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RESEARCH UPDATES 2018 VOLUME 3

FOR THE LATEST IN WORLDWIDE SUPPORTIVE CANCER CARE

IN THIS ISSUE: Treanor and colleagues explore the area of prehabilitation among cancer patients. Fagundes et al. discuss the biochemical ways in which stress may impact cancer development and progression. Vanbutsele's team discuss the benefits of early integration of palliative care within cancer treatment. In a review paper by Mourouti and colleagues, general recommendations are made for food intake, body composition and supplementation among cancer patients. And lastly, a systematic review performed by Baumann's team, examines the effect of different types of exercise on breast cancer related-lymphedema.

PREHABILITATION IN CANCER CARE

Treanor, C., Kyaw, T., & Donnelly, M.

An international review and meta-analysis of prehabilitation compared to usual care for cancer patients

Journal of Cancer Survivorship (2018), 12(1), 64-73, doi: 10.1007/s11764-017-0645-9

ABSTRACT | Purpose: The purpose of the study is to systematically review and synthesise randomised controlled trials investigating the effectiveness of prehabilitation compared to usual care for newly diagnosed, adult-onset cancer patients. **Methods:** MEDLINE, EMBASE, PsycINFO, CINAHL and SSCI were searched up to April 2017. Studies were included if disease-related, treatment-related, patient-reported and health service utilisation outcomes were assessed. Two reviewers independently reviewed and appraised the risk of bias of each study. **Results:** Eighteen studies were included. Interventions comprised one or more of the following components: psychological support, education and exercise. Meta-analyses found that pelvic floor muscle training (PFMT) significantly increased odds of continence at 3 months (OR = 3.29, 95% CI = 1.57-6.91), but did not significantly reduce daily pad use at 6 months post-surgery Mean Difference (MD)= (= - 0.96, 95% CI = - 2.04-0.12) for prostate cancer patients. Although quality of life improved due to PFMT, functional ability or distress did not. Further meta-analyses indicated that pre-surgical exercise significantly reduced length of hospital stay (MD = - 4.18, 95% CI = - 5.43-- 2.93) and significantly lowered odds of post-surgery complications (OR = 0.25, 95% CI = 0.10-0.66) for lung cancer patients. Psychology-based prehabilitation significantly improved mood, physical well-being and immune function for prostate cancer patients and improved fatigue and psychological outcomes and a trend for better quality of life among breast cancer patients. Risk of bias was high for most studies. **Conclusions:** Prehabilitation appears to benefit cancer patients. Rigorous trials are needed to investigate the effectiveness of prehabilitation among other cancer sites and other related effects. The cost-effectiveness of prehabilitation remains unanswered. **Implications for Cancer Survivors:** Providing interventions earlier in the care pathway may lead to better outcomes for patients during survivorship.

INSPIREHEALTH'S INTERPRETATION: This paper reports on 18 studies that compared prehabilitation to standard care in the time between a cancer diagnosis and treatment. Prehabilitation refers to the process of optimizing physical and/or psychological wellbeing to improve patients' recovery from treatment. The prehabilitation interventions in these studies included psychological (stress management training), specific physical therapy (for lungs and pelvic floor), general exercise therapy, and education.

Although not all studies were of the highest quality, the authors chose to include them in this paper because of the overall lack of research in this area. Consequently, in some cases the results of more than one study were pooled together to get a better

understanding of the issue, while in other cases the results of individual studies were reported.

Most of the studies focused on one type of cancer: lung, prostate, breast, and bladder were all represented, and one study involved patients with multiple cancer sites. Prostate cancer patients who performed pelvic floor muscle therapy before cancer treatment had improved urinary continence and quality of life following cancer treatment compared to a group of patients who did not do a prehabilitation program. Similarly, lung cancer patients who performed pre-operative exercises had improved objective measures of lung function after treatment compared with patients who did not participate in a prehabilitation program. Stress management therapy before treatment improved mood, well-being, and immune function in prostate cancer patients. In breast cancer patients, stress management therapy improved optimism. At three months post-surgery, measures of depression, anxiety, and fatigue were the same as pre-surgery in the intervention group but had increased in the control group that did not participate in stress management therapy.

The authors acknowledge that the results of other poorer quality studies (excluded from this review) may still be relevant to the topic so they included a general conclusion from these studies: while rehabilitation from treatment is incredibly valuable it appears that prehabilitation may provide more benefits. The overall positive patient outcomes as a result of prehabilitation support the recommendation of implementation of prehabilitation interventions as part of standard cancer treatment. InspireHealth's multidisciplinary team of health professionals works to support people emotionally, socially, and physically. We encourage engagement in our programs and services throughout a diagnosis (before, during, and after treatment).

PSYCHONEUROENDOCRINOLOGY

Fagundes, C.P., Murdock, K.W., Chirinos, D.A., et al.

Biobehavioral pathways to cancer incidence, progression, and quality of life

Current Directions in Psychological Science (2017), 26(6), 548-553

ABSTRACT | Cancer research within the fields of psychoneuro-endocrinology and psychoneuroimmunology has made substantial progress in understanding how psychological factors impact cancer. Although the pathways by which stress "gets under the skin" to impact cancer incidence, progression, and quality of life are not yet fully understood, the answers to key questions about how stressful life events and the negative emotions they generate can impact cancer initiation, progression, and survivorship have advanced quite dramatically. In this review, we summarize the state of the science in a way that is accessible to a broad audience. We then discuss future directions in cancer research, with a focus on ways psychological science can contribute to the next generation of cancer care.

INSPIREHEALTH'S INTERPRETATION: This paper examines the biological pathways by which stress and psychological factors may impact cancer development, progression and metastases. The interrelated disciplines of psychoneuroendocrinology (the study of the relationships between psychological health factors, the nervous system, and the hormone system) and psychoneuroimmunology (the study of the relationships between psychological factors, the nervous system and the immune system) help to provide some biological understanding of the complex relationships between stress and cancer.

The authors review the sympathetic nervous system (the "fight-or-flight" branch of the autonomic (or automatic) nervous system) which is activated in physically or emotionally stressful situations. When the fight-or-flight nervous system is activated, the catecholamine hormones epinephrine (or adrenaline) and norepinephrine (or noradrenaline) are released from the adrenal glands causing increased heart rate and respiratory rate. Some evidence suggests that tumour cells with increased numbers of catecholamine receptors on their surfaces are more likely to be high grade; that is, more likely to grow and spread in the presence of higher epinephrine/norepinephrine levels. Stress also stimulates the brain to send a hormone (a messenger molecule called ACTH) to the adrenal glands causing the release of cortisol ("the stress hormone") which raises blood sugar and in the long term can suppress the immune system. Animal studies have shown that stressful situations cause elevations of cortisol which are linked to increased tumour number and volume. Even memories of past stressors/traumas or current/past depression or social isolation can negatively impact our immune systems via the fight-or-flight and hormone systems.

The presence of increased levels of markers of chronic inflammation is also associated with cancer progression and spread. Although in the acute setting cortisol inhibits inflammation, it is thought that chronically high levels of cortisol can sometimes lead to cortisol insensitivity allowing immune cells to produce unhealthy levels of pro-inflammatory molecules. Activation of tumour catecholamine receptors by epinephrine and norepinephrine also promotes unhealthy chronic inflammation within tumour cells. The authors describe the immune system as "a brake and accelerator of cancer development and progression" and note that the sympathetic nervous system may help to modulate the newer immunotherapies and targeted tumour therapies. The relationship between stress and cancer is complex and complicated and it is important to note that stress alone does not cause cancer. Cancer is a multifactorial illness and many factors contribute to its development and progression. Many people who experience significant stress never develop cancer and many people with cancer haven't had particularly stressful lives.

However, most people with cancer benefit from understanding their life stressors and developing strategies to help manage and cope with stressful life events. For most of us, stress is a fact of life and our overall wellbeing can be optimized by learning stress reduction strategies such as meditation, relaxation, yoga, prayer, etc. Such strategies are thought to activate our more calming parasympathetic nervous system to help offset the negative physiological consequences of chronic sympathetic nervous system activation.

PALLIATIVE MEDICINE

Vanbutsele, G., Pardon, K., Van Belle, S., et al.

Effect of early and systematic integration of palliative care in patients with advanced cancer: A randomized controlled trial

Lancet Oncology (2018), https://doi.org/10.1016/S1470-2045(18)30060-3

ABSTRACT | Background: The benefit of early integration of palliative care into oncological care is suggested to be due to increased psychosocial support. In Belgium, psychosocial care is part of standard oncological care. The aim of this randomised controlled trial is to examine whether early and systematic integration of palliative care alongside standard psychosocial oncological care provides added benefit compared with usual care. **Methods:** In this randomised controlled trial, eligible patients were 18 years or older, and had advanced cancer due to a solid tumour, an European Cooperative Oncology Group performance status of 0–2, an estimated life expectancy of 12 months, and were within the first 12 weeks of a new primary tumour or had a diagnosis of progression. Patients were randomly assigned (1:1), by block design using a computer-generated sequence, either to early and systematic integration of palliative care into oncological care, or standard oncological care alone in a setting where all patients are offered multidisciplinary oncology care by medical specialists, psychologists, social workers, dieticians, and specialist nurses. The primary endpoint was change in global health status/quality of life scale assessed by the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 items (EORTC QLQ C30) at 12 weeks. The McGill Quality of Life Questionnaire (MQOL), which includes the additional existential wellbeing dimension, was also used. Analysis was by intention to treat. This trial is ongoing, but closed for accrual, and is registered with ClinicalTrials.gov, number NCT01865396. **Findings**: From April 29, 2013, to Feb 29, 2016, we screened 468 patients for eligibility, of whom 186 were enrolled and randomly assigned to the early and systematic palliative care group (92 patients) or the standard oncological care group (94). Compliance at 12 weeks was 71% (65 patients) in the intervention group versus 72% (68) in the control group. The overall quality of life score at 12 weeks, by the EORTC QLQ C30, was 54·39 (95% CI 49·23–59·56) in the standard oncological care group versus 61·98 (57·02–66·95) in the early and systematic palliative care group (difference 7·60 [95% CI 0·59–14·60]; p=0·03); and by the MQOL Single Item Scale, 5·94 (95% CI 5·50–6·39) in the standard oncological care group versus 7·05 (6·59–7·50) in the early and systematic palliative care group (difference 1·11 [95% CI 0·49–1·73]; p=0.0006). **Interpretation:** The findings of this study show that a model of early and systematic integration of palliative care in oncological care increases the quality of life of patients with advanced cancer. Our findings also show that early and systematic integration of palliative care is more beneficial for patients with advanced cancer than palliative care consultations offered on demand, even when psychosocial support has already been offered. Through integration of care, oncologists and specialised palliative care teams should work together to enhance the quality of life of patients with advanced cancer.

INSPIREHEALTH'S INTERPRETATION: There has been mounting evidence in the literature over the past ten years to suggest that palliative care offered in combination with standard oncologic treatment early in the disease course (i.e. early, systematic integration of palliative care) leads to significantly improved quality of life and other beneficial patient outcomes. A possible theory to explain this finding is the increased psychosocial support that patients might receive from involvement of a palliative care team.

To further explore this, the authors conducted an objective experiment (a randomized controlled design) in Belgium, where standard cancer care is multidisciplinary and psychosocial support is offered to all cancer patients. The authors looked at quality of life as the main outcome. The intervention in this study consisted of training the palliative care team members on cancer treatments; monthly visits between patients and palliative care nurses, which included monthly symptom assessments; and integrating the palliative care team into the patient's cancer care by including them in the weekly oncology team meetings.

The results of this study were that the patients in the intervention group (early palliative care group) had significantly better quality of life at 12 and 18 weeks compared to the control group. This difference was not related to symptom control, as symptoms were reported as similar between the two groups at 12 and 18 weeks. There was no significant difference in length of life between the two groups, a finding that has been reported in other studies in the literature. It is not clear what part(s) of the intervention is (are) responsible for this improvement in quality of life. Psychosocial support is an important factor that can be found in many forms. InspireHealth offers weekly classes and programs, including activity classes, cooking classes, and support groups.

DIET AND CANCER

Mourouti, N., Panagiotakos, D.B., Kotteas, E.A., et al.

Optimizing diet and nutrition for cancer survivors: A review

Maturitas (2017), 105, 33-36.

ABSTRACT | The number of cancer survivors is increasing and they are often highly motivated to search for Information about nutrition and about physical activity in order to try to improve their treatment outcomes, quality of life and overall survival. In the light of these concerns, the World Cancer Research Fund (WCRF)/American Institute for Cancer Research (AICR) as well as the American Cancer Society recommend a largely plant-based diet with limited consumption of red and processed meat, and limited consumption of alcohol, as well as the maintenance of a healthy weight throughout life and regular engagement in physical activity. There is a need for well-designed large observational and intervention studies to shed more light on the association between diet and cancer survivorship, and to suggest additional means for the secondary prevention of cancer.

INSPIREHEALTH'S INTERPRETATION: This review provides a short and general overview of recommendations for food consumption, supplements, body fat, and physical activity for cancer survivors. The authors reviewed guidelines from relevant cancer organizations (i.e., the World Cancer Research Fund, American Institute of Cancer, American Cancer Society, etc.) and summarized some of them in this article. It is important to note that these are broad guidelines directed towards the general cancer population. **Recommended foods:** Cancer survivors are encouraged to follow guidelines similar to primary cancer prevention (pre-diagnosis). Research supports the consumption of mostly plant-based foods. Cancer organizations recommend consuming a variety of non-starchy vegetables and fruits a day (at least 5 portions/servings) and unprocessed cereals or legumes. When possible, look to select whole grains over refined grains. Cancer survivors with the highest intakes of vegetables and fish had the lowest associated risk of cancer mortality. Fruits, vegetables, fish, and whole grains may protect against cancer due to the presence of healthy micronutrients and bioactive compounds. **Foods to limit or avoid:** The World Health Organization (2015) classifies red meat as a Group 2A 'probable carcinogen' (may cause cancer) and processed meat as a Group 1 'carcinogen' (cancer causing). The recommendations are to avoid or limit red meat to less than 500 grams (18 oz) per week and for processed meat to be avoided. Origins of red or processed meat's carcinogenetic mechanisms include elevated iron (a risk factor for several cancers), the presence of saturated fats, and substances added or formed during meat processing and cooking. Salted foods and sugary drinks are to be avoided. Alcohol consumption should be limited to no more than two drinks per day for men and one drink per day for women. Not mentioned by the authors is that alcoholic beverages are also labeled as a Group 1 'carcinogen' (cancer causing) by the World Health Organization. **Supplements:** Concisely, the authors report that consuming a product intended to supplement the diet by increasing the total dietary intake of a vitamin, mineral, herb or other botanical, an amino acid, or other dietary substance is not recommended for cancer prevention. Cancer survivors are encouraged to meet their needs through diet. The authors mention that supplements should only be considered if a nutrient deficiency exists and dietary intake falls below two-thirds of the recommended intake. Supplementation should be determined with a registered dietitian with the cooperation of other healthcare providers. **Body fat:** Excess body fat is correlated to an increase in concentrations of compounds (e.g., endogenous estrogens) known to increase cancer risk. It is also associated with systemic inflammation and suppression of the immune system, both of which may support cancer growth. Hormones increased by obesity such as insulin, leptin, and insulin-like growth factor are also associated with increased cancer incidence. The authors recommend that people maintain a healthy body weight in order to help prevent primary cancer and recurrence. **Physical Activity:** Physical activity promotes weight management, reduces inflammation, improves the immune system, helps to regain pre-treatment fitness health, lowers insulin, estrogen, and certain growth factors associated with cancer development, reduces fatigue, reduces depression, and improves overall quality of life (there are more benefits not listed by the authors). The authors recommend that cancer survivors be moderately active at least 30 minutes per day for five or more days a week as per condition and energy allows. **Summary:** Dietary and physical activity choices may improve or exacerbate cancer markers. Cancer survivors are thus recommended to follow the above guidelines.

EXERCISE AND LYMPHEDEMA

Baumann, F.T., Reike, A., Reminer, V., et al.

Effects of physical exercise on breast cancer-related secondary lymphedema: a systematic review

Breast Cancer Research and Treatment (2018). 170(1), 1-13. doi: 10.1007/s10549-018-4725-y

ABSTRACT | Purpose: The aim of this systematic review is to assess the effect of different types of exercise on breast cancer-related lymphedema (BCRL) in order to elucidate the role of exercise in this patient group. **Methods:** A systematic data search was performed using PubMed (December 2016). The review is focused on the rehabilitative aspect of BCRL and undertaken according to the PRISMA statement with Levels of Evidence (LoE) assessed. **Results:** 11 randomized controlled trials (9 with LoE 1a and 2 with LoE 1b) that included 458 women with breast cancer in aftercare were included. The different types of

exercise consisted of aqua lymph training, swimming, resistance exercise, yoga, aerobic, and gravity-resistive exercise. Four of the studies measured a significant reduction in BCRL status based on arm volume and seven studies reported significant subjective improvements. No study showed adverse effects of exercise on BCRL. **Conclusion:** The evidence indicates that exercise can improve subjective and objective parameters in BCRL patients, with dynamic, moderate, and high-frequency exercise appearing to provide the most positive effects.

INSPIREHEALTH'S INTERPRETATION: This article is a systematic review of 11 high quality studies examining the effect of various types of exercise programs on breast cancer related lymphedema, a common side effect of breast cancer and/or associated treatments. The lymphatic system filters and drains fluid throughout the body but if the system is compromised (from a tumour, surgery, and/or radiation), fluid can build up in the arm on the affected side. This may result in swelling, pain, and feelings of weakness and discomfort in the arm. The authors of this study report that over 1 in 5 women who survive breast cancer will develop lymphedema. Treatment of this condition usually includes some form of compression garment, manual lymph drainage, and skin care. It used to be that exercise was considered a possible risk factor for exacerbating symptoms, however research now shows that appropriate exercise is actually beneficial to prevent and manage lymphedema.

The exercise interventions considered in this paper varied between the studies: four were strength programs, two had an aerobic and strength component, and two were water-based exercise programs. The final three studies included arm exercises against gravity, yoga, and exercises plus relaxation (breathing, tai chi, qi gong). The frequency of the exercise sessions varied from daily to one session per week and the interventions varied in duration from eight weeks to one year. Some interventions had supervision throughout while others were only supervised for the initial sessions. Compression garments were used in the majority of studies, a few allowing participants to choose, and one study considering water as a compression stimulus. The National Lymphedema Network recommends wearing a compression garment to help manage lymphedema, and it is important to ensure that it is properly fitted with the appropriate compression. None of the studies demonstrated that an exercise program exacerbated lymphedema symptoms. Four of the 11 studies demonstrated improved lymphedema status (arm volume decreased) and in six of the studies participants reported improved lymphedema symptoms. The four studies that showed objective improvements in arm volume all included resistance training and sessions were 10-20 minutes long performed most days of the week. In addition to the lymphedema symptoms, shoulder function, upper body strength, quality of life, and mood improved in the majority of studies.

Overall, consistent participation in an exercise program with a resistance component and at least initial supervision by an exercise professional can improve lymphedema symptoms as well as overall function, strength, and quality of life. Knowing what types of exercise are appropriate may be a barrier for some. Booking an appointment with an Exercise Therapist at InspireHealth is a good place to start.

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