



RESEARCH UPDATES WINTER 2016

INSIDE:

Breast Cancer	1, 2
Colorectal Cancer	3
Pain Management	3
Physical Activity	4
Into the Vault	5

Research Updates is published quarterly to provide the latest supportive cancer care research to patients, health care providers, and the public.

To support this valuable educational service, please donate at: www.inspirehealth.ca/donate

FOR THE LATEST IN WORLDWIDE SUPPORTIVE CANCER CARE

IN THIS ISSUE: Morean and colleagues explore a variety of therapies for cognitive deficits associated with chemotherapy among breast cancer patients. A paper by Ennour-Idrissi's team reviews the impact that physical activity can have on circulating sex hormones in women. Encarnação and colleagues examine the influence of dietary fiber on colorectal cancer. Keenan and Keithley look at the relationship between music and cancer-related pain management. A study by Mundstock et al. reviews the relationship between physical activity and telomere length. Lastly, an Into the Vault study by Bryant and colleagues reviews the relationship between sleep and the immune system.

BREAST CANCER

Morean, D.F., O'Dwyer, L., & Cherney, L.R.

Therapies for cognitive deficits associated with chemotherapy for breast cancer: A systematic review of objective outcomes.

Archives of Physical Medicine and Rehabilitation (2015). 96, 1880-1897.

ABSTRACT | Objective: To systematically review evidence of treatments for cognitive impairments experienced by at least 20% of all women who undergo chemotherapy for breast cancer. **Data Sources:** Searches of 5 databases (PubMed, Embase, Cochrane CENTRAL, PsycINFO, CINAHL), with no date or language restrictions, identified 1701 unique results. Search terms included breast cancer, chemotherapy, chemobrain, chemofog, and terms on cognition and language deficits. **Study Selection:** Included only peer-reviewed journal articles that described therapies for cognitive dysfunction in women undergoing (or who had undergone) chemotherapy for breast cancer and provided objective measurements of cognition or language. **Data Extraction:** Data were extracted according to Cochrane recommendations, including characteristics of participants, interventions, outcomes, and studies. Quality assessment of all 12 eligible studies was performed using the Physiotherapy Evidence Database scale and treatment fidelity criteria. Screening, data extraction, and quality assessment reliability were performed. **Data Synthesis:** Six articles described interventions for cognition that took place during cancer treatment; 6, afterward. Five interventions were medical (including a strength-training program), 2 were restorative, and 5 were cognitive. Medicinal treatments were ineffective; restorative and exercise treatments had mixed results; cognitive therapy had success in varying cognitive domains. The domains most tested and most successfully treated were verbal memory, attention, and processing speed. **Conclusions:** Cognitive therapy protocols delivered after chemotherapy and aimed at improving verbal memory, attention, and processing speed hold the most promise. Future research is needed to clarify whether computerized cognitive training can be effective in treating this population, and to identify objective assessment tools that are sensitive to this disorder.

INSPIREHEALTH'S INTERPRETATION: Breast cancer is the most commonly diagnosed type of cancer in women. With improved survivorship comes the importance of understanding the long-term side effects of common treatments such as chemotherapy. This paper systematically reviewed 12 good quality studies designed to assess the effectiveness of various strategies for treating chemotherapy-associated cognitive deficits. Cognitive dysfunction (chemo-brain or chemo-fog) appears to affect at least 20% of women who have received standard-dose chemotherapy, and often persists long after treatment has ended. Rehabilitative therapies designed to mitigate this cognitive decline is an active area of research. Cognitive improvement strategies examined by these authors included medical treatments, restorative therapies, and specific cognitive therapies. Medical treatments included strength training exercise, and supplements and medications such as ginkgo biloba, Ritalin, and erythropoietin (red blood cell booster). Restorative therapies included choosing calming experiences (e.g., walking in

nature, time with pets) and Tibetan sound meditation. Cognitive therapies included memory and attention behavioural training, computerized training (see Kesler et al., August 2014 Research Updates), plus/minus training in self-awareness, relaxation and compensatory strategies (e.g., using planners, sticky notes).

While supplements and medications were ineffective, varying levels of success were observed for relaxation training (though not for Tibetan sound meditation), restorative activities, and strength training. However, cognitive therapy may provide the most benefit for treatment-associated cognitive deficits. Two comprehensive cognitive rehabilitation programs were particularly successful. They both included training in everyday memory and attention, compensatory strategies, relaxation, and self-pacing, as well as education on chemotherapy's cognitive effects. The authors concluded that cognitive therapies "delivered after chemotherapy and aimed at improving verbal memory, attention and processing speed" seem to hold the most promise.

Ennour-Idrissi, K., Maunsell, E., & Diorio, C.

Effect of physical activity on sex hormones in women: A systematic review and meta-analysis of randomized controlled trials.

Breast Cancer Research (2015). 17:139, DOI 10.1186/s13058-015-0647-3.

ABSTRACT | Introduction: Exposure to high levels of endogenous estrogens is a main risk factor for breast cancer in women, and in observational studies was found to be inversely associated with physical activity. The objective of the present study is to determine the effect of physical activity interventions on sex hormone levels in healthy women. **Methods:** Electronic databases (MEDLINE, EMBASE, CENTRAL), from inception to December 2014, and reference lists of relevant reviews and clinical trials were searched, with no language restrictions applied. Randomized controlled trials (RCTs) were included if they compared any type of exercise intervention to no intervention or other interventions, and assessed the effects on estrogens, androgens or the sex hormone binding globulin (SHBG) in cancer-free women. Following the method described in the Cochrane Handbook for Systematic Reviews of Interventions, data on populations, interventions, and outcomes were extracted, and combined using the inverse-variance method and a random-effects model. A pre-established protocol was drawn up, in which the primary outcome was the difference in circulating estradiol concentrations between the physical activity (experimental) and the control groups after intervention. Pre-specified subgroup analyses and sensitivity analysis according to the risk of bias were conducted. **Results:** Data suitable for quantitative synthesis were available from 18 RCTs (1994 participants) for total estradiol and from 5 RCTs (1245 participants) for free estradiol. The overall effect of physical activity was a statistically significant decrease of both total estradiol (standardized mean difference [SMD] -0.12; 95 % confidence interval [CI] -0.20 to -0.03; $P = 0.01$; $I^2 = 0\%$) and free estradiol (SMD -0.20; 95 % CI -0.31 to -0.09; $P = 0.0005$; $I^2 = 0\%$). Subgroup analyses suggest that this effect is independent of menopausal status and is more noticeable for nonobese women and for high intensity exercise. Meta-analysis for secondary outcomes found that physical activity induces a statistically significant decline of free testosterone, androstenedione, dehydroepiandrosterone-sulfate and adiposity markers, while a significant increase of SHBG was observed. **Conclusions:** Although the effect is relatively modest, physical activity induces a decrease in circulating sex hormones and this effect is not entirely explained by weight loss. The findings emphasize the benefits of physical activity for women.

INSPIREHEALTH'S INTERPRETATION: Prolonged exposure to high levels of endogenous (produced within our own bodies) sex hormones such as estrogen is thought to be a significant risk factor for female breast cancer. Physical activity has been associated with a lower risk of developing breast cancer and it has been postulated that this association may be mediated by the ability of physical activity to lower levels of circulating sex hormones. Because fatty tissue is a main source of extra-ovarian estrogen, it is also postulated that physical activity may be associated with lower estrogen levels by decreasing fat mass.

These authors performed a meta-analysis of data collected from 18 randomized controlled trials (RCTs) designed to assess the effect of physical activity on healthy women's sex hormone levels (according to the type and intensity, body mass index (BMI), and menopausal (pre-, peri-, post-) status). Although several hormones were examined, the primary outcomes were circulating total and free estradiol (the most biologically active form of estrogen). Only hormones that are not bound to proteins (i.e., free) are biologically active, so a total hormone assay measuring both bound and free hormones, is not usually the best indicator of hormone activity. Sex hormone binding globulin (SHBG) is the protein that binds the sex hormones to proteins. Total estradiol concentrations decreased most significantly when the exercise was high-intensity, when resistance training was performed 3-5 hours per week, and when overweight participants lost substantial weight. Circulating concentrations of free estradiol also decreased when the exercise was high-intensity and the effect was most notable in those whose BMI was less than 30 kg/m² (overweight is 25-30 kg/m² and obese is >30 kg/m²). In fact, the effect of exercise was more significant for free estradiol than for total estradiol. Lower concentrations of free estradiol occurred independent of menopausal status, weight loss after intervention, or type of exercise.

Interestingly, physical activity significantly increased SHBG concentrations. Because the findings showed that the decrease in total estradiol levels was related to weight loss, but the reductions in free estradiol were not, the authors suggest that the effect of exercise on estradiol is not mediated solely by weight loss and may be related to the sequestration of estradiol by increased levels of SHBG. In summary, these results support the hypothesis that physical activity induces a decrease in

circulating sex hormones regardless of menopausal status or exercise-induced weight loss. Though these studies were done in healthy, cancer-free women, the benefits of exercise in those diagnosed with breast cancer have been well documented. Future research is needed to examine the effect of exercise on sex hormone levels in women with an established breast cancer diagnosis.

COLORECTAL CANCER

Encarnaç o, J.C., Abrantes, A.M., Pires, A.S., & Botelho, M.F.

Revisit dietary fiber on colorectal cancer: butyrate and its role on prevention and treatment.

Cancer Metastasis Review (2015). 34:465–478.

ABSTRACT | Colorectal cancer is still a major health problem worldwide. Based on the most recent released data by the World Health Organization GLOBOCAN in 2012, colorectal cancer is the third most prevalent type of cancer in males and the second in females. In 1999, it was published the first report showing evidence of a strong correlation between diet and cancer incidence, being its positive or negative impact intimately linked to dietary patterns. A diet rich in fiber is associated with a low risk of developing colorectal cancer. The fermentation of the dietary fiber by intestinal microflora results in production of butyrate, which plays a plurifunctional role on the colonocytes, and it has also been reported as a chemopreventive agent. However, there are limited studies focusing its anti-cancer potential. Here, we review the recent new insights that focus butyrate and its role in colorectal cancer prevention and treatment, from its synthesis, metabolism, and transport, through its involvement on several cancer-related signaling pathways, to the novel existing approaches for its clinical use.

INSPIREHEALTH'S INTERPRETATION: Research has shown that consumption of dietary fiber has been linked to a reduced risk of developing colorectal cancer. The authors of this paper describe that the beneficial effects are derived largely from the by-products of the fermentation of dietary fiber by gut-based flora (bacteria). They explain that there is strong support that butyrate, a short-chain fatty acid produced from butyrate-producing bacteria, affects the function of the colon cells which line the lower part of the gastrointestinal tract. Butyrate is postulated to have cancer preventative properties due to being both anti-oxidant and anti-inflammatory in nature.

This review explains how a metabolic by-product of fiber (butyrate) may provide protective effects from colorectal cancer. The authors explain that there is strong evidence that butyrate is metabolized differently by normal colon cells when compared to colon cancer cells such that it does not inhibit growth for normal colon cells but does so with colon cancer cells. This is described as the 'butyrate paradox'. Butyrate is the primary energy source for normal colon cells but colon cancer cells produce energy primarily from a pathway that does not properly metabolize butyrate. Since butyrate is not readily broken down for energy in colon cancer cells, it accumulates inside the nucleus of these cells. Once inside the nucleus, it inhibits a class of enzymes which has broad effects on gene expression and cell function.

The authors describe several studies illustrating that inhibition of these enzymes may suppress tumor cell growth and may induce programmed cellular death (apoptosis). Butyrate also contributes to the healthy maintenance of the intestinal barrier and mucosal lining. Loss of the intestinal barrier may activate inflammatory immune cells and promote tumour growth and progression. As well, studies have found that butyrate aids the passage of stool through the large intestine which lowers certain risk factors for colon cancer development. Though butyrate exhibits strong anti-cancer properties, its clinical use may be limited due to its rapid uptake by healthy colon cells, reducing its availability to interact with colon cancer cells. Researchers are looking at practical dietary ways to increase butyrate levels.

PAIN MANAGEMENT

Keenan, A., & Keithley, J.K.

Integrative Review: Effects of Music on Cancer Pain in Adults.

Oncology Nursing Forum, 42(6), E368–E375. doi: 10.1188/15.ONF.E368-E375.

ABSTRACT | Problem Identification: To evaluate the literature for music's effect on adult cancer pain. **Literature Search:** An electronic literature search from 1986–2014 was conducted to evaluate the effects of quantitative music among adults with cancer pain in settings including homes, hospitals, and palliative care units. Databases used were PubMed (MEDLINE®) and Scopus. **Data Evaluation:** The study designs, methods, measures, outcomes, and limitations were evaluated independently by the primary author and verified by the second author. The primary outcome measure of interest was the effect of music in cancer pain. **Synthesis:** Of 82 studies, 5 of them—totaling 248 participants—met eligibility criteria. Review of findings suggests a paucity of innovative approaches for using music to mitigate cancer pain among adults. Psychological outcomes, anxiety, depression, and mood were understudied. Advanced pain, multiple cancer types, and lack of racial diversity characterize the samples. **Conclusions:** Modern treatments for cancer have improved survival rates; however, patients often experience tumor- and treatment-related pain. Pharmacologic and nonpharmacologic methods may minimize cancer pain. The use of music as an adjunct to pain medication requires additional studies, particularly on mechanisms of its effect on pain among

diverse, large samples with multiple cancer pain types. A limitation of this review is the small number of available studies to date. **Implications for Practice:** The evidence for music therapy in the management of pain is limited. Integrative methods using music may represent an important intervention that nurses may be able to suggest as an inexpensive, nontoxic, and readily available intervention for potentially minimizing cancer pain.

INSPIREHEALTH'S INTERPRETATION: Pain is the one of the most feared symptoms associated with cancer and often affects cancer survivors at some point during their treatment and recovery. Many non-pharmacological approaches to pain management have been studied, including music. Although music is known to have calming and pain-lessening effects, there are few published studies on music and cancer pain. As well, specific mechanisms on how pain is relieved by music are not well known. It is postulated that pain reductions may be related to the associated psychological outcomes including increased relaxation, reduced anxiety, improved mood, and distraction from pain.

This research review investigated all published studies which have used music for the relief of cancer pain in adults 21 years and older. Only five studies were found that used quantitative research methods (i.e., studies using statistical analysis) to investigate cancer pain and music. Additionally, the authors of this review reported that collectively these studies had inadequate sample sizes (low number of participants) to effectively measure whether music had an effect or not on cancer pain. Two of the five studies reported a statistically significant benefit of using music for cancer pain. One of these studies was a randomized controlled trial (typically the 'gold standard' for research) and found that music relieved pain by half in 42% of the music group, compared to improved pain in 8% of the controls.

Music and music therapy are becoming more popular in hospitals and outpatient settings as patients seem to respond positively to music as an adjuvant treatment. Typically, the type of music includes low tones with strings, instrumental music, and volumes no greater than that of a normal conversation. In summary, the authors reported that music may be a useful supplementary tool for cancer-related pain but more reliable and valid research is required to fully understand its effect.

PHYSICAL ACTIVITY

Mundstock, E., Zatti, H., Louzada, F.M., et al.

Effects of physical activity in telomere length: Systematic review and meta-analysis.

Ageing Research Reviews (2015). 22,72–80.

ABSTRACT | The aim of this systematic review is to assess the effects of exercise on telomeres length. We searched the following databases: MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials (CENTRAL, The Cochrane Library), Scopus, LILACS, SPORTDiscus and Web of Science from inception to August 2014. All articles that assessed the effects of exercise in telomere length were included in this review. The search strategy used the following combinations of terms: telomere AND "motor activity" OR exercise OR "physical activity". Two reviewers, working independently, screened all titles and abstracts to identify studies that could meet inclusion criteria. Whenever possible, and if appropriate, we performed a random effect meta-analysis of study outcomes. Thirty-seven original studies were included in this systematic review, including 41,230 participants. Twenty articles did not find statistically significant association, whereas 15 described a positive association. Two papers found an inverted "U" correlation. There is a tendency toward demonstrating an effect of exercise on telomere length. Few prospective studies were found, many studies did not reach statistical significance and there was an important methodological diversity. For this reason, a possible significant association between physical activity and telomere length remains an open question.

INSPIREHEALTH'S INTERPRETATION: Telomeres are repetitive DNA sequences that are found at the end of chromosomes and preserve genetic information. Telomeres shorten every time a cell divides and once they reach a critical size, they may stop cell division (cell senescence) or induce programmed cellular death (apoptosis), essentially impairing a cell from functioning properly. Oxidative stress, inflammation, cancer, and other factors have been associated with accelerating telomere shortening. Physical activity increases oxidative stress acutely but can improve antioxidant activity within cells over time. This systematic review and meta-analysis evaluated all scientific articles on physical activity and telomere length in humans. The studies investigated associations between levels of physical activity and telomere length and excluded case studies, editorials, and animal/cell culture models. Thirty seven studies were included for the systemic review (41,230 participants), and twenty five studies were included for the meta-analysis.

Of these studies, over half found no statistical relationship between physical activity and telomere length. There were no negative associations and approximately one third of the studies found that exercise was associated with longer telomere length. Two studies found that telomere length was greater for certain physical activity levels and lower if physical activity was too low or too high. However, the authors were not able to establish an association based on these studies. There were significant differences between studies that made it difficult to compare data. Although the results are promising, more quality data is needed to reach a conclusion on physical activity and telomere length.

INTO THE VAULT

Bryant, P.A., Trinder, J., & Curtis, N.

Sick and tired: Does sleep have a vital role in the immune system?

Nature Reviews: Immunology (2004). 4, 457-467.

ABSTRACT | It is a common belief that we are more susceptible to infections when deprived of sleep. Consistent with this, there is increasing evidence that sleep deprivation has detrimental effects on the immune response, indicating that sleep should be considered a vital part of the immune system and that there is a reciprocal relationship between sleep and immunity. This relationship is important because, over recent decades, there has been a documented decrease in the mean duration and quality of sleep in the population. The concept that lack of sleep might be compromising immunity in the population has far-reaching public-health implications for both individuals and society.

INSPIREHEALTH'S INTERPRETATION: The amount of time that we spend asleep has steadily declined over the past quarter century. Growing evidence indicates that sleep deprivation, even in the short term, can have negative behavioural and cognitive consequences. These consequences have lead researchers to consider the broader physiological (e.g. metabolic) and systemic effects of sleep deprivation. In particular, studying the association between sleep and immunity has been an area of intense research. While sleep deprivation may be associated with increased risk of infection and illness, infection and illness also seem to cause increased sleep. These researchers examined the evidence to answer the questions “Do changes in the immune system cause changes in sleep?”, and “Does sleep have an important role in restoring the immune system?”. There are two types of sleep: non-rapid-eye-movement (NREM) sleep, and rapid-eye-movement (REM) sleep, and four stages of NREM sleep based on electroencephalogram (EEG) characteristics (though some more recent papers have combined stages 3 and 4 into one stage). Stage one sleep occurs during the transition from wakefulness to sleep, while stages 2-4 are deeper sleep. Stages three and four are characterized by slow-wave sleep (SWS) on the EEG. Many (but not all) researchers believe that SWS is involved in restorative functions and that information processing occurs during REM sleep. Optimal sleep duration for adults is approximately seven hours, with NREM sleep constituting about 80% of total sleep.

These authors summarize the *in vitro* (petri dish) and *in vivo* (mostly animal rather than human) studies which have examined the many molecular and cellular pathways by which sleep affects cytokine activity during optimal sleep, sleep deprivation, and infection. Cytokines such as tumour-necrosis factor (TNF), interferons (IFNs), and interleukins (ILs) are small protein molecules that send signals from cell to cell and are important components of the immune and inflammatory systems. Understanding these pathways helps to understand how sleep and the immune system are connected to one another. Though research results are often conflicting and contradictory, it appears that sleep deprivation (particularly chronic sleep deprivation through shift-work, hectic lifestyles and stress) has a considerable negative influence on the immune system and that there is a reciprocal relationship between sleep and immunity. The authors conclude that sleep is a vital component of the immune system. Further understanding this complex relationship could provide a basis for the development of interventions to improve sleep, immunity, and overall health.

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

Lower Mainland Vancouver Centre

#200-1330 West 8th Ave.
Vancouver, BC, V6H 4A6
604.734.7125

Vancouver Island Victoria Centre

#212-2187 Oak Bay Ave.
Victoria, BC V8R 1G1
250.595.7125

Southern Interior Kelowna Centre

#123-565 Bernard Ave.
Kelowna, BC V8R 1G1
250.861.7125

inspirehealth.ca