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RESEARCH UPDATES 2019 VOLUME 2

FOR THE LATEST IN WORLDWIDE SUPPORTIVE CANCER CARE

IN THIS ISSUE: The benefits of exercise during cancer treatment are explored in a paper by Ashcraft and colleagues. Britton's team discuss the finding of a trial aimed at maximizing nutrition for patients with head and neck cancer. Pan-Weisz et al. review supportive care interventions among adults with brain tumors. Hardee and colleagues discuss the role of exercise in cancer cachexia. De Almeida's team explore how gut microbiota can influence colorectal cancer. Lastly, Alfano and Pergolotti discuss the next generation of cancer rehabilitation.

EXERCISE DURING CANCER TREATMENT

Ashcraft, K.A., Warner, A.B., Jones, L.W., & Dewhirst, D.V.M

Exercise as adjunct therapy in cancer

Seminars in Radiation Oncology (2018), 29, 16-24. doi: 10.1016/ j.semradonc.2018.10.001

ABSTRACT: Data from observational studies indicate that both physical activity as well as exercise (ie, structured physical activity) is associated with reductions in the risk of recurrence and cancer mortality after a diagnosis of certain forms of cancer. Emerging evidence from preclinical studies indicates that physical activity/exercise paradigms regulate intratumoral vascular maturity and perfusion, hypoxia, and metabolism and augments the antitumor immune response. Such responses may, in turn, enhance response to standard anticancer treatments. For instance, exercise improves efficacy of chemotherapeutic agents, and there is rationale to believe that it will also improve radiotherapy response. This review overviews the current preclinical as well as clinical evidence supporting exercise modulation of therapeutic response and postulated biological mechanisms underpinning such effects. We also examine the implications for tumor response to radiation, chemotherapy, and immunotherapy.

INSPIREHEALTH'S INTERPRETATION: This paper reviewed the research focused on understanding the mechanisms by which exercise can improve the effectiveness of cancer treatment (radiation and chemotherapy) and supports the body's immune response. Current research shows that safe, appropriate exercise done before, during and after cancer treatment has many benefits including reduced side effects, improved physical function and quality of life, and optimizing the effectiveness of chemotherapy, radiation therapy, and our own immune system. Researchers have examined microscopic changes in cell metabolism, blood flow, and the tumour environment in animal models in order to better understand cancer biology in humans. Exercise's benefits have been associated with reductions in inflammation and increased antioxidant capacity. It is still unclear whether these systemic changes lead to positive changes in the tumour microenvironment (the normal immune cells, blood vessels and other molecules that can influence and be influenced by the tumour) and/or if exercise also directly impacts the tumour microenvironment independently of systemic effects.

One of the main reasons exercise benefits the tumour microenvironment appears to be related to improved blood vessel structure and function. Cancer tumours are hypoxic (low oxygen) due to their many immature, sometimes leaky blood vessels which inhibit blood flow and oxygen delivery to all parts of the tumour. Cells that are hypoxic are more resistant to radiation and chemotherapy and also more likely to metastasize (spread to other parts of the body). Leaky, immature blood vessels also have a lower pressure which inhibits the transfer of molecules into the cells. Exercise promotes the development of healthier blood vessels that can more effectively deliver and transfer chemotherapy treatment to all parts of the tumour. Our bodies' own immune response is also improved with better blood flow for nutrient transfer and greater oxygenation.

In addition, tumour cells tend to use glucose for energy but with exercise promoting increased blood flow and better blood vessels, more oxygen is available to use for energy. Tumour cell metabolism can shift away from glucose metabolism to aerobic (using oxygen) metabolism which reduces lactic acid (a byproduct of glucose metabolism) build up thereby reducing the acidity of

the environment. Acidic environments have been linked to an increased likelihood of metastases while less acidic environments support better immune function.

The authors conclude that more research is needed to determine specific outcomes of different doses of exercise on treatment effectiveness and immune response.

NUTRITION AND HEAD AND NECK CANCER

Britton, B., Baker, A.L., Wolfenden, L., et al.

Eating As Treatment (EAT): A stepped-wedge, randomized controlled trial of a health behavior change intervention provided by dietitians to improve nutrition in patients with head and neck cancer undergoing radiation therapy (TROG 12.03)

International Journal of Radiation Oncology, Biology and Physics (2019), 103(2), 353-362

ABSTRACT | Summary: Malnutrition during treatment of head and neck cancer is associated with poorer morbidity and mortality outcomes. This trial assessed the effectiveness of a psychological intervention delivered by dietitians to prevent malnutrition in patients with head and neck cancer while having radiation therapy. Patients who received the intervention had significantly better nutritional scores, lost less weight, had fewer radiation therapy interruptions, had lower depression scores, and reported a higher quality of life. **Purpose:** Malnutrition in head and neck cancer (HNC) treatment is common and associated with poorer morbidity and mortality outcomes. This trial aimed to improve nutritional status during radiation therapy (RT) using a novel method of training dietitians to deliver psychological techniques to improve nutritional behaviors in patients with HNC. **Methods and Materials:** This trial used a stepped-wedge, randomized controlled design to assess the efficacy of the Eating As Treatment (EAT) program. Based on motivational interviewing and cognitive behavioral therapy, EAT was designed to be delivered by oncology dietitians and integrated into their clinical practice. During control steps, dietitians provided treatment as usual, before being trained in EAT and moving into the intervention phase. The training was principles based and sought to improve behavior-change skills rather than provide specific scripts. Patients recruited to the trial (151 controls, 156 intervention) were assessed at 4 time points (the first and the final weeks of RT, and 4 and 12 weeks afterward). The primary outcome was nutritional status at the end of RT as measured by the Patient-Generated Subjective Global Assessment. **Results:** Patients who received the EAT intervention had significantly better scores on the primary outcome of nutritional status at the critical end-of-treatment time point (β=-1.53 [-2.93 to -.13], P = .03). Intervention patients were also significantly more likely than control patients to be assessed as well-nourished at each time point, lose a smaller percentage of weight, have fewer treatment interruptions, present lower depression scores, and report a higher quality of life. Although results were not statistically significant, patients who received the intervention had fewer and shorter unplanned hospital admissions. **Conclusions:** This trial is the first of its kind to demonstrate the effectiveness of a psychological intervention to improve nutrition in patients with HNC who are receiving RT. The intervention provides a means to ameliorate malnutrition and the important related outcomes and consequently should be incorporated into standard care for patients receiving RT for HNC.

INSPIREHEALTH'S INTERPRETATION: It is well known that nutrition has many roles through a cancer diagnosis and treatment. One main role is to improve nutritional status, which can improve recovery, prevent weight loss, reduce the number and length of hospital admissions and decrease the need to suspend treatments. Patients with head and neck cancers are at high risk of malnutrition. The ability to eat and get intake the needed nutrients can be impacted by the cancer itself as well as treatments. Mouth sores, and difficulty chewing and swallowing can directly impact the ability to eat. Other common cancer-related side effects (such as fatigue and depression) can also reduce the desire to buy food, prepare and eat it. For those reasons, researchers have studied head and neck cancer patients to develop effective strategies (e.g. tube feeding) to help reduce the risk of malnutrition.

In this study, researchers explored if patients' nutritional status could be improved by changing the techniques dietitians used when counselling head and neck cancer patients without making dietary alterations. Five hospitals participated in this Australian study. All 307 patients included were receiving radiation therapy, and most of them were also receiving chemotherapy. A significant number of the patients had an advanced cancer stage. Patients were randomized to a control group (who met with a dietitian as usual) or an intervention group (participating in the Eat As Treatment (EAT) approach). The intervention included empowering patients in a collaborative and empathic conversation. Dietitians worked with patients to develop their own achievable, personalized and self-monitored plans. Checklists used for self- monitoring included different behaviours established by the patient. Patients had weekly dietitian visits during radiation, and every two weeks post-radiation. Patients were followed for up to one year at the time of the publication of this paper. Participant assessment included questionnaires about nutrition status (eating habits and weight changes), quality of life, mood, and depression. Patients were unaware of their control versus intervention group status.

Results indicated that the intervention group patients had statistically significant higher nutrition status scores, lower depression scores, less unintended weight loss and better quality of life scores. Interestingly, the nutrition status improvement was greater than shown with previous studies examining tube-feeding. For hospital-based dietitians with limited patient time, it was also important to find that the intervention neither increased the length of patients' visits, nor burdened existing services. This study confirms the importance of fostering patient-centred team-based care, and encourages health care professionals to be open to learning new skills (i.e. behavioural and psychological techniques). These results also show that behavioural strategies may be as or more important than nutrient-based interventions to improve nutritional status and quality of life in head and neck cancer patients.

SUPPORTIVE CANCER CARE IN BRAIN CANCER

Pan-Weisz, T.M., Kryza-Lacombe, M., Burkeen, J., et al.

Patient-reported health-related quality of life outcomes in supportive-care interventions for adults with brain tumors: A systematic review

Psycho-oncology (2019), 28, 11-21. doi: 10.1002/pon.4906

ABSTRACT | Objectives: The objectives of this systematic review were to (a) identify supportive care (psychosocial/behavioral, pharmacological, complementary, or alternative) interventions that have been evaluated via randomized controlled trials (RCTs) to improve patient-reported health-related quality of life (HRQoL) among adults with brain tumors, (b) evaluate the quality of the intervention studies, and (c) evaluate if developed interventions have been efficacious at improving HRQoL, as compared with control conditions in RCTs. **Methods:** This systematic review was conducted using preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines. Four databases were searched for RCTs of supportive-care interventions for adults with brain tumors, primary or metastatic, that included a patient-reported HRQoL outcome. Quality of the included studies was assessed using the Effective Public Health Practice Project Quality Assessment Tool for Quantitative Studies. **Results:** Ten RCTs involving 640 patients with either a primary or metastatic brain tumor investigating supportive-care interventions with a HRQoL outcome were identified. In terms of quality, three of the studies received a "strong" rating, three received a "moderate" rating, and four of the studies received a "weak" rating. Only two of the interventions (ie, a home-based psychosocial intervention and individualized acupuncture with standard rehabilitation) demonstrated improvements in HRQoL over control conditions. **Conclusions:** HRQoL is of the utmost importance when treating patients with brain tumors. Yet there is a notable paucity of research to inform clinical decisions and evidence- based practice. More high-quality studies of interventions aimed at improving HRQoL are needed.

INSPIREHEALTH'S INTERPRETATION: This systematic review examined which types of supportive care interventions have a positive impact on health related quality of life (HRQoL) in patients with primary or secondary brain cancer. HRQoL encompasses physical, mental, emotional, and social well-being and is often negatively impacted in those with primary and secondary brain cancers. The National Comprehensive Cancer Network guidelines identify quality of life as the most important factor to consider for patients with central nervous system cancers; therefore, understanding what factors can impact HRQoL in this population is very important for developing appropriate interventions. Systematic reviews group the results of all relevant studies to synthesize the scientific evidence. Of the 549 initially reviewed articles, 11 met this review's inclusion criteria. The studies reviewed included male and female participants, average age 24-59 years, who had primary or secondary brain cancer (diagnoses included a variety of types and stages). This study reviewed only good quality randomized controlled trials (those including one or more intervention group(s) and a control group of people who did not participate in the intervention). Supportive care interventions included studies that were psychosocial/behavioural (4 studies), pharmacological (4 studies), and complementary/alternative (2 studies). In all studies, HRQoL was measured before and after the interventions by patient self-report using questionnaires. Only two of the studies showed an improvement in HRQoL in the intervention group. The first intervention was a daily, individualized acupuncture and standard physical therapy program for two months. The second study was an individualized home-based 10 week psychosocial intervention that included modules focused on reflection, education, planning, and goals. Interestingly, both interventions had individually-tailored components. Interestingly, in the first study, a standard acupuncture treatment did not have an effect while the individualized treatment did. The authors caution that only three of the studies met established criteria for having strong evidence. Although these findings aren't robust, they do demonstrate that supportive care for patients with brain cancer can be beneficial especially if an individualized approach is utilized. InspireHealth offers counselling services and acupuncture as well as several supportive care workshops.

EXERCISE AND CANCER CACHEXIA

Hardee, J.P., Counts, B.R., & Carson, J.A.

Understanding the role of exercise in cancer cachexia therapy

American Journal of Lifestyle Medicine (2019), 13(1), 46-60

ABSTRACT | Cachexia, the unintentional loss of body weight, is prevalent in many cancer types, and the associated skeletal muscle mass depletion increases patient morbidity and mortality. While anorexia can be present, cachexia is not reversible with nutritional therapies alone. Pharmacological agents have been proposed to treat this condition, but there are currently no approved treatments. Nonetheless, the hallmark characteristics associated with cancer cachexia remain viable foundations for future therapies. Regular physical activity holds a promising future as a nonpharmacological alternative to improve patient survival through cachexia prevention. Evidence suggests exercise training is beneficial during cancer treatment and survival. However, the mechanistic examination of cachectic skeletal muscle's response to exercise is both needed and justified. The primary objective of this review is to discuss the role of exercise for the prevention and treatment of cancer associated muscle wasting. Initially, we provide an overview of systemic alterations induced by cancer and their role in the regulation of wasting processes during cachexia progression. We then discuss how exercise could alter disrupted regulatory pathways related to growth and metabolism during cancer-induced muscle atrophy. Last, we outline current exercise prescription guidelines and how exercise could be a potential behavioral therapy to curtail cachexia development in cancer patients.

INSPIREHEALTH'S INTERPRETATION: Cachexia is a complex multifactorial syndrome characterized by the unintentional loss of skeletal muscle mass (with or without fat mass loss) and is a common condition in cancer. It may or may not be associated with anorexia (loss of appetite) and cannot be reversed with nutritional interventions. Cancer cachexia can reduce

quality of life and is associated with an estimated 20-40% of cancer-related deaths. Cachexia is generally defined as >5% weight loss or >2% weight loss in those with a low body mass index (<20 kg/m2), over the previous six months. Muscle mass loss is associated with protein breakdown activation and protein synthesis suppression. The authors of this analytic review discuss the alterations to the systemic environment during cancer cachexia and the role of physical activity in both the potential prevention and treatment of it. Cancer cachexia can disrupt many physiological processes used to maintain our body's homeostasis (balance), by increasing systemic inflammation, and promoting insulin resistance (leading to unhealthy blood sugar levels). Both cancer tumours and the body's immune system release small molecules called pro-inflammatory cytokines causing systemic inflammation. These cytokines may enhance fat breakdown and muscle wasting and may also contribute to liver damage (increasing the body's energy needs which further exacerbates fat and muscle breakdown required to supply the excess energy). Liver dysfunction may also reduce sex hormones, also exacerbating muscle and fat wasting. Cancer-related anemia caused by increased red blood cell breakdown, and/or blood loss and/or impaired red blood cell production (all common in cancer) has also been associated with cachexia. In healthy individuals, exercise stimulates red blood cell production leading to increased total hemoglobin (the protein in red blood cells that carries oxygen to tissues). \

Because it is not known if this is the case in cancer patients, it is generally suggested that anemia be rectified (with iron or other specific red blood cell boosting medications) prior to exercise training. Physical activity has been shown to be effective in reducing the pro-inflammatory cytokine environment in cancer cachexia. In other words, exercise has anti-inflammatory effects. Interestingly, some pro-inflammatory cytokines are actually released during exercise but these particular molecules may stimulate the production of other more potent anti-inflammatory cytokines. Exercise may also improve circulating sex hormones and enhance their receptor expression on muscle cells, thereby stimulating protein synthesis while reducing protein breakdown. The authors state: "…targeting skeletal muscle has the potential to reduce systemic wasting and improve overall metabolism and physical function." The American College of Sports Medicine (ACSM) recommends cancer patients engage in 75 minutes of vigorous activity or 150 minutes of moderate activity plus 2-3 sessions of resistance exercise and stretching per week. Exercise should always be tailored to the individual and it is important to remember that any activity is preferable to being sedentary. Both aerobic and resistance exercise training are possible in those with advanced as well as less advanced cancers. InspireHealth exercise therapists are trained to provide individually tailored exercise prescriptions for patients' specific clinical situations.

GUT MICROBIOTA AND COLORECTAL CANCER

De Almeida, C.V., de Camargo, M.R., Russo, E., et al.

Role of diet and gut microbiota on colorectal cancer immunomodulation

World Journal of Gastroenterology (2019), 25(2): 151-162

ABSTRACT | Colorectal cancer (CRC) is one of the most commonly diagnosed cancers, and it is characterized by genetic and epigenetic alterations, as well as by inflammatory cell infiltration among malignant and stromal cells. However, this dynamic infiltration can be influenced by the microenvironment to promote tumor proliferation, survival and metastasis or cancer inhibition. In particular, the cancer microenvironment metabolites can regulate the inflammatory cells to induce a chronic inflammatory response that can be a predisposing condition for CRC retention. In addition, some nutritional components might contribute to a chronic inflammatory condition by regulating various immune and inflammatory pathways. Besides that, diet strongly modulates the gut microbiota composition, which has a key role in maintaining gut homeostasis and is associated with the modulation of host inflammatory and immune responses. Therefore, diet has a fundamental role in CRC initiation, progression and prevention. In particular, functional foods such as probiotics, prebiotics and symbiotics can have a potentially positive effect on health beyond basic nutrition and have anti-inflammatory effects. In this review, we discuss the influence of diet on gut microbiota composition, focusing on its role on gut inflammation and immunity. Finally, we describe the potential benefits of using probiotics and prebiotics to modulate the host inflammatory response, as well as its application in CRC prevention and treatment.

INSPIREHEALTH'S INTERPRETATION: Our immune system plays a critical role in cancer prevention and treatment. Immune response is deeply influenced by gut microbiota (GM) composition which helps modulate the host's immunity. GM is the community of micro-organisms in the gut. Approximately 100 trillion micro-organisms (mostly bacteria, but also viruses, fungi, and protozoa) exist in the human gastrointestinal tract. GM, in turn, is modulated by diet. Therefore, dietary interventions may be supportive in cancer prevention and also support its treatment. This review explores recent evidence of the impact of dietary and lifestyle habits as well as the GM on colorectal cancer (CRC).

The authors summarize that genetic factors, immune system dysfunction, chronic inflammation, and GM dysbiosis (imbalances) contribute to the pathogenesis of CRC. Chronic inflammation, as a result of obesity or certain diseases can lead to persistent production of harmful biochemicals that interact with our DNA to alter it in ways that may lead to the development of cancers. Because of the link between nutrients such as saturated fats, refined carbohydrates, processed and red meat and inflammation, diet is now considered one of the most important lifestyle factors in CRC etiology. Furthermore, diet has a major influence on the composition of GM, which helps to regulate tumor immune responses. Specifically, microbiota composition may modulate the host's sensitivity to chemo-/radiotherapy. Dietary intake of both prebiotics (high fibre foods such as whole grains, legumes, fruits and vegetables that feed our GM) and probiotics (beneficial live micro-organisms found in fermented foods such as yogurt and sauerkraut) strongly influence GM composition. On the other hand, intake of foods such as animal protein and saturated fat can alter the GM composition and reduce immune system effectiveness. An optimal intake of prebiotics and probiotics helps the GM to produce nutrients such as short chain fatty acids (SCFA) which then line intestinal cells to reduce inflammation,

prevent colonization of harmful microbes, and benefit the immune system. One SCFA, butyrate, is the main energy source for human colon cells and may induce apoptosis (death) of colon cancer cells. In conclusion, diet can affect the development and treatment of CRC by modulating the GM to either benefit or hinder immunity and promote or decrease chronic inflammation. Consequently, supporting a healthy GM by consuming dietary fibre (prebiotics) and probiotics, and reducing processed/refined foods and red meat, could potentially reduce CRC incidence and/or increase the effectiveness of its treatment. Given the current gaps in knowledge, we need randomized controlled studies that use consistent, valid assessments of dietary intake to assess GM composition and health outcomes.

CANCER REHABILITATION CARE

Alfano, C.M. & Pergolotti, M.

Next-generation cancer rehabilitation: A giant step forward for patient care

Rehabilitation Nursing (2018), 43(4), 186–194. doi: 10.1097/rnj.0000000000000174

ABSTRACT | Purpose: The aim of the study was to review the current state of cancer rehabilitation evidence and practice and delineate an agenda for building the future of cancer rehabilitation care. **Findings:** Despite the benefits of cancer rehabilitation interventions and the unmet needs among patients with cancer, very few patients receive these services. **Conclusions:** Interdisciplinary cancer rehabilitation should be implemented from diagnosis forward. Building this care involves coordinating efforts in four critical areas: innovating cancer rehabilitation care delivery, expanding the team of providers, creating precision medicine cancer rehabilitation, and demonstrating the value of cancer rehabilitation to drive referrals and reimbursement. **Clinical Relevance:** Creating next-generation cancer rehabilitation care has the potential to improve the lives of the growing population of cancer survivors.

INSPIREHEALTH'S INTERPRETATION: The purpose of this research paper is to discuss the next steps in cancer rehabilitation to best support patients and their families prior to, during, and following cancer treatments. Approximately 53% of adult cancer patients will report some degree of functional limitation. Some noted side effects and late effects of cancer treatment include fatigue, pain, lymphedema, neuropathies, balance issues, bowel/bladder changes, sexual function, cardiopulmonary function declines, anxiety, depression and poor overall quality of life. Comprehensive cancer rehabilitation programs are designed to utilize the knowledge base of multiple clinicians in order to best address these functional changes in a patient-centered way. The authors suggest that while the benefits of a comprehensive cancer rehabilitation program are well noted, the referral rates to such program remain incredibly low.

Through this discussion paper, the authors propose what they call "Next-Generation Cancer Rehabilitation" which addresses the gaps and needs within current cancer rehabilitation programs. It is suggested that programs track patients from the time of diagnosis in order to best identify those who would benefit from rehabilitation care. A multidisciplinary care team would support patients in all domains of life, to address home, work and medical concerns. Other suggestions include the use of precision medicine to provide personalized approaches to care with up-up-date feedback and modifications. This approach may include the incorporation of technology such as apps, text and email prompts, as well as more efficient communication with the care team. Lastly, rehabilitation programs need to be evaluated beyond patient testimonials with more formalized research and assessment. InspireHealth's multidisciplinary team (physicians, exercise therapists, counsellors, dietitians) provides comprehensive support to patients with cancer with individualized one-on-one support and group programming.