



## RESEARCH UPDATES APRIL / MAY 2015

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### FOR THE LATEST IN WORLDWIDE INTEGRATIVE CANCER CARE

**IN THIS ISSUE:** Larkin and colleagues review the literature pertaining to the management of cancer-related fatigue in men with prostate cancer. A paper by Touchefeu's team explores the role that gut microorganisms can play in the prevention of chemotherapy- or radiation-induced gastrointestinal mucositis. Garcia and Thomson look at physical activity and cancer survivorship recommendations. Fu and colleagues review the evidence-base for cancer-related lymphedema management. The Into the Vault study reviews the use of medicinal mushrooms as immune therapy for breast cancer survivors.

## PROSTATE CANCER

Larkin, D., Lopez, V., & Aromataris, E.

### Managing cancer-related fatigue in men with prostate cancer: A systematic review of non-pharmacological interventions.

*International Journal of Nursing Practice* (2014), 20(5), 549-560.

The aim of this systematic review was to synthesize the best available evidence informing the effectiveness of non-pharmacological interventions for managing cancer-related fatigue in men treated for prostate cancer. This review considered experimental studies that included men with prostate cancer (regardless of staging, previous treatment or comorbidities), aged 18 years and over who were undergoing any treatment, or had completed any treatment for prostate cancer within the previous 12 months. Three interventions were identified for the management of cancer-related fatigue in men with prostate cancer. Evidence from five studies including 447 participants demonstrates the effectiveness of physical activity, both aerobic and resistance exercise, and from three studies including 153 participants suggesting the benefits of psychosocial interventions including education and cognitive behavioural therapy. Health professionals require knowledge of a range of effective interventions aimed at reducing cancer-related fatigue in men with prostate cancer and should incorporate those interventions into their patient management. Although physical activity appears to show the greatest benefit, other non-pharmacological interventions such as education and cognitive behavioural therapy have demonstrated benefit and should also be considered as a strategy in treating this debilitating side effect of cancer and its treatment.

**INSPIREHEALTH'S INTERPRETATION:** Prostate cancer is the most common cancer among men, the third leading cause of death from cancer and represents almost 25% of all new cancers diagnosed in Canadian men. Cancer-related fatigue (CRF) is an extremely common symptom in those with cancer and it is difficult to understand or define. This fatigue can be overwhelming and disproportionate to activity; it isn't generally relieved with rest. Men with prostate cancer may experience fatigue from surgery, radiation therapy, chemotherapy, and androgen deprivation therapy (eg. Lupron, Zoladex, Casodex). Drugs used to treat prostate cancer such as mitoxantrone and docetaxel can cause profound fatigue. These Australian authors reviewed the current evidence for the use of non-pharmacological (non-medication) interventions to mitigate or alleviate CRF in men with prostate cancer. Good quality studies (using a methodological quality score) examining adult men with a diagnosis of any stage of prostate cancer who had received treatment within the previous 12 months was included. Fifteen such studies examining non-pharmacological interventions such as exercise (aerobic and resistance) and psychosocial approaches such as cognitive-behavioural therapy and education were ultimately included in the analysis. Results indicated that physical activity (either resistance or aerobic exercise) is beneficial in reducing CRF in men with prostate cancer. One study, however, clearly demonstrated that resistance training was more beneficial than aerobic training in the longer term. Less robust benefit was noted for cognitive behavioural and educational therapy, however methodological differences may have accounted for some discrepancies in the

results. With respect to the educational intervention, a brief nursing education program including two sessions designed to give general information on fatigue and strategies to increase activity was not beneficial. On the other hand, an initiative entitled 'Health Education Attention Condition Intervention' was associated with significant reductions in fatigue. This program provided eight weekly telephone sessions to deliver comprehensive and prostate-cancer specific information. The authors summarized that there is good evidence to recommend exercise as a beneficial intervention. Targeted, intensive education may also help to reduce fatigue in men with prostate cancer. Overall, the principles of patient-centered care as espoused at Inspirehealth will help to guide effective individualized approaches to this very common symptom.

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## GASTROINTESTINAL MUCOSITIS

Touchefeu, Y., Montassier, E., Nieman, K., et al.

### Systematic review: the role of the gut microbiota in chemotherapy- or radiation-induced gastrointestinal mucositis – current evidence and potential clinical applications.

*Aliment Pharmacol Ther* 2014; 40: 409–421.

**BACKGROUND:** Gastrointestinal mucositis is defined as inflammation and/or ulcers of the gastrointestinal tract occurring as a complication of chemotherapy and radiation therapy, and affects about 50% of all cancer patients. **AIM:** To assess the role of gut microbiota in the pathogenesis of gastrointestinal mucositis and the potential for manipulations of the microbiota to prevent and to treat mucositis. **METHODS:** Search of the literature published in English using Medline, Scopus and the Cochrane Library, with main search terms 'intestinal microbiota', 'bacteremia', 'mucositis', 'chemotherapy-induced diarrhoea', 'chemotherapy-induced mucositis', 'radiotherapy-induced mucositis'. **RESULTS:** The gut microbiota plays a major role in the maintenance of intestinal homeostasis and integrity. Patients receiving cytotoxic and radiation therapy exhibit marked changes in intestinal microbiota, with most frequently, decrease in Bifidobacterium, Clostridium cluster XIVa, Faecalibacterium prausnitzii, and increase in Enterobacteriaceae and Bacteroides. These modifications may contribute to the development of mucositis, particularly diarrhoea and bacteraemia. The prevention of cancer therapy-induced mucositis by probiotics has been investigated in randomised clinical trials with some promising results. Three of six trials reported a significantly decreased incidence of diarrhoea. One trial reported a decrease in infectious complications. **CONCLUSIONS:** The gut microbiota may play a major role in the pathogenesis of mucositis through the modification of intestinal barrier function, innate immunity and intestinal repair mechanisms. Better knowledge of these effects may lead to new therapeutic approaches and to the identification of predictive markers of mucositis.

**INSPIREHEALTH'S INTERPRETATION:** Mucositis is an inflammation of the mucous membrane lining of the gastrointestinal (digestive) tract. This can be very painful and also commonly seen following chemotherapy and radiation therapy. Symptoms can include mouth ulcers, diarrhea, abdominal pain, gastrointestinal (GI) bleeding and infection. Severe gastrointestinal mucositis can even be fatal. These symptoms can result in treatment dosage reductions or delays, contributing to suboptimal treatment outcomes. Various treatments including antibiotics and sucralfate (which acts as a protective coating for the GI tract) have failed to lessen the burden of mucositis. The authors of this paper reviewed the literature to summarize what is currently known about the underlying causes of chemotherapy- or radiation-induced mucositis, particularly related to the role of GI microorganisms (gut microbiota). They also discussed how knowledge of this pathology might inform better treatment options. Newer DNA technology has allowed researchers to more easily identify gut microorganisms thus facilitating the study of their roles in cancer treatment. Interest in the role of the gut microbiome in overall health has grown in recent years. Tens of trillions of microorganisms representing over 1000 bacterial species live in our GI tracts, and collectively can weigh up to 2 kg. Humans share about 1/3 of gut microbial species and about 2/3 are specific to each of us. Therefore, we each have a specific gut microbiome and its composition is largely determined by our diet and environment. The gut microbiome plays an important role in the normal and healthy functioning of the whole body. It is necessary for proper digestion and for the proper functioning of our immune system. It is known that the gut microbiome is significantly altered following cancer treatment and these changes are associated with the intestinal inflammation of mucositis. Interestingly, some microorganisms have been shown to cause inflammation while others change due to inflammation. Therefore, changes to the microbial population (flora) can either be the cause or consequence of an inflammatory process. To complicate matters further, the ways in which these microorganisms function (related to their gene expression) can change as a consequence of inflammation. These gene expression changes may be more important than actual microorganism composition changes. Chemotherapy and radiation therapy can cause mucositis through several pathways. Healthy gut bacteria can protect the gut by activating the body's own immune system to support mucosal repair to regulate intestinal barrier function. Thus, microbial disruption (by altered composition and/or gene expression changes) could play an important role in optimizing the protective mucous lining of the gut. Both animal and human studies have shown marked reductions in typical gut bacteria (eg. lactobacillus and bifidobacterium species) and significant increases in the less typical enterococci species following chemotherapy and radiation therapy. Enterococci and similar species are often found in blood cultures from septic (bacteria in the blood stream) cancer patients. How to prevent or treat mucositis is an area of much interest and study. The use of probiotics as a way to protect and augment the more beneficial gut bacteria is of particular interest because they are readily available and relatively inexpensive. Probiotics are defined as living

microorganisms that can provide health benefits to the host. Fermented foods such as yogurt and sauerkraut contain myriad probiotics and probiotic supplements often contain the beneficial lactobacillus and bifidobacterium species. While some clinical trials have shown gut protection during chemotherapy and radiation therapy, there are some concerns that some probiotics may actually increase the risk of sepsis due to cancer- or treatment-related immunosuppression. Different probiotics contain different bacterial strains and for each probiotic strain the risk/benefit ratio will, therefore, be different and high quality studies using properly identified and dosed strains still need to be done. Evidence to date indicates that those receiving chemotherapy or radiation therapy have significantly altered intestinal microorganisms. These changes may be due to the cancer itself or to inflammation, but the new flora may also contribute to the development of mucositis. Whether probiotic supplements mitigate these negative changes remains the matter of some debate. Better ways to identify gut microorganisms and analyze their gene expression may help develop strategies to prevent or treat the potentially life-threatening complication of mucositis. In the meantime, it may be reasonable to include some fermented foods as part of an overall healthy diet. (see also: “Emerging roles of lactic acid bacteria in protection against colorectal cancer” in the October 2014 issue of *Research Updates*).

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## EXERCISE

Garcia, D. O., & Thomson, C.A.

### Physical Activity and Cancer Survivorship.

*Nutrition in Clinical Practice* (2014), 29(6), 768-779

There has been an increase in the cancer survivor population in the United States over the past several decades primarily due to improvements in early detection of first malignancies and effective treatment modalities. A wealth of evidence has demonstrated that regular physical activity is associated with a lower risk of death, all-cause mortality, cancer recurrence, and several chronic diseases, including type 2 diabetes and cardiovascular disease, common comorbid conditions in people who have survived cancer. Physical activity also is a central component of weight management. **METHODS:** This review summarizes the current physical activity recommendations and the evidence linking physical activity to improvements in weight management, physiological effects, and psychological health outcomes for cancer survivors. **RESULTS:** The available literature suggests physical activity is safe and is positively associated with weight management, cardiorespiratory fitness, muscular strength and endurance, quality of life, fatigue, and other psychosocial factors in cancer survivors. Yet relationships related to specific cancer diagnoses, treatments, and underlying cardiometabolic mechanisms associated with survival have not been thoroughly examined in randomized controlled trials. Furthermore, factors that influence adherence to physical activity behaviors must be identified to develop effective exercise programs. The use of objective measures of physical activity and the standardization of reporting outcome measures within intervention trials are needed to complement this effort. **CONCLUSIONS:** Healthcare providers should consider individual differences among cancer survivors and tailor physical activity programs to meet the individual needs of the patient to assist in the adoption and maintenance of a physically active lifestyle.

**INSPIREHEALTH'S INTERPRETATION:** Physical activity is highly recommended to cancer survivors to improve health outcomes. This article reviewed how the body (physiology) and the mind (psychology) are affected by physical activity among cancer survivors. Current physical activity guidelines for cancer survivors are to avoid inactivity and return to normal activity as soon as possible after diagnosis or treatment. Appropriate exercise during chemotherapy and radiation is strongly recommended. Strength training, cancer-specific aerobic exercise ('cardio'), and flexibility exercises should be performed often and regularly. Survivors should aim for at least 150 minutes per week of moderate-intensity activity (moderate-intensity means you can carry on a conversation but not sing) or 75 minutes per week of vigorous activity (vigorous intensity means you can only say a few words before having to catch your breath). Several safety precautions exist for survivors with severe fatigue, compromised immune systems, comorbidities (more than one medical condition), peripheral neuropathy, cardiac conditions, bone metastases, gynecological cancers, and treatment for certain types of cancer. Cancer survivors should speak to their oncologist, family physician and exercise specialist to determine what type and how much exercise is appropriate. Care should be taken in public gyms and areas when undergoing radiation treatment or chemotherapy or who have weakened immune systems. Not too surprisingly, a number of studies have found that increasing physical activity has been shown to lower body weight among cancer survivors. Some cancer survivors are overweight which can be related to a poorer prognosis compared to survivors that are within a normal body weight range (see our February 2015 *Research Updates* for more on this). As well, increasing physical activity minimizes sarcopenia (decline in muscle mass due to aging). Sarcopenia is associated with chemotherapy toxicity and metastatic tumor progression during treatment as well as physical function, mobility, and mortality following treatment. Cardiorespiratory fitness, commonly referred to as 'cardio' fitness, is the ability to deliver oxygen from the air into the body and to the working muscles. It is strongly correlated with survival among cancer survivors. Increasing physical activity has been found to increase cardiorespiratory fitness among cancer survivors. As well, improvements in quality of life, social functioning, fatigue, and physical functioning are greater among survivors who engage in moderate- or vigorous-intensity versus mild-intensity exercise. Increasing physical activity may improve immune function, blood glucose, inflammatory markers, and metabolic markers. Exercise has far reaching effects of many aspects of health and more research is needed to understand the full capacity of how it improves our physical functioning. A 2011 meta-analysis (a 'pooling' of all relevant research studies) found that physical activity programs

increased quality of life in cancer survivors and that the effects persisted even after completion of the program. Some studies have found that aspects of quality of life such as stress, negative emotions, distress, and mental functioning improved after a cancer recurrence among participants enrolled in an exercise program. However, more research is necessary to understand the extent of psychological benefits that come from physical activity. Some studies have found no difference in quality of life between exercise and control groups, possibly due to the large variability in quality of life among cancer survivors during treatment. The biological mechanisms linking physical activity and quality of life are not fully understood. Physical activity can reduce cancer-related fatigue by improving quality of life, anxiety, depression, self-esteem, body image, happiness, muscular strength, functional capacity, and fitness. Improvements in cancer-related fatigue may only be found with aerobic (cardio) exercise versus strength or flexibility exercise, although further research is needed. Also, most research data is limited to breast and prostate cancer. More research is needed to investigate how the type of exercise (e.g., aerobic versus strength or flexibility training) affects fatigue and psychosocial factors. A final recommendation from this review is that physical activity programs should be individualized to meet the specific needs of each patient and to increase exercise adherence (i.e. to keep people exercising throughout their life). Past and present research studies have found physical activity to have wide reaching effects. Improvements in virtually all domains of health are often observed with increasing physical activity, provided that the activity is appropriate for the individual. Additionally, exercise does not need to cost anything. Aside from quitting smoking, there is virtually no greater lifestyle behavior that a person can do on their own that will obtain the health benefits from exercise.

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## LYMPHEDEMA

Fu, M.R., Deng, J., Armer, J.M.

### Putting Evidence into practice: Cancer-Related Lymphedema: Evolving Evidence for Treatment and Management From 2009–2014.

*Clinical Journal of Oncology Nursing* (2014), 18(6), 68-79.

Cancer-related lymphedema is a progressive and chronic syndrome of abnormal swelling and multiple symptoms resulting from cancer treatment. Even with modern medical advances, lymphedema remains a major health problem affecting thousands of cancer survivors. To provide healthcare professionals with evidence-based clinical practice guidelines for lymphedema treatment and management, a systematic review was conducted to evaluate 75 selected articles from 2009–2014 by the Oncology Nursing Society Putting Evidence Into Practice lymphedema team. Findings of the systematic review support complete decongestive therapy, compression bandages, and compression garments with highest evidence for best clinical practice. Weight management, full-body exercise, information provision, prevention, and early intervention protocols are likely to be effective for clinical practice. Historic recommendations for activity restriction and avoidance of aerobic and resistive exercises that limit cancer survivors' daily lives have been challenged with more evidence. Cancer survivors may not need to restrict activities such as resistive or aerobic exercises and weightlifting with gradual exercise progression. Future research should focus on providing high-level evidence using randomized clinical trials with larger samples and studying lymphedema beyond breast cancer.

**INSPIREHEALTH'S INTERPRETATION:** This article reviewed the literature to provide current guidelines for the management of cancer-related lymphedema. These guidelines are based on research conducted from 2009-2014 and are categorized into 'levels of evidence'. Complete decongestive therapy (CDT) and compression bandaging and garments were among the strongest recommendations for the management of lymphedema. CDT is a collection of the following techniques: manual lymph drainage, gentle exercise, skin care, education, and specific compression garments and bandaging. While this collection of techniques can be effective in reducing limb volume, this does not imply that each technique used in CDT is beneficial. Although percentages were not given in this review, compression garments and bandaging decreased limb volume and provided increased comfort for cancer survivors with lymphedema in some but not all studies. Weight management, full-body exercise, patient education, and prevention were classified as "likely to be effective". An increase in arm volume is not associated with full-body exercise. In 2009, exercise was not considered "likely to be effective" but as the number of studies on exercise and lymphedema increased, the benefits of exercise with lymphedema have become clearer. Breast cancer patients that are provided with lymphedema information may exhibit fewer symptoms and practice more risk-reduction behaviors than those who are not provided any information. Prevention may include early physiotherapy, early use of elastic sleeves, or preoperative imaging techniques to identify lymph drainage basins (lymphoscintigraphy). The third level of recommendations is classified as "benefits balanced with harms" and includes activity restriction and avoidance of weight lifting and kinesio tape (K-tape) bandaging. High intensity weight training with both lower- and upper-body exercises has not been found to increase lymphedema symptoms, provided patients increase their weights progressively. Restricting strength training is unlikely to improve lymphedema outcomes. In fact, restricting activities may reduce the physical fitness of cancer survivors and worsen health outcomes. K-tape is less difficult and more comfortable and convenient to use compared to bandaging. However, patients that use K-tape typically have more wounds compared to those who use bandaging. Under "effectiveness not established," authors found manual lymph drainage, low-level laser therapy, pneumatic compression, and hyperbaric oxygen. Manual lymph drainage is a component of CDT and was considered "likely to be effective" in a previous 2009 review, highlighting that further research is needed for conclusive results. Only one study was published on low-level laser therapy. A significant reduction in limb volume was found with the low-level laser

group. However, one study is not strong enough to provide general recommendations. Pneumatic compression gave mixed results. One study reported adverse effects such as arm swelling, breast inflammation, pain, fibrosis and infection, which may have been due to the pneumatic compression device. Overall, the authors suggest engaging in proper skin hygiene and care, avoiding having blood pressure taken on the affected limb, avoiding venipuncture on the affected limb, and wearing compression garments while flying. Drug therapy (diuretics, benzopyrones) were not recommended for the management of lymphedema.

## INTO THE VAULT

Standish, L.J., Wenner, C.A., Sweet, E.S., et al.

### **Trametes versicolor Mushroom Immune Therapy in Breast Cancer.**

*Journal of the Society for Integrative Oncology* (2008), 6(3), 122-128.

Data from epidemiologic studies of African American women, immune studies of the effect of chemotherapy drugs and radiotherapy, on immune status, and the Asian literature on the clinical benefit of polysaccharide immune therapy suggest that immune function has a role in primary and secondary prevention of breast cancer. High-priority research areas for breast cancer immunotherapy include clinical trials of *Trametes versicolor* (*Tv*) and the semipurified polysaccharide peptide Krestin (PSK). Two types of trials are called for; first, we need clinical trials of *Tv* as a concurrent adjuvant therapy along with chemotherapy, radiotherapy, and *HER2/neu* monoclonal antibody therapy (trastuzumab; Herceptin). Second, in keeping with its potential role in secondary prevention and common use of *Tv* in Asian oncology, we need clinical trials of *Tv* immunotherapy after completion of standard cancer treatment.

**INSPIREHEALTH'S INTERPRETATION:** About 270 species of mushrooms have been recognized for having specific immunomodulatory (ability to modulate or influence the immune system) effects. Of these, 50 have been determined to be nontoxic, and have been studied in a number of animal model studies. Of these 50 species of mushrooms, six have been studied in human cancer models. Of these six, one, *Trametes Versicolor* (also known as *Coriolus Versicolor* or Turkey Tail mushrooms), has been studied in multi-phase clinical trials with stomach, colorectal, esophageal, and breast cancer patients. This research paper discussed these immunomodulatory effects. There have been two anti-cancer constituents of these mushrooms identified: krestin and polysaccharide peptides. A number of trials performed primarily in Japan and China have looked further at the specific effects of these two constituents. Both of these components have been shown to help with immune regulation by influencing and strengthening the activity of certain immune cells which may result in higher survival rates among breast cancer survivors. There are a few ways by which krestin exerts its effect on the immune system: 1) it helps the body recover from immunosuppression from cancer treatments such as chemotherapy, 2) it activates certain anti-tumor immune responses by immune cells like dendritic cells, T helper cells and monocytes, and 3) it enhances the anti-tumor effect of chemotherapy by promoting apoptosis (programmed cell death or "cell suicide") and inhibits metastases by cancer cells. The research isolating polysaccharide peptides show that they may be able to restore immune function following immunosuppression. These mushrooms taken as supplements appear to have very few side effects and some positive immune building results. Although North American research is limited and more is needed, these mushrooms are used in conjunction with other cancer therapies in many Asian countries, as they have been shown to contribute to higher survival rates among cancer survivors.

**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 integrative cancer care knowledge management database. The editorial board includes: Dr. Hal Gunn, MD, CEO and Co-founder, Dr. Janice Wright, MD, Dr. Hannah Nette, MD, Dr. Lori McFarlane, MD, Terry Heidt, M.Sc., and Dr. Jannémé Frouws, MD. For more information, email [library@inspirehealth.ca](mailto:library@inspirehealth.ca)

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