



RESEARCH UPDATES JULY 2014

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FOR THE LATEST IN WORLDWIDE INTEGRATIVE CANCER CARE

IN THIS ISSUE: Xu et al. reviewed both human and animal studies on the effects and potential mechanisms by which vitamin D may reduce cancer metastasis and tumour angiogenesis. Luoma and colleagues found that women with breast cancer appreciated exercising in a group setting with other breast cancer patients because among other benefits, it reduced their feelings of anxiety around their appearance and low fitness levels. Wassertheil-Smoller and colleagues found that post-menopausal women with breast cancer who took multivitamins had a lower risk of breast cancer mortality than those who did not. Lira and associates reviewed the current literature on exercise as a treatment for cancer cachexia and found that both endurance and resistance training can be beneficial in reducing muscle loss in cancer cachexia. Zhou et al. found that while body mass index was not associated with mortality in ovarian cancer patients, participating in vigorous physical activity significantly reduced the risk of both cancer-related mortality, and all-cause mortality. Ornish and associates found that intensive lifestyle change in early stage prostate patients who independently decided not to undergo any conventional treatment had favorable associations with prostate specific antigen levels.

VITAMIN D

Xu, J, W. Li, J. Ma, et al.

Vitamin D - Pivotal Nutraceutical in the Regulation of Cancer Metastasis and Angiogenesis.

Curr Med Chem. 2013 2033: 4109-4120.

Various epidemiological studies have demonstrated that vitamin D may play important roles in the pathogenesis and progression of cancer. Vitamin D is one of the most pivotal nutraceuticals whose active metabolite, calcitriol (1,25-dihydroxyvitamin D₃), possesses anti-proliferative, pro-apoptotic, and pro-differentiating capabilities. Accumulating evidence indicates that the potential benefits of using vitamin D in cancer are not only anti-cancer cell proliferation which is linked with its anti-inflammatory effects, including the suppression of prostaglandin metabolism and inhibition of NF-κB signaling, but also suppressing tumor metastasis and angiogenesis. Here, we present a systematic summary of the effects of vitamin D in the chemoprevention and chemotherapy of cancer, especially anti-metastatic and anti-angiogenic actions.

INSPIREHEALTH'S INTERPRETATION: The authors of this study reviewed the current state of knowledge regarding the potential molecular mechanisms by which vitamin D may have anti-cancer effects, including inhibition of cancer metastasis and angiogenesis. In order for cancer cells to metastasize (distant spread from the original tumour site), a complex series of steps needs to happen. These authors review two critically important steps and discuss how vitamin D might block them. The first reviewed step is called epithelial-mesenchymal transition (EMT), a normal physiological process whereby an epithelial cell transforms into a mesenchymal cell. Epithelial cells are arranged in adhesive compact sheets; they line body cavities, and form our skin and many other glands. Cancers such as prostate, breast, lung, gastrointestinal and melanoma are derived from epithelial cells. Mesenchymal cells (stem cells), on the other hand, lack cell to cell adhesion, have migratory and invasive properties, and can differentiate into many cell types. EMT is important for the development of many tissues and organs in the growing embryo, in wound healing, and day to day physiological processes. However, it is thought that the transition from epithelial cells to mesenchymal cells is necessary for cancer metastasis. The second reviewed step required for metastasis that vitamin D may impact is angiogenesis – the formation and growth of new blood vessels. Blood vessels supply a tumour with nutrients to grow and a method of transportation for tumour cells to metastasize. Many in-vitro (petri dish) studies have demonstrated mechanisms by which calcitriol, the active metabolite of vitamin D, blocks several steps in both EMT and angiogenesis. Interestingly, vitamin D's anti-proliferative (arresting cell growth) and pro-apoptotic (causing cell death) properties – which are crucial to stop uncontrolled cell proliferation (cancer development) – do not appear to be active in healthy epithelial cells. There is a lot of research interest in the role of inflammation in cancer development and metastasis. In this paper, the

inflammatory mediators Nuclear Factor kappa B (NF- κ B) and prostaglandins (PG) were reviewed in detail. Calcitriol has been shown in-vitro and in-vivo (in animal models) to modulate NF- κ B levels in many cancer cells and regulate the expression of several genes in the PG pathway to reduce inflammation and cancer growth and metastasis. Though not the focus of this review, epidemiological research has shown promising results for vitamin D supplementation in cancer prevention and treatment. The authors summarize that given vitamin D's promise as a therapeutic agent, more well-designed clinical trials are needed to best understand its role as an anti-cancer agent. InspireHealth practitioners continue to recommend vitamin D supplementation for most people with a diagnosis of cancer. If you are interested in participating in InspireHealth's vitamin D trial for patients with stage 4 colorectal cancer, check out the "Clinical Trials" section of our research website.

EXERCISE

Luoma ML, L. Hakamies-Blomqvist, C. Blomqvist, et al.

Experiences of Breast Cancer Survivors Participating in a Tailored Exercise Intervention - A Qualitative Study.

Anticancer Res. 2014 Mar; 34(3):1193-9.

AIM: The aim of the study was to investigate how tailored exercise is experienced by cancer survivors. **PATIENTS AND METHODS:** Twenty-five breast cancer survivors who were recently treated with systemic adjuvant treatments attended tailored exercise classes as a part of a randomized controlled exercise intervention study (Breast Cancer and Exercise, BREX). Focus group discussions with a median of four (range 3-6) participants in each group were conducted to capture their individual experiences of their course of illness, taking part in the exercise trial, the personal meaning of tailored exercise classes and the group. **RESULTS:** Attending the intervention in which the focus of attention was on physical rehabilitation was highly valued, since the participants experienced both improved physical fitness and improved coping. Due to altered physical appearance and poor physical fitness, the participants felt that tailored exercise for patients with breast cancer reduced their barrier to start exercising. Peer support from the group was valued, especially that of sharing experiences, receiving psychological support and gaining a sense of normality. A sense of mastery over their disease through participating in the intervention, i.e. better psychological functioning and improved mood, was a consequence of better physical fitness and of meeting other breast cancer survivors. Also participating in the study per se increases a sense of comfort and security with extra medical examinations and follow-up. **CONCLUSION:** Participating in the tailored exercise group for breast cancer survivors helped patients gain a sense of mastery, restoring their self-esteem and constructing a meaning for their cancer experience and its impact on their lives.

INSPIREHEALTH'S INTERPRETATION: This interesting study followed 25 Finnish breast cancer patients from the BREX trial who were recently treated with chemotherapy or radiation. The average age of participants was 54 years old. The patients went through a 12-month aerobic (cardiovascular) exercise program that included a supervised aerobic exercise class once per week, and a similarly tailored home exercise program, which the patients completed on their own 3 times per week. Physical benefits of the BREX trial are published in another study. For this study, the patients were split up into small focus groups of 3-6 people each. The focus groups were semi-structured and included discussion of the following topics: the course of their illness and treatments, experiences in the exercise trial, personal feelings exercising with other breast cancer patients in a tailored setting, exercise barriers, and other topics brought up by the patients. Notes were taken by the investigators and evaluated afterwards by grouping experiences using psychological terms. Overall, the patients felt like they received multiple benefits from the exercise program and from participating in the research study. A common issue among patients was their changed appearance. They felt that participating in an exercise program specifically for breast cancer patients made it easier to not wear a wig or worry about how they looked because everyone was going through something similar, and therefore understood. Patients expressed a desire to change their identity from being a breast cancer patient to being a healthy woman. The exercise program helped them to do that because they felt like the instructor treated them like normal people, not patients. They also felt comfortable with their limitations because everyone had some. As a research subject, patients received extra medical follow-ups for 10 years and unlimited access to the Oncology Department at the University Hospital. Many patients felt left alone after their cancer treatment and these extra visits helped the patients to feel safe and supported. Some patients found that after a while, the exercise classes reminded them of their cancer. This was an important transition point for some of the women as it helped them transition from being a patient to being a healthy woman again. InspireHealth patients have the option to attend group exercise classes and to meet with our exercise therapists to develop both cardiovascular and resistance exercise programs.

MULTIVITAMINS

Wassertheil-Smoller, S, A. P. McGinn, N. Budrys, et al.

Multivitamin and Mineral use and Breast Cancer Mortality in Older Women with Invasive Breast Cancer in the Women's Health Initiative.

Breast Cancer Research & Treatment. 2013 Oct; 141(3): 495-505.

Multivitamin use is common in the United States. It is not known whether multivitamins with minerals supplements (MVM) used by women already diagnosed with invasive breast cancer would affect their breast cancer mortality risk. To determine prospectively the effects of MVM use on breast cancer mortality in postmenopausal women diagnosed with invasive breast cancer, a prospective cohort study was conducted of 7,728 women aged 50-79 at enrollment in the women's health initiative (WHI) in 40 clinical sites across the United States diagnosed with incident invasive breast cancer during WHI and followed for a mean of 7.1 years after breast cancer diagnosis. Use of MVM supplements was assessed at WHI baseline visit and at visit closest to breast cancer diagnosis, obtained from vitamin pill bottles brought to clinic visit. Outcome was breast cancer mortality. Hazard ratios and 95 % confidence intervals (CIs) for breast cancer mortality comparing MVM users to non-users were estimated using Cox proportional hazard regression models. Analyses using propensity to take MVM were done to adjust for potential differences in characteristics of MVM users versus non-users. At baseline, 37.8 % of women reported MVM use. After mean post-diagnosis follow-up of 7.1 + 4.1 (SD) years, there were 518 (6.7 %) deaths from breast cancer. In adjusted analyses, breast cancer mortality was 30 % lower in MVM users as compared to non-users (HR = 0.70; 95 % CI 0.55, 0.91). This association was highly robust and persisted after multiple adjustments for potential confounding variables and in propensity score matched analysis (HR = 0.76; 95 % CI 0.60-0.96). Postmenopausal women with invasive breast cancer using MVM had lower breast cancer mortality than non-users. The results suggest a possible role for daily MVM use in attenuating breast cancer mortality in women with invasive breast cancer but the findings require confirmation.

INSPIREHEALTH'S INTERPRETATION: The data for this research study were obtained from the Women's Health Initiative (WHI). This well designed US trial enrolled over 160,000 post-menopausal women aged 50-79 from 1993-1998. The WHI followed women for just over 7 years on average and included both a clinical trial, which investigated the use of post-menopausal hormone therapy on the risk of cancer and cardiovascular disease, and a long-term prospective observational study. The observational study is the topic of this paper, and was designed to determine what, if any, the effects of a multivitamin with minerals (MVM) supplement have on breast cancer mortality in women diagnosed with invasive breast cancer during the study period. Previous studies cited by these authors examining MVM use in women with breast cancer yielded mixed results. Some of the reasons for this include methodological challenges such as type, consistency and duration of MVM use, as well as use of adjuvant chemotherapy and/or radiation therapy. Participants of this study were physically assessed, and completed detailed questionnaires about their health history, lifestyle and medication/supplement use. Many potentially confounding variables such as age, cancer stage, estrogen/progesterone receptor status, education, smoking and alcohol history, body mass index and activity were statistically accounted for to increase the validity of the findings. After adjusting for these potential confounders, the authors found that women who took MVM had a 30% significantly lower breast cancer mortality compared to non-users. The absolute risk reduction was not reported in the paper. It is important to note that absolute risk and relative risk can be very different numbers. For example, imagine that the absolute risk of being hit by lightning is 1%. Next, imagine that people who wore rubber boots were 30% less likely to be hit by lightning than people who did not (relative risk). Therefore the absolute risk of being hit by lightning while wearing rubber boots is 0.7% (1% minus 30% of 1%). As you can see, in this fictional scenario the absolute and relative risks are very different numbers. Despite these promising results, the authors caution that their study does have some limitations. Data were not provided on the specific treatments that each patient went through so the authors could not comment on any potential interactions of concurrent MVM and chemotherapy or radiation therapy. The observational study design can only find association, so causal interpretation is limited. Nevertheless, these observational findings support the use of MVM after diagnosis of invasive breast cancer in post-menopausal women. For stronger evidence, the next step would be an intervention study.

CANCER CACHEXIA

Lira, FS, J.C. Neto, M. Seelaender.

Exercise Training as Treatment in Cancer Cachexia.

Appl Physiol Nutr Metab. 2014 Jun; 39(6):679-86.

Cachexia is a wasting syndrome that may accompany a plethora of diseases, including cancer, chronic obstructive pulmonary disease, AIDS, and rheumatoid arthritis. It is associated with central and systemic increases of pro-inflammatory factors, and with decreased quality of life, response to pharmacological treatment, and survival. At the moment, there is no single therapy able to reverse cachexia many symptoms, which include disruption of intermediary metabolism, endocrine dysfunction, compromised hypothalamic appetite control, and impaired immune function, among other. Growing evidence, nevertheless, shows that

chronic exercise, employed as a tool to counteract systemic inflammation, may represent a low-cost, safe alternative for the prevention/attenuation of cancer cachexia. Despite the well-documented capacity of chronic exercise to counteract sustained disease-related inflammation, few studies address the effect of exercise training in cancer cachexia. The aim of the present review was hence to discuss the results of cachexia treatment with endurance training. As opposed to resistance exercise, endurance exercise may be performed devoid of equipment, is well tolerated by patients, and an anti-inflammatory effect may be observed even at low-intensity. The decrease in inflammatory status induced by endurance protocols is paralleled by recovery of various metabolic pathways. The mechanisms underlying the response to the treatment are considered.

INSPIREHEALTH'S INTERPRETATION: Participation in physical activity and its various forms have long had positive implications on health for the prevention, treatment and rehabilitation of acute and chronic disease. Cachexia/Cancer cachexia is defined as a 'wasting syndrome' on muscle, bone and fat tissues within the body, culminating in weight loss. Its cause is related to inflammation, particularly chronic inflammation brought on by diseases such as cancer, which can be destructive to the aforementioned tissues. Cancer cachexia can reduce both recovery from and receptiveness to cancer treatments as well as overall quality of life. Suggested pharmacological treatments for cachexia have been associated with contributing to anorexia, asthenia (weakness), fatigue, skeletal muscle wasting and further inflammation. One proposed form of treatment is the use of exercise to reduce the wasting effects associated with cachexia. The review examined 14 studies which looked into the anti-inflammatory, and anti-cachetic effects of both resistance and endurance exercise. The studies that looked at endurance exercise found increases in cardiovascular fitness, and the following anti-inflammatory effects: increased blood levels of the anti-inflammatory cell signal regulators Interleukin-10 and Interleukin-1 receptor antagonist, decreased levels of Tumor Necrosis Factor alpha (TNF- α) which is associated with tumor growth and metastasis, and increased use of lipids (fat) as an energy source in skeletal muscle and the liver. Resistance exercise reduced circulating levels of TNF- α , increased use of carbohydrate in skeletal muscle, increased muscle growth, and reduced muscle breakdown. Based on the studies reviewed in this article, the authors concluded that resistance exercise has a positive impact on skeletal muscle maintenance and growth which helps in the treatment and recovery from cancer and cancer cachexia. This review also suggested that a combination of both resistance and endurance exercise may reduce inflammation and muscle wasting, increase fitness and the effectiveness of cancer fighting clinical treatments. Specifically for cancer cachexia patients, The American Cancer Society recommends 150 minutes per week of moderate intensity activity, or 75 minutes per week of vigorous activity. This review provides an excellent overview of the many physiological benefits of exercise during cancer cachexia. However, especially for cancer and cancer cachexia patients, it is important not to "over-do it" with exercise as that can lead to intense fatigue. With careful exercise progression and an awareness of current clinical treatments and how one is feeling, both endurance and resistance exercise can be very beneficial. Though some of the studies reviewed in this paper were done on animal subjects, and therefore may not represent the exact adaptations and physiological processes which occur in humans, their results are extremely encouraging and provide positive evidence for the significant benefit of exercise in the treatment of cancer cachexia.

PHYSICAL ACTIVITY AND OVARIAN CANCER

Zhou, Y, R. Chlebowski, M. J. Lamonte, et al.

Body Mass Index, Physical Activity, and Mortality in Women Diagnosed with Ovarian Cancer: Results from the Women's Health Initiative.

Gynecol Oncol. 2014 April 2014; 1331: 4-10.

BACKGROUND: Ovarian cancer is often diagnosed at late stages and consequently the 5-year survival rate is only 44%. However, there is limited knowledge of the association of modifiable lifestyle factors, such as physical activity and obesity on mortality among women diagnosed with ovarian cancer. The purpose of our study was to prospectively investigate the association of (1) measured body mass index (BMI), and (2) self-reported physical activity with ovarian cancer-specific and all-cause mortality in postmenopausal women enrolled in the Women's Health Initiative (WHI). **METHODS:** Participants were 600 women diagnosed with primary ovarian cancer subsequent to enrollment in WHI. Exposure data, including measured height and weight and reported physical activity from recreation and walking, used in this analysis were ascertained at the baseline visit for the WHI. Cox proportional hazard regression was used to examine the associations between BMI, physical activity and mortality endpoints. **RESULTS:** Vigorous-intensity physical activity was associated with a 26% lower risk of ovarian cancer specific-mortality (HR=0.74; 95% CI: 0.56-0.98) and a 24% lower risk of all-cause mortality (HR=0.76; 95% CI: 0.58-0.98) compared to no vigorous-intensity physical activity. BMI was not associated with mortality. **CONCLUSIONS:** Participating in vigorous-intensity physical activity, assessed prior to ovarian cancer diagnosis, appears to be associated with a lower risk of ovarian cancer mortality.

INSPIREHEALTH'S INTERPRETATION: This study sought to answer the question, "among women diagnosed with ovarian cancer, are body mass index (BMI) and physical activity level before diagnosis associated with mortality risk (death)?" BMI is a rough indicator of a person's weight relative to their height and is divided into four main categories: underweight, normal,

overweight, and obese. Obesity and low levels of physical activity are putative risk factors for ovarian cancer mortality but the scientific evidence is either weak or inconsistent. Participants came from a larger study entitled the Women's Health Initiative, which included 161,808 women who were free from ovarian cancer. The average follow-up period was 10.9 years and 600 women among this cohort were diagnosed with invasive ovarian cancer and had data on BMI and physical activity levels. This study found that BMI was not associated with all-cause or ovarian cancer mortality. This was true after controlling for time from study enrollment to ovarian cancer diagnosis, cancer stage, hormone therapy, smoking, physical activity, and dietary modifications. The 'no difference' results differ from a recent review, which found a slightly greater risk of death due to ovarian cancer among obese women compared to non-obese women. In terms of physical activity levels, only vigorous-intensity activity was associated with a lower risk of all-cause (24%) and ovarian cancer (26%) mortality. Ovarian cancer stage did not affect associations between BMI, physical activity, and mortality. The association between vigorous physical activity and ovarian cancer mortality differs from the lack of association found in other published studies. However, this study is the largest to use prospectively (baseline measurements taken before outcome has occurred) collected physical activity data. Limitations of this study include using BMI to estimate obesity and the self-reported assessment of physical activity. BMI is only a crude estimate of relative body fat. As well, people typically overestimate their physical activity level. This study found a relationship only between vigorous physical activity and ovarian cancer mortality, with no relationships found between BMI or any other physical activity levels. Possibly, a dose response with physical activity exists such that an intensity threshold must be reached in order to reduce risk of ovarian cancer mortality. As a side note, exercise may provide additional benefits for women diagnosed with ovarian cancer such as cancer-related fatigue and quality of life.

INTO THE VAULT

Ornish D, G. Weidner, W.R. Fair, et al.

Intensive Lifestyle Changes May Affect the Progression of Prostate Cancer.

J Urol. 2005 Sep; 174(3):1065-70.

PURPOSE: Men with prostate cancer are often advised to make changes in diet and lifestyle, although the impact of these changes has not been well documented. Therefore, we evaluated the effects of comprehensive lifestyle changes on prostate specific antigen (PSA), treatment trends and serum stimulated LNCaP cell growth in men with early, biopsy proven prostate cancer after 1 year. **MATERIALS AND METHODS:** Patient recruitment was limited to men who had chosen not to undergo any conventional treatment, which provided an unusual opportunity to have a nonintervention randomized control group to avoid the confounding effects of interventions such as radiation, surgery or androgen deprivation therapy. A total of 93 volunteers with serum PSA 4 to 10 ng/ml and cancer Gleason scores less than 7 were randomly assigned to an experimental group that was asked to make comprehensive lifestyle changes or to a usual care control group. **RESULTS:** None of the experimental group patients but 6 control patients underwent conventional treatment due to an increase in PSA and/or progression of disease on magnetic resonance imaging. PSA decreased 4% in the experimental group but increased 6% in the control group ($p = 0.016$). The growth of LNCaP prostate cancer cells (American Type Culture Collection, Manassas, Virginia) was inhibited almost 8 times more by serum from the experimental than from the control group (70% vs 9%, $p < 0.001$). Changes in serum PSA and also in LNCaP cell growth were significantly associated with the degree of change in diet and lifestyle. **CONCLUSIONS:** Intensive lifestyle changes may affect the progression of early, low grade prostate cancer in men. Further studies and longer term followup are warranted.

INSPIREHEALTH's INTERPRETATION: This popular study assessed how a multitude of behavioural changes in lifestyle may affect prostate cancer growth. This was a randomized controlled trial in which 93 men with low to moderate grade prostate cancer were randomly assigned to an intensive lifestyle intervention group or a control group. At the beginning of this study the men had elected not to undergo conventional treatment, predominantly due to their relatively low cancer grade and personal physician's recommendations. The intensive lifestyle group involved 30 minutes of aerobic (cardiovascular) exercise 6 days per week, 60 minutes of stress management techniques daily, a 1-hour support group weekly, a vegan diet (no meat, dairy, eggs, or any animal products), and daily supplements of soy, fish oil, vitamin E, selenium, and vitamin C, for the duration of a year. The primary measure of the study was serum prostate specific antigen (PSA) level. PSA is the most widely used intermediate measure for assessing prostate cancer progression and response to treatment. The researchers also assessed the growth of prostate cancer cells in a 'petri dish' after being exposed to serum from the participants. Although participants in the control group were asked not to make dietary and lifestyle changes, this group did make positive changes, though not to the extent that the experimental group made. Despite the fact that both groups made lifestyle changes, the researchers measured a 4% decrease in PSA levels in the experimental group, as compared to baseline, and a 6% increase in the control group. As well, 6 patients in the control group received medical treatment due to possible prostate cancer progression, whereas no patients in the lifestyle group received treatment. The differences in PSA may have been even greater if the 6 patients were not excluded from the PSA analysis. When cultured with serum from both the intervention and control groups, LNCaP prostate cancer cell growth was inhibited by 9% by the

control serum, and 70% by the lifestyle group serum. The two year follow-up to this study (published as a separate paper) found that 27% of control patients progressed to medical treatment whereas only 5% of the lifestyle group progressed to treatment. Additionally, after two years the lifestyle group had lower cholesterol levels, suggesting an improvement in cardiovascular health. This is important because prostate cancer patients are at increased risk of cardiovascular disease mortality. Because of the variety of changes made by the intervention group, the results of this study cannot be attributed to any single intervention. At InspireHealth, we aim to empower patients to practice self-care and make positive lifestyle changes, but we do not recommend all components of this study's lifestyle intervention to our patients. This intervention serves as an example of how lifestyle changes may positively affect patients with prostate cancer.

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www.prostatecancerbc.ca
www.cbcbf.org

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 team selects authoritative articles based on their evidence and their relevance to this area of medicine. The editorial board includes: Dr. Hal Gunn, MD, CEO and Co-founder, Dr. Janice Wright, MD, Dr. Hannah Nette, MD, Dr. Lori McFarlane, MD, and Terry Heidt, M.Sc.

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