



RESEARCH UPDATES OCTOBER 2014

INSIDE:

Resistance Exercise	1
Androgen Deprivation Therapy	2
Fish Oil Supplementation	3
Healthy Lifestyle Barriers	4
Probiotics	4
Into the Vault	5

Research Updates is published once a month to provide the latest integrative 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 INTEGRATIVE CANCER CARE

IN THIS ISSUE: Hardee and colleagues found that cancer survivors who participated in resistance exercise at least once per week lowered their all-cause mortality risk by 33%. Cormie et al. found that prescribed supervised exercise reduced both the physical and psychological side effects of androgen deprivation therapy in men with prostate cancer. Hutchins-Wiese et al. found that high dose fish oil supplementation in postmenopausal breast cancer survivors lowered circulating levels of bone turnover markers. Ventura and associates learned that perceived barriers to healthy eating and physical activity in young breast cancer survivors were associated with unhealthy weight, depression, and fatigue. In their randomized controlled trial, Zhong and associates reviewed the specific benefits of probiotics in relation to colorectal cancer prevention and treatment. In our Into the Vault study, Ornish and colleagues provided evidence that lifestyle change can positively influence gene expression.

RESISTANCE EXERCISE

Hardee, JP, R. R. Porter, X. Sui, et al.

The effect of resistance exercise on all-cause mortality in cancer survivors.

Mayo Clin Proc. 2014 Aug; 89(8):1108-15.

OBJECTIVE: To examine the independent associations of leisure-time aerobic physical activity (PA) and resistance exercise (RE) on all-cause mortality in cancer survivors. **PATIENTS AND METHODS:** Patients included 2863 male and female cancer survivors, aged 18 to 81 years, who received a preventive medical examination between April 8, 1987, and December 27, 2002, while enrolled in the Aerobics Center Longitudinal Study in Dallas, Texas. Physical activity and RE were assessed by self-report at the baseline medical examination. Cox proportional hazards regression analysis was performed to determine the independent associations of PA and RE with all-cause mortality in participants who had a history of cancer. **RESULTS:** Physical activity in cancer survivors was not associated with a lower risk of all-cause mortality. In contrast, RE was associated with a 33% lower risk of all-cause mortality (95% CI, 0.45-0.99) after adjusting for potential confounders, including PA. **CONCLUSION:** Individuals who participated in RE during cancer survival had a lower risk for all-cause mortality. The present findings provide preliminary evidence for benefits of RE during cancer survival. Future randomized controlled trials examining RE and its effect on lean body mass, muscular strength, and all-cause mortality in cancer survivors are warranted.

INSPIREHEALTH'S INTERPRETATION: Research has consistently shown that exercise has a positive impact on the human body and mind. This picture has been painted with reduced risk of chronic disease development, improved strength and fitness, reduced bodily pain, and improved quality of life – all in response to exercising. This study focused on the effects of aerobic physical activity, and resistance exercise on all-cause mortality in cancer survivors. All-cause mortality is a good outcome to focus on because people diagnosed with cancer have a 50% higher risk of dying from non-cancer causes than the general public. The other important reason to look at all-cause mortality is to ensure that if the treatment is beneficial for one outcome, it is not detrimental to another.

This prospective observational study followed 2863 men and women (18-81 years old) for an average of 7.3 years; during that time 121 deaths were recorded. Interestingly, leisure time aerobic physical activity by itself was not associated with reduced all-cause mortality risk. However, resistance exercise at least once per week was associated with a 33% reduction in mortality

risk. Upon further examination, the researchers found that resistance exercise provided this benefit only to the group of people who were physically active in their leisure time, and not to those who did resistance exercise, but were inactive otherwise. Those who did resistance exercise had lower cholesterol, blood triglycerides, fasting blood glucose, body mass index (BMI), and blood pressure than those who did not.

Though this data is only observational in nature, it mirrors what some recent randomized controlled trials have found – that doing both resistance exercise and aerobic exercise is very beneficial for cancer survivors. At the time of publication, this was to the authors' knowledge the only study to prospectively examine the relationship between resistance exercise and all-cause mortality in cancer survivors. With many cancer survivors over the age of 65, prescribing resistance exercise may be specifically important as it also improves muscular strength and bone density. The next step would be a randomized controlled trial that examines the relationship between exercise and survival in cancer survivors. InspireHealth offer accessible exercise classes that include resistance exercise at all three of our sites – Vancouver, Victoria, and Kelowna.

ANDROGEN DEPRIVATION THERAPY

Cormie, P, D. A. Galvão, N. Spry, et al.

Can supervised exercise prevent treatment toxicity in patients with prostate cancer initiating androgen-deprivation therapy: a randomised controlled trial.

BJU Int. 2014 epub; Jan 27.

OBJECTIVE: To determine if supervised exercise minimises treatment toxicity in patients with prostate cancer initiating androgen-deprivation therapy (ADT). This is the first study to date that has investigated the potential role of exercise in preventing ADT toxicity rather than recovering from established toxicities. **PATIENTS AND METHODS:** Sixty-three men scheduled to receive ADT were randomly assigned to a 3-month supervised exercise programme involving aerobic and resistance exercise sessions commenced within 10 days of their first ADT injection (32 men) or usual care (31 men). The primary outcome was body composition (lean and fat mass). Other study outcomes included bone mineral density, physical function, blood biomarkers of chronic disease risk and bone turnover, general and prostate cancer-specific quality of life, fatigue and psychological distress. Outcomes were compared between groups using analysis of covariance adjusted for baseline values. **RESULTS:** Compared to usual care, a 3-month exercise programme preserved appendicular lean mass ($P = 0.019$) and prevented gains in whole body fat mass, trunk fat mass and percentage fat with group differences of -1.4 kg ($P = 0.001$), -0.9 kg ($P = 0.008$) and -1.3% ($P < 0.001$), respectively. Significant between-group differences were also seen favouring the exercise group for cardiovascular fitness (peak oxygen consumption 1.1 mL/kg/min, $P = 0.004$), muscular strength (4.0 - 25.9 kg, $P \leq 0.026$), lower body function (-1.1 s, $P < 0.001$), total cholesterol: high-density lipoprotein-cholesterol ratio (-0.52 , $P = 0.028$), sexual function (15.2 , $P = 0.028$), fatigue (3.1 , $P = 0.042$), psychological distress (-2.2 , $P = 0.045$), social functioning (3.8 , $P = 0.015$) and mental health (3.6 - 3.8 , $P \leq 0.022$). There were no significant group differences for any other outcomes. **CONCLUSION:** Commencing a supervised exercise programme involving aerobic and resistance exercise when initiating ADT significantly reduced treatment toxicity, while improving social functioning and mental health. Concurrent prescription of supervised exercise when initiating ADT is therefore advised to minimise morbidity associated with severe hypogonadism.

INSPIREHEALTH'S INTERPRETATION: Nearly 1.3% of men (in the United States) have prostate cancer. Androgen deprivation therapy is a well-established treatment for these men, but it comes with considerable side effects including: decreased lean mass, increased fat mass, reduced bone mineral density, reduced functional capacity, and significant decline in sexual health. This randomized controlled trial from Edith Cowan University in Australia looked at whether supervised aerobic and resistance exercise minimized the side effects of androgen deprivation therapy in patients with prostate cancer. Sixty-three men scheduled to receive androgen deprivation therapy were randomly assigned to either the exercise group (EG) or the usual care group (CG). The EG participated in 60 minutes of progressive, supervised, moderate to high-intensity aerobic and resistance exercise twice weekly over the course of 3 months, starting 10 days before androgen deprivation therapy began. Aerobic exercise elements of the program consisted of 30 minutes cardiovascular exercise at 70-85% of each patient's estimated maximum heart rate. Resistance exercise also lasted 30 minutes with participants lifting the maximal amount of weight they could for 6-12 controlled repetitions, 1-4 sets per exercise. Resistance exercise weight was increased progressively each session or weekly. Additionally, patients were encouraged to accumulate at least 150 minutes of home based moderate intensity aerobic exercise per week.

Following the intervention, whole body lean mass was better preserved in the EG (-0.6 kg) compared to the CG (-1.4 kg). Whole body fat mass increased in CG ($+1.5$ kg) and decreased in the EG (-0.6 kg). The exercise intervention resulted in further benefits including increased cardiovascular fitness, and significantly increased upper and lower body strength. Blood biomarker changes were observed in the EG with high density lipoprotein (HDL, the healthy cholesterol) concentrations increasing from baseline values as well a reduction in C reactive protein (-47% compared with baseline). The EG reported significantly less

decline in sexual function, lower fatigue levels, and less psychological distress. This study demonstrated the effectiveness of supervised, progressive exercise in maintenance and in some cases improvement of both physical and psychological function during androgen deprivation therapy. Further, improvements in the measured blood biomarkers represented a potential risk reduction for other co-morbidities such as heart disease and diabetes. Overall, this very well done study illustrated some of the benefits of doing both aerobic and resistance training during androgen deprivation therapy.

FISH OIL SUPPLEMENTATION

Hutchins-Wiese, HL, K. Picho, B. A. Watkins, et al.

High-dose eicosapentaenoic acid and docosahexaenoic acid supplementation reduces bone resorption in postmenopausal breast cancer survivors on aromatase inhibitors: a pilot study.

Nutr Cancer. 2014; 66(1):68-76.

Postmenopausal breast cancer survivors are living longer; however, a common class of drugs, aromatase inhibitors (AI), depletes estrogen levels, promotes bone loss, and heightens fracture risk. Eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) may offset AI effects to bone because of the known effects on cellular processes of bone turnover. Therefore, we hypothesized that 4 g of EPA and DHA daily for 3 mo would decrease bone turnover in postmenopausal breast cancer survivors on AI therapy in a randomized, double-blind, placebo controlled pilot study that included 38 women. At baseline and 3 mo, serum fatty acids, bone turnover, and inflammatory markers were analyzed. Serum EPA and DHA, total and long-chain (LC) omega (n)-3 polyunsaturated fatty acids (PUFA) increased, whereas arachidonic acid, total and LC n-6 PUFA, and the LC n-6:n-3 PUFA ratio decreased compared to placebo (all $P < .05$). Bone resorption was inhibited in the fish oil responders compared to placebo ($P < .05$). Inflammatory markers were not altered. This short-term, high-dose fish oil supplementation study's findings demonstrate that fish oil can reduce bone resorption; however, longer-term studies are needed to assess bone density preservation and to explore mechanistic pathways in this population at high risk for bone loss.

INSPIREHEALTH'S INTERPRETATION: Aromatase inhibitors (AIs) can significantly lower recurrence rates and increase survival in postmenopausal woman diagnosed with estrogen receptor positive breast cancer. However, AI treatment can increase bone resorption (breakdown of bone) and decrease bone mineral density. Studies have found that EPA and DHA supplementation may decrease bone breakdown and protect the development of bone-forming cells (osteoblasts) in animal studies and cell cultures. However, intervention studies in adults have produced mixed results. This study included a randomized, double-blind, placebo-controlled design that investigated the effects of EPA and DHA supplementation on bone resorption and bone mineral density in postmenopausal breast cancer survivors. Double-blind means that neither the researchers nor the participants knew which subjects received EPA/DHA or placebo. The purpose of randomization, blinding, and placebo-controlled experiments is to prevent bias, which may interfere with results. Women in the treatment group supplemented daily with EPA (2520mg) and DHA (1680mg), whereas women in the control group received safflower oil (placebo) daily. Subjects in both groups received calcium carbonate (1000mg) and a form of vitamin D (800IU of cholecalciferol) daily. Differences in bone turnover, regulatory and inflammatory markers, and absolute change in serum fatty acids between baseline measurements and after 3 months were compared between the two groups.

No significant differences in diet (via 3-day food record) were found between the two groups at baseline. Interestingly, no change in bone turnover was found among the placebo group despite the AI treatment. The authors offer three possible explanations. First, because the participants were already on AI treatment for 6 months they may have reached a stable rate of bone turnover before the study began. Second, that safflower oil was not a true placebo. Finally, that the vitamin D and calcium provided to all participants assisted in stabilizing bone turnover. Though there was no difference in bone turnover, after three months the bone resorption markers DFD and sCTX were significantly reduced in the treatment group, however sCTX was only reduced in those subjects who were "fish oil responders" (those who consumed fish oil and had an increase in circulating EPA and DHA). The inflammatory marker hs-CRP (high-sensitivity C-reactive protein) was correlated with BMI but not fish oil consumption. Overall, this study suggests that consumption of high levels of fish oil may influence bone resorption, but more research is needed. The control group in this study was expected to have higher bone resorption (breakdown) in response to the AI treatment, but they did not. This may have masked a potentially positive result in the intervention group.

This study provides evidence that fish oil supplementation during AI treatment reduces circulating bone resorption markers, however, this is not evidence enough to say that fish oil supplementation reduces bone turnover in this study population.

HEALTHY LIFESTYLE BARRIERS

Ventura, EE, P. A. Ganz, J. E. Bower, et al.

Barriers to physical activity and healthy eating in young breast cancer survivors: modifiable risk factors and associations with body mass index.

Breast Cancer Res Treat (2013) 142:423–433.

Physical activity (PA) and healthy eating (HE) are important behaviors to encourage in breast cancer survivors (BCS). We examined associations between various factors and barriers to PA (BPA) and barriers to HE (BHE), as well as relationships between barriers and body mass index (BMI) in younger BCS. Self-reported data from 162 BCS (mean age 48 years) were used. BPA were assessed with a 21-item scale and BHE with a 19-item scale. Participants were classified as high or low on each scale. Sociodemographic, medical, and psychosocial characteristics were compared by high/low barriers. Correlates of continuous BPA and BHE were assessed as were associations among BHE, BPA, and BMI. 61 % of participants were characterized as having low BHE and low BPA; 12 % were high for both. High BHE/high BPA participants had the least favorable scores for depression, perceived stress, social support, fatigue, bladder control, and weight problems. Factors associated with BHE were lower education, higher perceived stress, and more severe weight problems. Factors associated with BPA were more severe bladder control problems and lower physical well-being. Higher BHE and BPA were significantly and uniquely associated with higher BMI, controlling for covariates. Several biopsychosocial factors (e.g., depression, stress, and fatigue) characterize young BCS who experience barriers to both HE and PA. The correlates of BHE and BPA are distinct. Both BHE and BPA are associated with BMI. These results should be considered in designing interventions for younger women with breast cancer.

INSPIREHEALTH'S INTERPRETATION: Past research has confirmed the important relationships between healthy eating, regular physical activity, and breast cancer recurrence risk. In this study, the authors looked at barriers that breast cancer survivors experience towards engaging in physical activity and healthy eating behaviours, and also how these perceived barriers may relate to body composition. Study participants were 162 women who had been diagnosed with stage I, II, or III breast cancer prior to the age of 50. In order to qualify for the study, women were required to have been diagnosed more than one year before the study start date, and to have been finished treatment for at least six months. Subjects completed questionnaires regarding height, weight, quality of life, fatigue, depression, and barriers to healthy eating and physical activity. Only 12% of women were classified as having high barriers for physical activity and healthy eating, whereas 61% were classified as having low barriers for both activities. The top listed barriers for healthy eating were lack of education, higher stress levels, and weight problems. The top barriers listed in relation to physical activity were severe bladder control problems, and lower levels of physical well-being. Having a higher number of perceived barriers to both behaviours was related to a higher body mass index (less healthy body composition).

Although the study did not have an objective measure of actual eating behavior, it did use a self-report scale for physical activity behavior, which showed that those individuals with higher barriers engaged in less activity compared to those with fewer perceived barriers. This study surpassed others in the same line of research by distinguishing the barriers for each of these distinct health behaviours. It also was the first to examine the relationship between perceived barriers and body composition. Additionally, this study helped to identify future areas of research related to health behaviours for cancer survivors. Current levels of regular physical activity and healthy eating behaviors are known to be less than 40% among cancer survivors, although this study indicates that over 60% perceive themselves as having a low number of barriers to these actions.

Further research should investigate the relationship between perceived barriers and actual behavior, and why these numbers are not congruent. InspireHealth's exercise therapists and nutritionists can work with you to create a personal health plan which will address any barriers that are preventing you from engaging in a healthy lifestyle.

PROBIOTICS

Zhong, L, X. Zhang, M. Covasa.

Emerging roles of lactic acid bacteria in protection against colorectal cancer.

World J Gastroenterol. 2014 Jun 28;20(24):7878-86.

Colorectal cancer (CRC) is the third leading cause of cancer deaths worldwide and the fourth most common cancer diagnosed among men and women in the United States. Considering the risk factors of CRC, dietary therapy has become one of the most effective approaches in reducing CRC morbidity and mortality. The use of probiotics is increasing in popularity for both the prevention and treatment of a variety of diseases. As the most common types of microbes used as probiotics, lactic acid bacteria (LAB) are comprised of an ecologically diverse group of microorganisms united by formation of lactic acid as the primary

metabolite of sugar metabolism. LAB have been successfully used in managing diarrhea, food allergies, and inflammatory bowel disease. LAB also demonstrated a host of properties in preventing colorectal cancer development by inhibiting initiation or progression through multiple pathways. In this review, we discuss recent insights into cellular and molecular mechanisms of LAB in CRC prevention including apoptosis, antioxidant DNA damages, immune responses, and epigenetics. The emerging experimental findings from clinical trials as well as the proposed mechanisms of gut microbiota in carcinogenesis will also be briefly discussed.

INSPIREHEALTH'S INTERPRETATION: In this study, researchers reviewed the literature to summarize the mechanisms by which lactic acid bacteria (LAB) may help to prevent colorectal cancer incidence and progression. LAB, especially lactobacillus and bifidobacterium strains, are the most common microbes found in probiotic supplements. According to the World Health Organization, probiotics are "live microorganisms which when administered in adequate amounts confer a health benefit to the host". Traditionally, humans have obtained a myriad of such microbes from ingesting fermented foods such as yogurt and sauerkraut. LAB have been successfully used in medicine for a number of different conditions. They have beneficial effects in digestive issues such as diarrhea and inflammatory bowel disease (Crohn's disease and ulcerative colitis). In pediatrics, they have been used as an inexpensive and very effective way to prevent the very serious and potentially fatal condition necrotizing enterocolitis (bowel death) in premature infants. In in-vitro and animal research, LAB have demonstrated anti-cancer effects via promoting apoptosis (programmed cell death), possible synergistic action with chemotherapeutic agents such as 5-fluorouracil, antioxidant activity, improved immune system function (reduced inflammation and increased production of anti-tumor immune cells), and the ability to modify gene expression (see this month's Into the Vault study).

In human clinical trials, the use of probiotics reduced the infection rate and improved quality of life post-operatively in patients who had colorectal cancer surgery. More clinical trials examining the use of LAB to prevent or treat CRC are still needed. Though probiotics are inexpensive and easy to take, they are not all created equally. In the premature pediatric population one type of probiotic supplement actually caused widespread fungal infection, while another prevented necrotizing enterocolitis. A good probiotic should contain a variety of different microorganisms. If you have digestive issues and/or a history of CRC or adenomatous colonic polyps talk to your health care provider about adding probiotics to your regime. In the meantime, adding fermented foods to your diet may help modulate your gut microorganisms for better health.

INTO THE VAULT

Ornish, D, M.J. Magbanua, G. Weidner, et al.

Changes in prostate gene expression in men undergoing an intensive nutrition and lifestyle intervention.

Proc Natl Acad Sci U S A. 2008 Jun 17; 105(24):8369-74.

Epidemiological and prospective studies indicate that comprehensive lifestyle changes may modify the progression of prostate cancer. However, the molecular mechanisms by which improvements in diet and lifestyle might affect the prostate microenvironment are poorly understood. We conducted a pilot study to examine changes in prostate gene expression in a unique population of men with low-risk prostate cancer who declined immediate surgery, hormonal therapy, or radiation and participated in an intensive nutrition and lifestyle intervention while undergoing careful surveillance for tumor progression. Consistent with previous studies, significant improvements in weight, abdominal obesity, blood pressure, and lipid profile were observed (all $P < 0.05$), and surveillance of low-risk patients was safe. Gene expression profiles were obtained from 30 participants, pairing RNA samples from control prostate needle biopsy taken before intervention to RNA from the same patient's 3-month postintervention biopsy. Quantitative real-time PCR was used to validate array observations for selected transcripts. Two-class paired analysis of global gene expression using significance analysis of microarrays detected 48 up-regulated and 453 down-regulated transcripts after the intervention. Pathway analysis identified significant modulation of biological processes that have critical roles in tumorigenesis, including protein metabolism and modification, intracellular protein traffic, and protein phosphorylation (all $P < 0.05$). Intensive nutrition and lifestyle changes may modulate gene expression in the prostate. Understanding the prostate molecular response to comprehensive lifestyle changes may strengthen efforts to develop effective prevention and treatment. Larger clinical trials are warranted to confirm the results of this pilot study.

INSPIREHEALTH'S INTERPRETATION: In our July 2014 Research Updates, we reviewed a 2005 study by Ornish and colleagues examining the relationship between intensive lifestyle change and the progression of low- to moderate-grade prostate cancer. This 2008 follow-up study explored changes in prostate gene expression in 30 men with low-grade (mean PSA 4.8 ng/ml, Gleason score 6) prostate cancer who chose active surveillance over immediate surgery, hormone therapy or radiation. Like those in the 2005 study these men were prescribed an intensive lifestyle modification program including a low fat/whole foods/plant-based diet, 60 minutes of stress management (e.g. gentle yoga, meditation) per day, walking 30 minutes

per day/6 days a week, and a weekly 1 hour support group. All men had prostate biopsies at baseline and after 3 months. Compliance with the prescribed lifestyle changes was excellent and not surprisingly significant improvements in cardiovascular disease risk factors were observed. These included reduced body mass index (BMI), lower blood pressure, and improved blood lipid profile. Significant reductions in psychological stress were also observed.

Most interestingly, the expression of several genes from normal (not cancerous) prostate tissue changed after the lifestyle intervention. The authors detected 43 up-regulated (turned on) and 453 down-regulated (turned off) genes. Genes are sections of DNA that encode information to synthesize products such as proteins. Gene expression is the extent to which a gene is turned on or off to make its product; there are many factors that influence gene expression. In cancer, gene expression goes awry in many ways. For example, genes coding for molecules which normally halt out-of-control cell growth and division are inappropriately down-regulated and genes which foster abnormal blood vessel formation are inappropriately up-regulated. In this study the down-regulated genes were identified as having critical roles in cancer development and progression. In other words, the observed changes in gene expression could explain how lifestyle changes may work to inhibit cancer initiation and progression/recurrence. The authors caution that the tissue analyzed was from normal prostate tissue and not from the cancer cells themselves so further research is needed to determine if the normal tissue surrounding the tumor or the tumor tissue itself best responds to lifestyle changes.

Though subjects in this study served as their own control, future studies would benefit from also including a separate control group to ensure that the observed gene expression changes were truly related to the lifestyle intervention. To summarize, this study found that eating well, exercising regularly, and practicing relaxation techniques were associated with lower expression of genes related to cancer development and progression in healthy prostate cells from men with low-grade prostate cancer.

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 Josh McKay, M.Sc.—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 Brendan Murphy, M.Sc.

For more information, email library@inspirehealth.ca