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INTEGRATIVE CANCER CARE

RESEARCH UPDATES SEPTEMBER 2014

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FOR THE LATEST IN WORLDWIDE INTEGRATIVE CANCER CARE

IN THIS ISSUE: Courneya and colleagues found that higher levels of weekly vigorous aerobic exercise (150 – 180 minutes vs. 75 – 90 minutes) significantly improved sleep quality in breast cancer patients during chemotherapy treatment. In their animal study, Dauchy and associates found that dim light exposure at night reduced circulating melatonin levels and the effectiveness of tamoxifen in rats with cancer. Nagata and associates found in their review that higher levels of soy intake in Japanese post-menopausal women were associated with a decreased risk of breast cancer. Lee et al.'s prospective cohort study found that exercise following a cancer diagnosis was significantly associated with reduced risk of death from any cause, cancer, and cardiovascular disease. In their randomized, controlled trial, Chandwani and colleagues found that 3 times weekly yoga practice improved quality of life in female breast cancer patients more than stretching alone. Zhang et al. provided observational evidence that moderate consumption of green tea enhanced survival in patients with epithelial ovarian cancer.

SLEEP

Courneya, KS, R.J. Segal, J.R. Mackey, et al.

Effects of Exercise Dose and Type on Sleep Quality in Breast Cancer Patients Receiving Chemotherapy: A Multi-Center Randomized Trial.

Breast Cancer Res Treat. 2014 Apr; 144(2):361-9.

To examine the effects of different doses and types of exercise on sleep quality in breast cancer patients receiving chemotherapy. A multicenter trial in Canada randomized 301 breast cancer patients between 2008 and 2011 to thrice weekly, supervised exercise during chemotherapy consisting of either a standard dose of 25-30 min of aerobic exercise (STAN; n = 96), a higher dose of 50-60 min of aerobic exercise (HIGH; n = 101), or a combined dose of 50-60 min of aerobic and resistance exercise (COMB; n = 104). The secondary sleep outcomes in the trial were assessed by the Pittsburgh Sleep Quality Index (PSQI) at baseline, twice during chemotherapy, and post-chemotherapy. We analyzed the global PSQI and the component scores. Repeated measures analyses of variance indicated that the HIGH group was statistically superior to the STAN group for global sleep quality (mean group difference = -0.90; 95 % CI -0.05 to -1.76; p = 0.039) as well as subjective sleep quality (p = 0.028) and sleep latency (p = 0.049). The COMB group was borderline statistically superior to the STAN group for global sleep quality (mean group difference = -0.76; 95 % CI +0.11 to -1.62; p = 0.085) as well as sleep duration (p = 0.051); and statistically superior for sleep efficiency (p = 0.040), and percentage of poor sleepers (p = 0.045). Compared to a standard volume of aerobic exercise, higher volumes of both aerobic and combined exercise improved some aspects of sleep quality during breast cancer chemotherapy. Exercise may be an attractive option to manage sleep dysfunction in cancer patients during chemotherapy.

INSPIREHEALTH'S INTERPRETATION: Sleep is a natural requirement for healthy physiological and psychological function. Sleeplessness can negatively impact health by reducing melatonin secretion, impairing glucose regulation, increasing blood pressure and slowing cognitive processes. Sleep qualities such as sleep latency (the time it takes to fall asleep), sleep duration, and quality of sleep can be affected by cancer treatment. Pharmacological treatments are the primary response to such issues, however, they have been associated with fatigue, depression, poor functioning and reduced quality of life. Exercise has been shown to positively affect sleep quality with no side effects. This study compared the effect of three different exercise programs

on sleep parameters in 301 stage I-IIIc breast cancer patients older than 18 years without documented sleeping disorders. All subjects were beginning chemotherapy and were randomized into one of three exercise groups. Subjects in the standard exercise group (STAN) completed the minimum exercise guidelines approved by the American College of Sports Medicine (ACSM) of 3 days per week of 25-30 minutes of vigorous aerobic exercise. The high exercise group (HIGH) followed double the minimum ACSM guidelines of 3 days of 50-60 minutes vigorous aerobic exercise. The combined exercise group (COMB) completed the same aerobic exercise as STAN group plus 30-35 minutes of resistance training 3 days per week. Sleep quality, latency, duration, efficiency, disturbances, medication use, and daytime dysfunction were assessed at baseline prior to exercise, throughout chemotherapy, and 3-4 weeks post chemotherapy using the Pittsburgh Sleep Quality Index questionnaire.

Results showed that participants in the HIGH group had significantly better outcomes than the STAN exercise group: displaying greater subjective sleep quality by 14.2%, and sleep latency by 18.7%. COMB exercise participants were superior to the STAN group in sleep duration by 17.7%, and sleep efficiency by 19.9%. The HIGH group was superior to the COMB group in sleep latency only, by 19.5%. This study demonstrated that an increase in vigorous aerobic exercise can significantly improve sleep quality in breast cancer patients undergoing chemotherapy with no previously documented sleeping disorders. This is an important factor as improved sleep helps the body to regenerate and recover from cancer and cancer treatment.

Further, as opposed to chronic use of sleep medication, exercise as a treatment to improve sleep has no documented side effects. In addition to improving sleep and overall quality of life, exercising on a regular basis has consistently been shown to improve survival from cancer, cardiovascular disease, and all-cause mortality.

SLEEP

Dauchy RT, S. Xiang, L. Mao, et al.

Circadian and Melatonin Disruption by Exposure to Light at Night Drives Intrinsic Resistance to Tamoxifen Therapy in Breast Cancer.

Cancer Res. 2014 Aug 1; 74(15):4099-110.

Resistance to endocrine therapy is a major impediment to successful treatment of breast cancer. Preclinical and clinical evidence links resistance to antiestrogen drugs in breast cancer cells with the overexpression and/or activation of various pro-oncogenic tyrosine kinases. Disruption of circadian rhythms by night shift work or disturbed sleep-wake cycles may lead to an increased risk of breast cancer and other diseases. Moreover, light exposure at night (LEN) suppresses the nocturnal production of melatonin that inhibits breast cancer growth. In this study, we used a rat model of estrogen receptor (ERα(+)) MCF-7 tumor xenografts to demonstrate how altering light/dark cycles with dim LEN (dLEN) speed the development of breast tumors, increasing their metabolism and growth and conferring an intrinsic resistance to tamoxifen therapy. These characteristics were not observed in animals in which the circadian melatonin rhythm was not disrupted, or in animals subjected to dLEN if they received nocturnal melatonin replacement. Strikingly, our results also showed that melatonin acted both as a tumor metabolic inhibitor and a circadian-regulated kinase inhibitor to reestablish the sensitivity of breast tumors to tamoxifen and tumor regression. Together, our findings show how dLEN-mediated disturbances in nocturnal melatonin production can render tumors insensitive to tamoxifen.

INSPIREHEALTH'S INTERPRETATION: In humans, all breast cancer tumors are tested for the presence or absence of estrogen (ER), progesterone (PR) and HER2 receptors. For those with ER positive tumors, various anti-estrogen medications are typically recommended in addition to standard treatments. The selective estrogen receptor modulator tamoxifen is the most common hormone therapy for ER positive breast cancer. However, intrinsic and acquired resistance to tamoxifen therapy can be a major impediment to its effectiveness. In several in-vitro and in-vivo studies the hormone and antioxidant melatonin has been shown to have several anti-cancer properties. Melatonin is secreted by the pineal gland at the base of the brain during nighttime darkness and its release is inhibited by even dim light exposure at night (dLEN).

In this very interesting study, the authors used a rat model to test the hypothesis that melatonin suppression by dLEN would induce tumor progression and resistance to tamoxifen therapy and that supplemental melatonin could reverse these effects. Estrogen receptor positive human breast cancer cells were implanted into rats that were then exposed to either 12 hours of nighttime darkness or 12 hours of dLEN. Additional subgroups were also given tamoxifen and/or melatonin. The advantage of using an animal model is that human cancer cells can be examined in very controlled conditions increasing the likelihood of a cause and effect relationship for the study's variables. Rats exposed to nighttime darkness produced 70 times more melatonin at night than during daylight hours and those exposed to dLEN had consistently low to undetectable levels of melatonin. Supplementation restored the typical nighttime spike in melatonin levels. Tumors from rats in the dLEN group grew much faster than those in the night darkness group and showed complete intrinsic resistance to tamoxifen. This resistance

was reversed when the dLEN rats were given melatonin supplementation. In other words, melatonin restored tamoxifen's anti-cancer effects. Conversely, tumor growth from the rats in the nighttime darkness group was suppressed when the rats were given tamoxifen. Thus, the presence of endogenous (i.e. within the body) or exogenous (i.e. supplemental) melatonin not only attenuated tamoxifen resistance, it increased tumor sensitivity to tamoxifen. The dLEN conditions were equivalent to a crack of light under a door in a completely dark room; that is, a very small amount of light exposure.

Although results from animal models may not translate to humans, this study supports the theory that sleeping in complete darkness is ideal. Black out blinds/curtains or eye pads could be utilized to this end. Although further research is needed, supplementation with melatonin could be considered in consultation with your health care provider for those exposed to light at night.

NUTRITION

Nagata, C, T. Mizoue, K. Tanaka, et al.

Soy Intake and Breast Cancer Risk: An Evaluation Based on a Systematic Review of Epidemiologic Evidence Among the Japanese Population.

Jpn J Clin Oncol. 2014; 44(3)282–295.

OBJECTIVE: We reviewed epidemiological studies of soy intake and breast cancer among Japanese women. This report is one among a series of articles by our research group, which is evaluating the existing evidence concerning the association between health-related lifestyles and cancer. **METHODS:** Original data were obtained from MEDLINE searches using PubMed or from searches of the Ichushi database, complemented with manual searches. Evaluation of associations was based on the strength of evidence and the magnitude of association, together with biological plausibility. **RESULTS:** Five cohort studies and six case-control studies were identified. Among the cohort studies, two studies observed that total soy intake (in terms of total amounts of soy foods or soy isoflavones) was associated with a moderate ($0.5 \leq$ relative risk ≤ 0.67 with statistical significance) or strong (relative risk ≤ 0.5 with statistical significance) risk reduction of breast cancer in postmenopausal women. Among the case-control studies, two studies reported a weak ($0.67 \leq$ odds ratio ≤ 1.5 with statistical significance or $0.5 \leq$ odds ratio ≤ 0.67 without statistical significance) inverse association between total soy intake and the risk of breast cancer. In the former, this association was observed in all women combined-premenopausal and postmenopausal women-but in the latter, the association was confined to postmenopausal women. The associations of intakes of individual soy foods with the risk of breast cancer were generally null. There is some evidence that supports the biological plausibility of a protective effect of isoflavones on breast cancer risk. **CONCLUSIONS:** We conclude that soy intake possibly decreases the risk of breast cancer among Japanese women.

INSPIREHEALTH'S INTERPRETATION: This article is a review of research that has been published on soy intake and risk of breast cancer among the female Japanese population. Soybeans have been postulated to reduce the risk of breast cancer because they contain isoflavones, a large class of phytoestrogens. Phytoestrogens are naturally occurring plant compounds that closely resemble the human estrogen molecule. Phytoestrogens are important because they act on the same receptors that our endogenous estrogen does. When a phytoestrogen molecule binds an estrogen receptor it results in a lower level of estrogenic activity than if the human estrogen molecule had bound the same receptor. In this way, phytoestrogens compete for binding sites with endogenous estrogen and lower overall estrogenic activity. Isoflavone consumption in Asian countries is typically higher than in other places around the world, however there is still significant heterogeneity. To reduce the influence of other confounding variables, the authors of this review limited their analysis to the Japanese population, a population that typically consumes high amounts of soy-based foods.

Eleven studies were included in this review; five cohort studies and six case-control studies. Cohort studies follow a group of subjects over time and then compare which participants developed disease with the variable in question (soy intake in this study). Two out of five cohort studies reported a reduction in breast cancer risk with higher soy intake while the others did not report a significant correlation. Important to note here is that the two studies that reported beneficial effects quantified total soy intake, whereas the three studies that did not show benefit quantified intake of specific soy containing foods. When separated into pre and post-menopausal status, the beneficial effect was only found in postmenopausal women. Mixed results were found in the reviewed case-control studies. Case-control studies aim to determine if specific variables (soy intake in this case) differ between groups of subjects, those with a disease or condition (case), and those without the disease or condition (control). Data from the case-control studies provided similar insight. Subjects who had higher overall soy intake were at reduced risk. One case control study reported a weak association showing higher levels of breast cancer in subjects who consumed the highest amounts of miso soup. However, when these subjects were separated into pre and post-menopausal groups the weak association disappeared.

Though the data from the studies reviewed were observational, they showed a benefit of reduced breast cancer risk in postmenopausal Japanese women who consumed high levels of soy in their diet and phytoestrogens provide biological plausibility for this association. InspireHealth nutritionists recommend a moderate amount of whole food form, traditionally prepared soy-containing foods for adult women.

EXERCISE

Lee IM, K.Y. Wolin, S.E. Freeman, et al.

Physical Activity and Survival after Cancer Diagnosis in Men.

J Phys Act Health. 2014 Jan;11(1):85-90.

BACKGROUND: The number of cancer survivors is increasing rapidly; however, little is known about whether engaging in physical activity after a cancer diagnosis is associated with lower mortality rates in men. **METHODS:** We conducted a prospective cohort study of 1021 men (mean age, 71.3 years) who were diagnosed with cancer (other than nonmelanoma skin cancer). Men reported their physical activities (walking, stair climbing, and participation in sports and recreational activities) on questionnaires in 1988, a median of 6 years after their cancer diagnosis. Physical activity was updated in 1993 and men were followed until 2008, with mortality follow-up > 99% complete, during which 777 men died (337 from cancer, 190 from cardiovascular disease). **RESULTS:** In multivariate analyses, the relative risks for all-cause mortality associated with expending < 2100, 2100-4199, 4200-8399, 8400-12,599, and ≥ 12,600 kJ/week in physical activity were 1.00 (referent), 0.77, 0.74, 0.76, and 0.52, respectively (P-trend < 0.0001). Higher levels of physical activity also were associated with lower rates of death from cancer and cardiovascular disease (P- trend = 0.01 and 0.002, respectively). **CONCLUSIONS:** Engaging in physical activity after cancer diagnosis is associated with better survival among men.

INSPIREHEALTH'S INTERPRETATION: This prospective cohort study investigated the effect of exercise following a cancer diagnosis on mortality in 1021 male Harvard alumni. Subjects completed two physical activity questionnaires; the first was approximately 6 years after their initial diagnosis, and the second was 5 years after that. Although questionnaires are an imperfect measurement tool, the questionnaire used in this study was previously validated against the gold-standard (doubly-labelled water) for energy expenditure. Amount of time spent exercising per week (walking, stair climbing, sports and recreational activities) was divided into five categories: <1h15min, 1h15min – 2h29min, 2h30min – 4h59min, 5h – 7h29min, and >7h30min. Less than 1h15min was the reference category that the other categories were compared to. For cancer patients, the American College of Sports Medicine currently recommends 150 minutes of moderate intensity exercise per week.

In this study, 150 minutes of exercise per week was associated with a 31% reduced risk of both all-cause, and cancer-related mortality. Subjects in the highest quartile of weekly exercise (>7h30min, which works out to just over 1 hour per day) were 50% less likely to die from any cause, 42% less likely to die from cancer, and 53% less likely to die from cardiovascular complications. The data from this study show that higher levels of exercise significantly reduce the risk of death in men diagnosed with cancer. Results were very similar and still statistically significant after the authors controlled for potentially confounding variables (smoking, body mass index, early parental death, alcohol intake, and diet). It is never too late to start exercising; this study adds to the growing literature on the significant survival benefit of physical activity following a cancer diagnosis.

YOGA AND RADIOTHERAPY

Chandwani, KD, G. Perkins, H.R. Nagendra, et al.

Randomized, Controlled Trial of Yoga in Women with Breast Cancer Undergoing Radiotherapy.

J Clin Oncol. 2014 Apr 1;32(10):1058-65.

PURPOSE: Previous research incorporating yoga (YG) into radiotherapy (XRT) for women with breast cancer finds improved quality of life (QOL). However, shortcomings in this research limit the findings. **PATIENTS AND METHODS:** Patients with stages 0 to III breast cancer were recruited before starting XRT and were randomly assigned to YG (n = 53) or stretching (ST; n = 56) three times a week for 6 weeks during XRT or waitlist (WL; n = 54) control. Self-report measures of QOL (Medical Outcomes Study 36-item short-form survey; primary outcomes), fatigue, depression, and sleep quality, and five saliva samples per day for 3 consecutive days were collected at baseline, end of treatment, and 1, 3, and 6 months later. **RESULTS:** The YG group had significantly greater increases in physical component scale scores compared with the WL group at 1 and 3 months after XRT (P = .01 and P = .01). At 1, 3, and 6 months, the YG group had greater increases in physical functioning compared with both ST and WL groups (P < .05), with ST and WL differences at only 3 months (P < .02). The group differences were similar for general health reports. By the end of XRT, the YG and ST groups also had a reduction in fatigue (P < .05). There were no group differences for mental health and sleep quality. Cortisol slope was steepest for the YG group compared with the ST and

WL groups at the end (P = .023 and P = .008) and 1 month after XRT (P = .05 and P = .04). **CONCLUSION:** YG improved QOL and physiological changes associated with XRT beyond the benefits of simple ST exercises, and these benefits appear to have long-term durability.

INSPIREHEALTH'S INTREPRETATION: Previous research published on the effects of yoga in cancer patients has demonstrated many benefits including improvements in physical and mental health, fatigue, quality of life, pain levels, and feelings of vitality. This study followed women who were diagnosed with breast cancer through radiation treatment and a 6 month follow-up period. Participants were randomized into a yoga group, a stretching group, or a wait-list control group. Both the yoga group and stretching group took part in their respective sessions three days per week for six weeks during radiotherapy treatment. The wait-list control group did not attend any classes. Subjects filled out validated questionnaires to measure components of both physical and mental health. Cortisol levels (a hormone that is normally produced during stress) were measured by saliva sample. Data collection for the above variables occurred prior to beginning radiotherapy, at the end of radiotherapy treatments, and one, three, and six months following the end of treatments.

The yoga group had greater increases in the physical component scale than the wait-list control group at 1, 3, and 6 months following radiation, as well as higher physical functioning ratings than the other two groups at the same time periods. General health ratings increased more in the yoga group than both the stretching and waitlist groups at 1 and 3 months post-radiation. Those in the yoga and stretching groups also showed a decrease in fatigue levels following radiation treatments. Compared to the stretching and control groups, the cortisol slope was steeper (a steeper slope is indicative of better cortisol regulation) in the yoga group both immediately following treatment, and one month afterwards. No difference between groups was observed for sleep or mental health. This study draws attention to some of the longer-term benefits that may be achieved through a regular yoga practice. One of the strengths of this study was its three-arm approach: comparing a traditional method of yoga instruction to a physiotherapist-led stretching class, and to a wait-list control group.

These data help us to better understand the potential benefits of a yoga program over simply stretching the body's muscles. It seems that while stretching alone is important physiologically, the focus on relaxation through physical postures and breathing within a yoga class may have greater benefits in the long-term, perhaps through improved cortisol regulation. Some of the benefits associated with the yoga program lasted up to six months following treatment. InspireHealth offers weekly yoga classes for patient and support members at all of our centres.

INTO THE VAULT

Zhang M, A.H. Lee, C.W. Binns, et al.

Green Tea Consumption Enhances Survival of Epithelial Ovarian Cancer.

Int J Cancer. 2004 Nov 10; 112(3):465-9.

Our study investigates whether tea consumption can enhance the survival of patients with epithelial ovarian cancer, a prospective cohort study was conducted in Hangzhou, China. The cohort comprised 254 patients recruited during 1999-2000 with histopathologically confirmed epithelial ovarian cancer and was followed up for a minimum of 3 years. Two hundred forty four (96.1%) of the cohort or their close relatives were traced. The variables examined included their survival time and the frequency and quantity of tea consumed post-diagnosis. The actual number of deaths was obtained and Cox proportional hazards models were used to obtain hazard ratios and associated 95% confidence intervals (CI), adjusting for age at diagnosis, locality, BMI, parity, FIGO stage, histologic grade of differentiation, cytology of ascites, residual tumour and chemotherapeutic status. The survival experience was different between tea drinkers and non-drinkers ($p < 0.001$). There were 81 (77.9%) of 104 tea-drinkers who survived to the time of interview, compared to only 67 women (47.9%) still alive among the 140 non-drinkers. Compared to non-drinkers, the adjusted hazard ratios were 0.55 (95% CI = 0.34-0.90) for tea-drinkers, 0.43 (95% CI = 0.20-0.92) for consuming at least 1 cup of green tea/day, 0.44 (95% CI = 0.22-0.90) for brewing 1 batch or more of green tea/day, 0.40 (95% CI = 0.18-0.90) for consuming more than 500 g of dried tea leaves/year, and 0.38 (95% CI = 0.15-0.97) for consuming at least 2 g of dried tea leaves/batch. The corresponding dose-response relationships were significant ($p < 0.05$). We conclude that increasing the consumption of green tea post-diagnosis may enhance epithelial ovarian cancer survival.

INSPIREHEALTH'S INTERPRETATION: In our April 2014 issue of Research Updates, we commented on a 2012 systematic review of green tea for ovarian cancer prevention and treatment. This Zhang et al. study was an important cohort study included in that review. Two-hundred and fifty-four Chinese women with epithelial ovarian cancer (EOC) were recruited from 1999-2000 and followed up for post-diagnosis mortality in 2003. The authors collected data on pre and post-diagnosis tea consumption, and other factors known to be associated with EOC incidence and progression including age, body-mass-index, cancer stage, smoking and alcohol consumption, and family history of EOC. Tea consumption was quantified by type of tea, cups per day,

batches brewed per day, and grams of dried tea leaves per batch and per year. Ninety-six percent of patients were available for follow-up; 148 were still alive and 96 had died (all related to EOC complications). At follow-up, 81 of the 104 (78%) tea drinkers were alive and 67 of the 140 (48%) non-tea drinkers were alive. Over 90% of tea drinkers drank green tea exclusively.

Most women who started drinking green tea after diagnosis or continued its use did so to improve their sense of taste, a potential side effect of chemotherapy. In other words, these women were not necessarily drinking green tea for positive therapeutic effect; a fact that would tend to minimize the "placebo effect" and strengthen green tea's observed benefits. Compared to non-tea drinkers, tea drinkers were 45% less likely to die from their disease. Further, for those who consumed at least one cup per day (approximately 2g, or one tea bag's worth of steeped tea leaves), mortality from any cause was reduced by 57%. Green tea's benefits are thought to be related to its epigallocatechin gallate (EGCG) components. This phytochemical has been shown to have several anti-cancer properties including inhibition of both cancer cell growth and new blood vessel formation (angiogenesis), and promotion of cancer cell death (apoptosis).

This study's main strengths were its accuracy in quantifying green tea exposure and its high follow-up rate; its main limitation was its failure to collect other dietary information post-diagnosis. Nevertheless, current data, including those examined in this study, do suggest a beneficial effect of including 1-2 cups of green tea/day to both help prevent and treat ovarian cancer.

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