer control categories including prevention, detection, treatment preparation/coping, treatment effectiveness/coping, recovery/rehabilitation, disease prevention/health promotion, palliation, and survival. The authors reviewed PA research as it pertained to each of the eight cancer control categories.

Cancer Prevention: The relationship between PA participation and cancer prevention remains the most widely studied. Convincing evidence has been found for the existence of a relationship between regular PA participation and decreased risk of a number of different types of cancer.

Cancer Detection: Although research has been limited, the authors suggest that PA may influence the sensitivity and/or specificity of screening tests (i.e. the likelihood a screening test would give an accurate positive or negative result). They also suggest that those individuals who maintain an active lifestyle may be more likely to engage in regular screening and detection practices.

Treatment Preparation/Coping: The authors describe several ways in which PA can aid in treatment preparation and coping. First, they suggest that PA can help with the physical and mental-emotional aspects of coping while waiting for treatment. PA has been known to help with temporary relief in anxiety, depression, mood disturbances as well as assist with stress reduction and coping. PA is also able to prepare the body through fitness and health for upcoming treatments. Lastly, the authors suggest that regular PA may be able to delay the need for treatment through the management of the disease and its symptoms.

Treatment Effectiveness/Coping: PA is known to mitigate some treatment-related side effects and toxicities by helping to maintain physical functioning, maintaining a healthy body composition, improving mood, and maintaining energy levels. By helping to maintain a strong and efficient body, regular PA participation may help with treatment completion and even efficacy. Human trials are still in its infancy; however, there have been a number of animal model studies showing that regular PA participation improves chemotherapy uptake and efficacy.

Recovery/Rehabilitation: Most cancer survivors choose to begin a PA program immediately or soon after finishing treatment. Research has really grown in this area and includes studies showing beneficial effects of engaging in both resistance training and yoga. PA participation during this time can help to lessen long-term side effects, mitigate fatigue, and improve surgical recovery.

Disease Prevention/Health Promotion: Research in this area suggests a number of benefits to regular PA participation following the rehabilitation stage. First, regular PA can help minimize or manage long-term or late appearing treatment side effects such as fatigue, lymphedema, changes to body composition, and bone mineral density loss. Exercise may help to lower certain risk factors for cancer recurrence as well as lower risk of other possible chronic diseases (e.g. cardiovascular disease, osteoporosis, diabetes, etc.).

Palliation: PA participation has been shown to improve daily functioning, reduce side effects and improve quality of life at end of life. The authors note that research in this area is preliminary, though promising. They suggest that PA participation may slow physical decline and improve fatigue.

Survival: Research suggests that PA participation may improve survival rates following cancer by decreasing risk or recurrence, comorbidities and secondary cancers, as well as slowing cancer progression. In summary, PA has shown benefit across the cancer continuum from early detection and treatment to palliation at the end of life.

InspireHealth provides patients with the knowledge, tools, and services to support their overall health during and after cancer treatment. Our medical doctors value conventional cancer treatments such as chemotherapy, radiation, and surgery. At the same time, they recognize the importance of supporting health, immune function, body, mind, and spirit.

InspireHealth's programs are supported by current research and can be safely integrated with patient's conventional treatments.

InspireHealth's *Research Updates* are compiled by Rachel Mark, M.A. (kin)—with guidance from the editorial board—using InspireHealth's Research Information System, a unique supportive cancer care knowledge management database. The editorial board includes: Dr. Janice Wright, MD, CEO, Dr. Hannah Nette, MD, Dr. Lori McFarlane, MD, and Terry Heidt, M.Sc. For more information, email library@inspirehealth.ca

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