



## RESEARCH UPDATES AUG/SEPT 2015

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### FOR THE LATEST IN WORLDWIDE INTEGRATIVE CANCER CARE

**IN THIS ISSUE:** Irwin and colleagues conduct an exercise intervention aimed at decreasing aromatase-inhibitor induced joint pain in women with breast cancer. A paper by Lin's team reviews nutrition and diet among prostate cancer survivors. Hwang and Choi review the anti-cancer properties of phytoestrogens in the diet. Ray and Jakbec study the role that nature can play for cancer survivors' quality of life. The Into the Vault Study reviews vegetable intake among women taking tamoxifen.

## BREAST CANCER

Irwin, M.L., Cartmel, B., Gross, C., et al.

### Randomized Exercise Trial of Aromatase Inhibitor-Induced Arthralgia in Breast Cancer Survivors

*Journal of Clinical Oncology* (2015), 33(10), 1104-1111.

**PURPOSE:** Arthralgia occurs in up to 50% of breast cancer survivors treated with aromatase inhibitors (AIs) and is the most common reason for poor AI adherence. We conducted, in 121 breast cancer survivors receiving an AI and reporting arthralgia, a yearlong randomized trial of the impact of exercise versus usual care on arthralgia severity. **PATIENTS AND METHODS:** Eligibility criteria included receiving an AI for at least 6 months, reporting  $\geq 3$  of 10 for worst joint pain on the Brief Pain Inventory (BPI), and reporting < 90 minutes per week of aerobic exercise and no strength training. Participants were randomly assigned to exercise (150 minutes per week of aerobic exercise and supervised strength training twice per week) or usual care. The BPI, Western Ontario and McMaster Universities Osteoarthritis (WOMAC) index, and Disabilities of the Arm, Shoulder and Hand (DASH) questionnaire were completed at baseline and at 3, 6, 9, and 12 months. Intervention effects were evaluated using mixed-model repeated measures analysis, with change at 12 months as the primary end point. **RESULTS:** Over 12 months, women randomly assigned to exercise (n = 61) attended 70% ( $\pm$  standard deviation [SD], 28%) of resistance training sessions and increased their exercise by 159 ( $\pm$  SD, 136) minutes per week. Worst joint pain scores decreased by 1.6 points (29%) at 12 months among women randomly assigned to exercise versus a 0.2-point increase (3%) among those receiving usual care (n = 60; P < .001). Pain severity and interference, as well as DASH and WOMAC pain scores, also decreased significantly at 12 months in women randomly assigned to exercise, compared with increases for those receiving usual care (all P < .001).

**CONCLUSION:** Exercise led to improvement in AI-induced arthralgia in previously inactive breast cancer survivors.

**INSPIREHEALTH'S INTERPRETATION:** Traditional treatment for post-menopausal hormone-receptor positive breast cancer patients often includes receiving an aromatase-inhibitor. Adherence to aromatase inhibitors is often poor and it is thought to be partially due to commonly associated side effects. The most common side effect leading to discontinued use is arthralgia (joint pain or stiffness). Drawing from previous research showing benefit to osteoarthritis-related joint pain from exercise, as well as the extensive literature supporting exercise for health and recovery during a cancer diagnosis, the authors hypothesized that regular exercise would benefit arthralgia among women taking aromatase inhibitors when compared to a control group. In order to be eligible to participate in this study, women had to be performing less than 90 minutes of physical activity per week in the past six months and no strength training in the past year, be post-menopausal, diagnosed between 6 months and four years ago with stage I, II, or III hormone receptor-positive breast cancer, been taking an aromatase inhibitor for at least six months, and experiencing mild to severe arthralgia for at least two months. Eligible participants were randomized to an exercise intervention or control group.

The exercise intervention involved supervised resistance training two times per week, as well as a home-based aerobic exercise program consisting of 150 minutes per week. The control group continued with their regular activities. The program lasted for 12 months and measurements of pain levels, pain medication use, aromatase-inhibitor adherence, and overall physical activity were taken. Results showed a 29% decrease in pain scores for women in the exercise group, compared to a 3% increase for the control group. Those women in the exercise group also saw significant improvements in cardiorespiratory fitness, upper and lower body strength and weight loss.

Overall, this study would suggest that appropriate exercise may help lower pain levels from aromatase-inhibitor induced arthralgia. This is a promising finding as it could help to mitigate some of the primary side effects leading to discontinued use of aromatase inhibitors. It is suggested that you consult with an exercise professional to determine the best exercises for your condition.

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## PROSTATE CANCER

Lin, P., Aronson, W., & Freedland, S.J.

### Nutrition, Dietary Interventions and Prostate Cancer: The Latest Evidence

*BMC Medicine* (2015), 13(3), DOI 10.1186/s12916-014-0234-y

**ABSTRACT:** Prostate cancer (PCa) remains a leading cause of mortality in US men and the prevalence continues to rise world-wide especially in countries where men consume a 'Western-style' diet. Epidemiologic, preclinical and clinical studies suggest a potential role for dietary intake on the incidence and progression of PCa. 'This minireview provides an overview of recent published literature with regard to nutrients, dietary factors, dietary patterns and PCa incidence and progression. Low carbohydrates intake, soy protein, omega-3 (w-3) fat, green teas, tomatoes and tomato products and zylamend showed promise in reducing PCa risk or progression. A higher saturated fat intake and a higher  $\beta$ -carotene status may increase risk. A 'U' shape relationship may exist between folate, vitamin C, vitamin D and calcium with PCa risk. Despite the inconsistent and inconclusive findings, the potential for a role of dietary intake for the prevention and treatment of PCa is promising. The combination of all the beneficial factors for PCa risk reduction in a healthy dietary pattern may be the best dietary advice. This pattern includes rich fruits and vegetables, reduced refined carbohydrates, total and saturated fats, and reduced cooked meats. Further carefully designed prospective trials are warranted.

**INSPIREHEALTH'S INTERPRETATION:** This review provides readers with current evidence regarding the health effects of food factors and prostate cancer. A reductionist approach was taken such that each food component was examined separately. The results are largely inconsistent, likely because the effects of single food components were too small to be detected in clinical trials. Differences in eating habits between participants and the size and length of the clinical trial may outweigh the effects of a single food factor. As well, food components may interact with each other and influence prostate cancer. However, some important findings were reported and a summary of food factors listed in the article are given here. There are insufficient clinical trials to determine whether total carbohydrates and/or protein intake may affect prostate cancer. Skinless poultry was not associated with recurrence or progression of prostate cancer. Fish or baked poultry was inversely associated with advanced prostate cancer. However, fish cooked at high temperatures and cooked red meat may contribute to prostate cancer progression. Dairy protein and dairy products have been associated with an increased risk of prostate cancer. However, there was evidence that whole milk or low-fat milk consumption may promote or delay prostate cancer progression. Soy products are promising and may be beneficial but more research is needed. In terms of fat consumption, the type of fat may be more important than how much is consumed. Saturated fat may increase prostate cancer risk whereas plant-based fat may decrease prostate cancer risk. Omega-3 fatty acids may decrease risk of prostate cancer or delay progression. Supplementation of beta-carotene (converts to vitamin A) may increase risk of prostate cancer and is not recommended.

A lack of clinical trials for vitamin C, E, and K prevented this article from making recommendations for these vitamins, although pre-clinical trials have given some promise. A U-shaped relationship with vitamin D may exist, such that too little or too much may be harmful for prostate cancer. Green tea reduces PSA (blood marker for prostate cancer) levels and reduces prostate cancer progression. Fruits and vegetables may protect against prostate cancer and are recommended. In a randomized controlled trial, a blend of pomegranate, green tea, broccoli and turmeric significantly reduced the rate increase of PSA in men with prostate cancer. However, the contribution of each component on PSA levels is not well known. A recent meta-analysis found that coffee consumption may reduce prostate cancer risk due to antioxidant components. Studies have found that populations who consume a Mediterranean diet (high in vegetables, olive oil, complex carbohydrates, and lean meats) have lower prostate cancer rates compared to those who consume a typical Western-style diet.

In conclusion, the authors state that 'heart healthy' equals 'prostate healthy' in regards to dietary recommendations for prostate cancer patients. Recommendations include increasing fruits and vegetables, reducing total and saturated fat, replacing refined carbohydrates with whole grains, limiting red meat and overcooked meat, and aiming to maintain a healthy body weight.

## DIETARY PHYTOESTROGENS

Hwang, K.A. & Choi, K.C.

### Anticarcinogenic Effects of Dietary Phytoestrogens and Their Chemopreventive Mechanisms

*Nutrition and Cancer* (2015), 67:5, 796-803, DOI: 10.1080/01635581.2015.1040516

**ABSTRACT:** Phytoestrogens are phenolic compounds derived from plants and exert an estrogenic as well as an antiestrogenic effect and also various biological efficacies. Chemopreventive properties of phytoestrogens has emerged from epidemiological observations indicating that the incidence of some cancers including breast and prostate cancers is much lower in Asian people, who consume significantly higher amounts of phytoestrogens than Western people. There are 4 main classes of phytoestrogens: isoflavones, stilbenes, coumestans, and lignans. Currently, resveratrol is recognized as another major phytoestrogen present in grape and red wine and has been studied in many biological studies. Phytoestrogens have biologically diverse profittabilities and advantages such as low cytotoxicity to patients, lack of side effects in clinical trials, and pronounced benefits in a combined therapy. In this review, we highlighted the effects of genistein, daidzein, and resveratrol in relation with their anticarcinogenic activity. A lot of in vitro and in vivo results on their chemopreventive properties were presented along with the underlying mechanisms. Besides well-known mechanisms such as antioxidant property and apoptosis, newly elucidated anticarcinogenic modes of action including epigenetic modifications and topoisomerase inhibition have been provided to examine the possibility of phytoestrogens as promising reagents for cancer chemoprevention and/or treatment and to suggest the importance of plant-based diet of phytoestrogens.

**INSPIREHEALTH'S INTERPRETATION:** Phytoestrogens are plant-based compounds that are structurally or functionally similar to the hormone estradiol (the main human estrogen). Interestingly, these compounds can exert both estrogenic and anti-estrogenic properties. Evidence to date suggests that diets high in phytoestrogens are associated with reduced risk of developing several diseases including cancer, cardiovascular disease, and osteoporosis. The four main classes of phytoestrogens are isoflavones, lignans, coumestans and stilbenes. Soybeans are the richest source of isoflavones but they are also present in kidney beans, chick peas, lentils and peanuts. Genistein and daidzein are the two main isoflavones in soybeans. Lignans are found in flaxseed, seaweed, and whole grains. Clover and alfalfa are good sources of coumestans and the stilbene resveratrol is plentiful in the skin of red grapes (and hence red wine). The incidence of hormone related cancers such as breast and prostate is much lower in Asian populations than in Western populations and it has been postulated that this may be due, in part, to higher dietary consumption of phytoestrogens. In addition, studies on women with estrogen-positive breast cancer who are taking hormone therapy with either tamoxifen or anastrozole have shown that those with a high dietary intake of soy isoflavones have a lower risk of recurrence. Asians consume an average of 20-50 mg/d of phytoestrogens, while Europeans and North Americans consume about 0.1-0.5 mg/d. These Korean researchers summarized the various biochemical mechanisms by which three phytoestrogens (genistein, daidzein and resveratrol) might exert both cancer prevention and cancer treatment effects. In vitro (petrie dish) and animal studies have shown these three phytoestrogens to act as antioxidants, inhibit abnormal cell proliferation, and induce tumor suppression gene expression and apoptosis (programmed cell death).

However, the overall picture is far from clear. In vitro studies have also shown that very high concentrations of the isoflavone genistein are required for anti-cancer effects and that low levels can actually stimulate cancer growth. These high anti-cancer concentrations cannot be achieved by diet alone, and even those with an isoflavone-rich diet have low isoflavone blood levels in their bodies. On the other hand, epidemiological (population-based studies) and some human clinical trials have shown reductions in both cancer incidence and recurrence in those who consume an isoflavone-rich diet even though their isoflavone blood levels are as low as those thought to be cancer-promoting in in vitro studies. These discrepancies illustrate the complexities of nutrient absorption, distribution and function within our body's complex biological ecosystem. Petrie dish findings may not always reflect how nutrients act within our bodies. Serum (blood) levels of a given nutrient may not represent actual tissue levels. Also, phytoestrogens may act synergistically with one another and with other nutrients to enhance their anti-cancer effects. In summary, although there are in vitro concerns that low (ie. dietary) concentrations of isoflavones may act in a pro-carcinogenic way, the bulk of the evidence to date supports the consumption of plentiful plant-based foods for increased phytoestrogen intake. Consider choosing vegetables, fruits, nuts, seeds, beans, legumes and soy foods (eg. tofu and soy beans) as the most important building blocks of a healthy diet. In addition to phytoestrogens, plant-based foods contain many other healthy nutrients and are, in fact, considered the most nutrient dense foods available.

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## NATURE-BASED PHYSICAL ACTIVITY

Ray, H., & Jakbec, S.L.

### Nature-based experiences and health of cancer survivors

*Complementary Therapies in Clinical Practice* (2014). 20, 188-192.

**PURPOSE:** Although exposure to, and interaction with, natural environments are recognized as health promoting, little is understood about the use of nature contact in treatment and rehabilitation for cancer survivors. **METHODS:** This narrative review summarizes the literature exploring the influence of nature-based experiences on survivor health. Key databases included CINAHL, EMBASE, Medline, Web of Science, PubMed, PsycArticles, ProQuest, and Cancerlit databases. **RESULTS:** Sixteen articles met inclusion criteria and were reviewed. Four major categories emerged: 1) Dragon boat racing may enhance breast cancer survivor quality of life, 2) Natural environment may counteract attentional fatigue in newly diagnosed breast cancer survivors,

3) Adventure programs provide a positive experience for children and adolescent survivors, fostering a sense of belonging and self-esteem, and 4) Therapeutic landscapes may decrease state-anxiety, improving survivor health. **CONCLUSIONS:** This review contributes to a better understanding of the therapeutic effects of nature-based experiences on cancer survivor health, providing a point of entry for future study.

**INSPIREHEALTH'S INTERPRETATION:** The Calgary authors of this paper reviewed the literature to explore the influence of nature-based experiences on health-related quality of life in cancer survivors. Nature was defined as “outdoor natural ecosystems” and cancer survivorship as the “physical, psychological and economic issues of cancer from diagnosis until the end of life”. Much research has been done showing myriad benefits of physical activity throughout the survivorship continuum and a growing body of literature supports the importance of performing physical activity in nature as a particularly effective way to improve overall well-being. Sixteen publications regarding nature-based participation in cancer survivors were reviewed for this paper. While most studies focused on women with breast cancer, several explored the role of nature-based activities for children and adolescents with cancer. The authors identified four main themes: 1) dragon boat racing can enhance quality of life in women with breast cancer; 2) in women with newly diagnosed breast cancer time in nature may help to reduce attentional fatigue (ie. improve concentration); 3) adventure therapy (eg. camping) can improve self-esteem and social connectedness in children and adolescents with cancer; and 4) female cancer survivors may experience less anxiety and improved quality of life after time in natural landscapes. The authors conclude that while much more research is needed to better understand the mechanisms underlying nature's benefits, the overall positive picture of the value between nature and well-being is most encouraging. Significantly, physical activity in nature appears to benefit many aspects of quality of life including improved psycho-social, physical and spiritual well-being.

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## LUNG CANCER

Pouwels, S., Fiddelaers, J., Tejjink, J.A.W., et al.

### Preoperative exercise therapy in lung surgery patients: A systematic review

*Respiratory Medicine* (2015). doi: 10.1016/j.rmed.2015.08.009

**OBJECTIVES:** The impact of postoperative complications after lung surgery for cancer is substantial, with the increasing age of patients and the presence of comorbidities. This systematic review summarises the effects of Preoperative Exercise Therapy (PET) in patients scheduled for lung surgery on aerobic capacity, physical fitness, postoperative complications, length of hospital stay, quality of life and recovery. **METHODS:** A systematic search on PET prior to lung surgery was conducted. The methodological quality of the included studies was rated using the Physiotherapy Evidence Database (PEDro) scale. The agreement between the reviewers was assessed with Cohen's kappa. **RESULTS:** A total of eleven studies were included with a methodological quality ranging from poor to good. The agreement between the reviewers, assessed with the Cohen's kappa, was 0.79. Due to substantial heterogeneity in the interventions across the included studies, it was impossible to conduct a metaanalysis. The most important finding of this systematic review was that PET based on moderate to intense exercise in patients scheduled for lung surgery has beneficial effects on aerobic capacity, physical fitness and quality of life. Also PET may reduce postoperative complications and length of hospital stay. **CONCLUSION:** PET may have beneficial effects on various physical fitness variables and postoperative complications in patients with lung cancer scheduled for surgery. Future research must focus on developing patient tailored exercise programs and investigate the influence of co-existing comorbidities on the outcome measures. Definitions of PET, including timing, (acceptable) duration, intensity and exercise training methods should be determined and compared.

**INSPIREHEALTH'S INTERPRETATION:** One of the most common methods of treatment for lung cancer is surgical removal of the area of the lung affected by cancer growth. Preoperative exercise therapy (PET) has been highlighted as an effective way to improve well-being and reduce negative symptoms after this type of procedure. These researchers performed a systematic review (an academic review of multiple studies) in order to explore the outcomes of PET programs for individuals with lung cancer undergoing surgery. Specifically, they wanted to explore the effects of PET on post-operative complications, length of hospital stay, pulmonary function, fitness, and quality of life. The authors explored academic databases in search of randomized controlled trials or prospective cohort studies, and found a total of 11 studies that fit their inclusion criteria. These studies varied greatly from each other (e.g., the length of the programs ranged from one day to four weeks), which made it difficult to directly compare the effects of the programs. However, the selected studies pointed to some interesting outcomes. The PET programs reportedly reduced hospital stay and post-operative complications in three different studies. The results in regards to pulmonary function were mixed, with two studies finding improvements and three finding no improvements after a PET program. Physical fitness was generally found to increase after PET programs, with five studies noting improvements in cardiovascular health following a PET program, and one study finding no cardiovascular improvements for participants. One particular study that included resistance training in their program reported improvements in muscular strength in some muscle groups, but not others. Quality of life results were also mixed among three studies that reported this outcome. Three studies reported adherence to PET programs, which ranged between 72-88%, and only one study indicated any adverse effects as a consequence of a PET program (in which two subjects experienced temporary abnormal declines in their systolic blood pressure). In summary, although it is difficult to come to definitive conclusions about PET programs (because the programs evaluated in this review were quite different from each other), they appear beneficial, particularly in regards to post-operative complications, hospital stay, and physical fitness outcomes.

## INTO THE VAULT

Thomson, C.A., Rock, C.L., Thomson, P.A., et al.

### Vegetable intake is associated with reduced breast cancer recurrence in tamoxifen users: a secondary analysis from the Women's Healthy Eating and Living Study

*Clinical Journal of Oncology Nursing* (2011), 15(1), E3-E12.

**ABSTRACT:** The protective effect of vegetables on the risk of breast cancer recurrence is uncertain. We sought to evaluate the association between breast cancer recurrence and vegetable intake including analyses stratified on tamoxifen use. Experimental evidence of anti-carcinogenic activity of phytochemicals in cruciferous vegetables in combination with tamoxifen led to specific evaluation of this class of vegetables as well. To assess the association between vegetable intake and breast cancer recurrence, vegetable intake from repeat 24-h dietary recalls were examined as a secondary analysis of 3,080 breast cancer survivors enrolled in the Women's Healthy Eating and Living (WHEL) Study. At the time of enrollment women were, on average, 23.5 months post-diagnosis. The hazard of recurrence, controlling for relevant and significant clinical and demographic variables, with vegetable intake was assessed overall and separately for women taking tamoxifen. WHEL participants reported mean baseline intakes ( $\bar{x}$ , SE) of  $3.1 \pm 0.05$  and  $0.5 \pm 0.02$  servings/day of total and cruciferous vegetables, respectively. Baseline vegetable intake in the highest as compared to lowest tertiles was associated with an overall lower adjusted hazard ratios (HR) for recurrence of 0.69, 95% CI 0.55–0.87. Among women taking tamoxifen, the HRs were 0.56, 95% CI 0.41–0.77 for total vegetables and 0.65, 95% CI 0.47–0.89 for cruciferous vegetable intake. The hazard in women using tamoxifen who reported cruciferous vegetable intake above the median and who were within the highest tertile of total vegetable intake was HR 0.48; 95% CI 0.32–0.70. This secondary analysis in over 3,000 breast cancer survivors suggests that baseline vegetable intake may be associated with a reduction in the risk of breast cancer recurrent or new events particularly for those using tamoxifen. Such associations should be explored further as the possibility that vegetable intake is simply a surrogate for other health-promoting behaviors cannot be ruled out.

**INSPIREHEALTH'S INTERPRETATION:** This randomized controlled trial was conducted to see if a vegetable-heavy diet was effective in preventing cancer recurrence in female breast cancer survivors. Although no effects were found as a result of this experimental diet, it was noted that survivors that were physically active and ate at least five fruit and vegetable servings per day at the beginning of the study had decreased recurrence of cancer during the duration of the study. Furthermore, there is evidence to suggest that there may be a protective effect created by the use of tamoxifen (a drug commonly used in breast cancer treatment protocols) and the consumption of cruciferous vegetables (e.g., broccoli, cauliflower, cabbage, bok choy). This paper was a secondary analysis of the data which examined the relationship between baseline consumption of total and cruciferous vegetables, tamoxifen use, and cancer recurrence.

The results indicated that women who consumed more total vegetables at baseline (i.e., women in the top 33% of vegetable consumption) had a lower risk of cancer recurrence. This effect was not found for cruciferous vegetable intake alone. When the researchers evaluated the effects of tamoxifen use, vegetable consumption, and cancer recurrence, they found that women on tamoxifen had a reduced risk of recurrence when vegetable intake (both total and cruciferous) was higher at baseline. This effect was found to be stronger for women on tamoxifen than for women not on tamoxifen. Additionally, the researchers also found a decreased risk of cancer recurrence for women on tamoxifen when cruciferous vegetable intake was above average and total vegetable consumption was in the top 66%. As such, increased consumption of total and cruciferous vegetables may lead to a protective effect for women on tamoxifen. As this was not an experimental study, results should be interpreted cautiously, and more work in this area would have to be done in order to better understand the mechanisms at work. On top of the preliminary evidence from this study, there is an abundance of literature supporting vegetable intake for overall health and wellbeing. Trying to take in an assortment of colours in your diet (eat the rainbow) can ensure that adequate nutrition requirements are being met.

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