



## RESEARCH UPDATES APRIL 2014

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### FOR THE LATEST IN WORLDWIDE INTEGRATIVE CANCER CARE

**IN THIS ISSUE:** In a prospective cohort study, Hashibe and associates found that regular exercise was associated with a 42% reduction in head and neck cancer risk. Streckmann et al. found that exercise improved balance, and reduced symptoms of peripheral neuropathy in lymphoma patients undergoing treatment. Shin and Temel found that patients who received early palliative care had better quality of life and lived longer than those who did not. In their literature review, Trudel and associates found that in-vitro, some compounds in green tea inhibit the growth of ovarian cancer cells, and that people who consume green tea have a lower risk of developing epithelial ovarian cancer. Massa et al. found that taking a multivitamin regularly was associated with a reduction in colorectal cancer risk. Wang and colleagues found that melatonin supplementation in conjunction with standard therapy resulted in improved 1-year survival and reduced treatment-related symptoms.

## EXERCISE

Hashibe, M, J. Hunt, M. Wei, et al.

### Tobacco, Alcohol, Body Mass Index, Physical Activity, and the Risk of Head and Neck Cancer in the Prostate, Lung, Colorectal, and Ovarian (PLCO) Cohort.

*Head Neck.* 2013 Jul; 357: 914-922.

**BACKGROUND:** Estimation of attributable fractions for tobacco and alcohol, and investigation of the association between body mass index (BMI) and head and neck cancer risk have largely been in case-control studies. These aspects and physical activity need to be assessed as possible head and neck cancer risk/protective factors in a cohort study. **METHODS:** In the Prostate, Lung, Colorectal, and Ovarian (PLCO) cancer screening trial, of the 101,182 study subjects, 177 individuals developed head and neck cancer. **RESULTS:** The proportion of head and neck cancer cases attributed to tobacco and/or alcohol was 66% (50.5% tobacco alone, 14.7% alcohol alone, 0.9% tobacco and alcohol combined). BMI was not associated with head and neck cancer risk, but increasing hours of physical activity per week was associated with a reduced head and neck cancer risk (odds ratio [OR] = 0.58; 95% confidence interval [CI] = 0.35-0.96). **CONCLUSIONS:** Cigarette smoking is clearly the most important head and neck cancer risk factor in this population. The reduced cancer risk due to physical activity was consistent with results from a pooled analysis of case-control studies.

**INSPIREHEALTH'S INTERPRETATION:** In this well done prospective cohort study, the authors looked at the relationship between head and neck cancers and tobacco use, alcohol use, body mass index (BMI), and physical activity. Previous large investigations into head and neck cancer development have been case-control studies (retrospective). Cohort studies are prospective in nature and therefore aren't as affected by recall bias. Recall bias negatively affects the validity of a study and occurs when a subject inaccurately reports previous events, experiences, or their behaviour. If a person already has cancer, they may recall their previous exposures differently than a person who does not. In this study, all subjects began without cancer and were followed for an average of 11.5 years. Over 100,000 subjects were included and of the 177 who developed head and neck cancer, 143 were men.

Not surprisingly, cigarette smoking was the most important risk factor in head and neck cancer development; current smokers were 6.5 times more likely to develop head and neck cancer than non-smokers. Drinking more than 2 alcoholic beverages per day resulted in approximately 2 times the risk of developing head and neck cancer compared to less than 2 drinks per day. Interestingly, BMI was not associated with cancer risk, but physical activity was. Subjects who exercised at least three hours per week, or just under 30 minutes per day, were 42% less likely to develop head or neck cancer. These results are in line with many other research studies that correlate reduced voluntary toxin intake, and regular exercise with reduced cancer risk.

## EXERCISE

Streckmann, F, S. Kneis, J. A. Leifert, et al.

### Exercise Program Improves Therapy-Related Side-Effects and Quality of Life in Lymphoma Patients Undergoing Therapy.

*Annals of Oncology.* 2014 Feb; 252: 493-499.

**BACKGROUND:** Lymphoma patients undergoing therapy must cope with the side-effects of the disease itself, therapy and associated immobility. Peripheral neuropathy (PNP), loss of balance control and weakness not only diminishes patients' quality of life (QOL), it can also affect planning and the dosage of therapy. Exercise may enable patients to reverse these declines, improving their performance level and QOL. **PATIENTS AND METHODS:** We carried out a randomized, controlled trial, assigning 61 lymphoma patients either to a control group (CG; N=31) or to a 36-week intervention (IG; N=30), consisting of sensorimotor-, endurance- and strength training twice a week. Primary end point was QOL; secondary end points included movement coordination, endurance, strength and therapy-induced side-effects. **RESULTS:** Intergroup comparison revealed improved QOL- ( $\Delta T1-T0$ ;  $P=0.03$ ) and PNP-related deep sensitivity in the IG: 87.5% were able to reduce the symptom, compared with 0% in the CG ( $P<0.001$ ). Significant differences in the change of balance control could be found between the groups, with the IG improving while the CG steadily declined (monopodal static  $\Delta T3-T0$ ;  $P=0.03$ ; dynamic  $\Delta T3-T0$ ;  $P=0.007$ ; perturbed mono- $\Delta T3-T0$ ;  $P=0.009$  and bipedal  $\Delta T3-T0$ ;  $P=0.006$ ), failed attempts (monopodal static  $\Delta T3-T0$ ;  $P=0.02$ , dynamic  $\Delta T3-T0$ ;  $P<0.001$  and perturbed  $\Delta T3-T0$ ;  $P=0.006$ ) and improved time to regain balance ( $\Delta T3-T0$ ;  $P=0.04$ ). Moreover, the change in the aerobic performance level ( $\Delta T3-T0$ ;  $P=0.05$ ) and additional amount of exercise carried out per week [metabolic equivalent (MET);  $P=0.02$ ] differed significantly across groups. **CONCLUSIONS:** Exercise, especially sensorimotor training, is a feasible and promising method to support cancer patients during therapy. It improves patients QOL, reduces restrictions from side-effects such as PNP and improves patients' balance control, physical performance level and mobility.

**INSPIREHEALTH'S INTERPRETATION:** To the authors' knowledge, this was the first study to directly measure the effects of exercise in people with therapy-induced peripheral neuropathy. Sixty-one subjects with lymphoma were randomized into either the intervention group or the control group. The benefit of this type of study, a randomized controlled trial (RCT), is that its results can imply causation – differences between the control and intervention groups are likely due to the intervention. In this study, both groups received standard clinical care including physiotherapy. Additionally, the intervention group participated in a one hour supervised exercise class twice a week for 36 weeks. The class included aerobic (cardiovascular), sensorimotor (balance and coordination), and strength training. Following 36 weeks of training, 7 subjects in the intervention group had reduced peripheral neuropathy symptoms compared to 0 in the control group.

All subjects who attended the exercise classes were able to tolerate a small physical perturbation (2.5 cm horizontal movement of the surface they balanced on) during a single leg balance test while more than half of the control subjects were unable to maintain their balance. Balance and coordination exercises may stimulate positive changes in the nervous system to partially reverse some of the effects of chemotherapy induced neuropathy. The exercise program may also have promoted participants to increase their physical activity outside of the intervention, although the reason for this effect was not stated. While this study provides evidence about the positive effects of exercise on therapy-related side-effects in people living with lymphoma, it is currently a one-of-a-kind RCT and further research is needed to determine the full range of benefits exercise can offer this population. This study adds to the growing evidence of the benefits of exercise during and after cancer treatment.

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## PALLIATIVE CARE

Shin, J and J. Temel.

### Integrating Palliative Care: When and How?

*Curr Opin Pulm Med.* 2013 Jul; 194: 344-349.

**PURPOSE OF REVIEW:** Lung cancer is the leading cause of cancer mortality in men and women. Most patients present with advanced disease and face significant morbidity, with many reporting distressing symptoms throughout the course of their illness. The purpose of this review is to highlight the recent studies that support the integration of early palliative care into the standard oncology care of patients with advanced lung cancer. **RECENT FINDINGS:** Historically, palliative care was provided predominantly as a hospital-based consultation service; however, recent data support an outpatient delivery model of early palliative care alongside standard oncology care. In two randomized controlled trials, patients with advanced cancer who were assigned to early palliative care reported improved quality of life and mood. Numerous organizations have published guidelines to support the integration of palliative care into the routine care of patients with lung cancer. **SUMMARY:** Palliative care is appropriate for patients at any point in a serious illness. Unlike hospice, palliative care is not limited by prognosis and may be provided at the same time as disease-directed therapies. There is strong evidence underscoring the importance of integrating palliative care across the trajectory of lung cancer. The primary oncology team should routinely assess for pain and other symptoms, and regularly inquire about a patient's understanding of his disease and his goals of care. Specialty palliative care

can provide an extra layer of support for patients with lung cancer and their families by helping with more challenging symptom management, psychosocial support, complex decision-making, advance care planning, and transitions in care.

**INSPIREHEALTH'S INTERPRETATION:** For many patients and health care practitioners the term palliative care is synonymous with end-of-life care in a community-based or hospital-based hospice. Indeed, the old model of palliative care generally referred to providing symptom management in the final days or weeks of life and there is often fear that by exploring the concept of palliative care we are “giving up” or “losing hope”. The new model of palliative care exemplifies whole person care and the need to preserve hope throughout the illness trajectory. In 1998, the World Health Organization defined palliative care as “An approach that improves the quality of life of patients and their families facing the problems associated with life-threatening illness, through the prevention and relief of suffering by means of early identification and impeccable assessment and treatment of pain and other problems physical, psychosocial and spiritual.” In the new model, palliative care is incorporated throughout the course of serious chronic illness, alongside therapies that are specifically disease-directed.

In addition to discussion of symptoms and disease status (which are normally covered in depth during oncology visits), palliative care visits address decision-making, coping strategies, goals of care, and psychosocial issues. In this article, the authors summarize the results of 2 randomized controlled trials evaluating the effects of adding early palliative care on quality of life (QOL), mood, and survival in patients with advanced cancer receiving standard oncologic care. Palliative care in the first study consisted of psycho-educational and problem-solving sessions with a palliative care nurse followed by monthly telephone sessions. In the second study, patients explored decision-making, physical and psychosocial symptoms, and goals of care with a palliative care physician or nurse on a monthly basis. Both studies found that patients who received palliative care reported improved quality of life and better mood. Survival was also increased in the groups receiving palliative care, though not statistically so in one study. These data support the benefits of incorporating early palliative care into comprehensive cancer care. In the presence of life-limiting or life-threatening illness, a palliative approach fosters discussion of all aspects of care: physical, psychosocial, and spiritual. Most importantly, compared with standard oncologic care alone, those who received early palliative care lived longer and with improved QOL and better mood.

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## GREEN TEA

Trudel D, D.P. Labbé, I. Bairati, et al.

### Green Tea for Ovarian Cancer Prevention and Treatment: A Systematic Review of the In Vitro, In Vivo and Epidemiological Studies.

*Gynecol Oncol.* 2012 Sep; 126(3):491-498.

**OBJECTIVE:** This systematic review was conducted to examine the effects of green tea or green tea components on the prevention and progression of epithelial ovarian cancer. **METHODS:** Using Medline, EMBASE and SciVerse (last researched: July 2011), we retrieved 22 articles including 5 epidemiological studies. **RESULTS:** In epithelial ovarian cancer cell lines, green tea and green tea components have been shown to downregulate the expression of proteins involved in inflammation, cell signalization, cell motility and angiogenesis. Green tea and green tea components would induce apoptosis and could potentiate the effects of cisplatin, a chemotherapeutic agent. In human observational studies, significant associations between green tea intake and both decreased ovarian cancer occurrence and better prognosis were reported. **CONCLUSIONS:** Available literature suggests potential molecular targets for green tea in ovarian cancer treatment and also provides data supporting the clinical evaluation of the role of green tea or green tea components in ovarian cancer prevention and treatment.

**INSPIREHEALTH'S INTERPRETATION:** This article reviewed studies that have been published on the effects of green tea on epithelial ovarian cancer (EOC) cells in-vitro, as well as studies that investigated relationships between green tea consumption and EOC occurrence. This review is important because it investigates the effects on just one type of cancer. The National Cancer Institute determined that over 1000 phytochemicals (plant based compounds) possessing anticancer properties exist, including green tea catechins. In particular, the catechin epigallocatechin gallate (EGCG) is the most abundant catechin in green tea and is thought to be responsible for most of green tea's benefits. In vitro studies have shown that adding catechins and/or green tea to EOC cells inhibits cancer growth, and can alter gene expression such that inflammation and new blood vessel formation are curtailed. Studies have also found catechins to impair migration of EOC cells, which could impair metastatic processes.

EGCG also increased the potency of cisplatin (a chemotherapy drug) when added four hours after administration of the drug. Only one ‘whole organism’ (in vivo) study was published when this review was compiled. Researchers measured a 60% reduction in tumour size of human ovarian cells that had been injected into mice that drank green tea compared to mice that only drank water. Retrospective population studies on the effects of green tea and EOC in humans are difficult to assess because the concentrations of cancer-inhibiting compounds in tea vary depending on total mass of green tea used per batch, volume of water in each pot, total steeping time, and type of green tea. Despite these limitations, current data from several observational studies show that green tea intake is associated with a reduction in EOC occurrence.

## MULTIVITAMINS

Massa, J, E. Cho, E. J. Orav, et al.

### Long-Term use of Multivitamins and Risk of Colorectal Adenoma in Women.

*Br J Cancer.* 2014 Jan 7; 1101: 249-255.

**BACKGROUND:** Use of multivitamins may reduce the risk of colorectal adenoma, but the duration of use needed is unclear. **METHODS:** We prospectively examined years of multivitamin use and risk of colorectal adenoma among 43,641 women who had a first endoscopy between 1991 and 2007 in the Nurses' Health Study II. Use of multivitamins was assessed through biennial questionnaires since 1989. **RESULTS:** We documented 2277 colorectal adenoma cases. Reporting multivitamin use at any time during the study period compared with never reporting its use was associated with a reduced risk of adenoma (multivariable relative risk (RR)=0.86, 95% confidence interval (CI): 0.76-0.97). There was no clear trend with duration of multivitamin use: years of use compared with never use,  $\leq 4$  years (RR=0.84, 95% CI: 0.74-0.96), 5-9 years (RR=0.89, 95% CI: 0.77, 1.02), 10-14 years (RR=0.86, 95% CI: 0.74, 1.01), 15-19 years (RR=0.85, 95% CI: 0.70, 1.02), and 20-26 years (RR=0.80, 95% CI: 0.64, 1.01); (P trend=0.87). The strongest associations (years of use vs never user) were for size of adenoma: large ( $\geq 1$  cm)  $<4$  years (RR=0.75, 95% CI: 0.58-0.96) and in alcohol users ( $\geq 1.4$  g per day) 20-26 years (RR=0.67, 95% CI: 0.49-0.91). **CONCLUSION:** Our findings suggest that use of multivitamins is associated with lower risk of colorectal adenoma, even with relatively short duration of use.

**INSPIREHEALTH'S INTERPRETATION:** This study examined the correlation between multivitamin use and the risk of colorectal adenoma among women in the Nurses' Health Study II. The Nurses' Health Study II began in 1989 with a lifestyle and medical questionnaire. Every 2 years after that, the subjects filled out follow-up questionnaires. Among other things, these follow-up questionnaires inquired about dietary patterns, and alcohol consumption. For this particular study, 43,641 subjects were eligible, and of those, 2,277 developed colorectal adenoma. Compared with subjects who never used multivitamins, those who used them for at least one year had a 14% reduced risk of developing a colorectal adenoma.

Interestingly, there was no statistical pattern for duration of multivitamin use – using multivitamins for 20 years did not provide a greater risk reduction than using them for 4 years. In subjects who consumed alcohol on a daily basis, taking a multivitamin reduced their risk of colorectal adenoma by 33% compared to those who drank alcohol and did not take a multivitamin. The authors propose that this could be because alcohol consumption reduces folate levels and low folate levels are associated with increased risk of colorectal cancer. The take home message from this study is that taking a quality multivitamin, even for a relatively short period of time is associated with reduced risk of colorectal adenoma, and especially for those who consume alcohol daily.

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## MELATONIN

Wang YM, B.Z. Jin , F. Ai, et al.

### The Efficacy and Safety of Melatonin in Concurrent Chemotherapy or Radiotherapy for Solid Tumors: A Meta-Analysis of Randomized Controlled Trials.

*Cancer Chemother Pharmacol.* 2012 May; 69(5):1213-1220.

**BACKGROUND:** Recently, melatonin has been associated with cancer both in vitro and in vivo. However, the value of melatonin in the treatment of cancer remains disputable. Hence, we performed a systematic review of randomized controlled trials (RCTs) of melatonin in solid tumor cancer patients and observed its effect on tumor remission, 1-year survival, and side effects due to radiochemotherapy. **METHODS:** An electronic search was conducted using the databases Pubmed, Medline, EMBASE, Cochrane library, and CNKI, from inception to November 2011. Trials using melatonin as adjunct treatment concurrent with chemotherapy or radiotherapy for cancer were included. Pooled relative risk (RR) for the tumor remission, 1-year survival, and radiochemotherapy-related side effects were calculated using the software Revman 5.0. **RESULTS:** The search strategy identified 8 eligible RCTs (n = 761), all of which studied solid tumor cancers. The dosage of melatonin used in the 8 included RCTs was 20 mg orally, once a day. Melatonin significantly improved the complete and partial remission (16.5 vs. 32.6%; RR = 1.95, 95% CI, 1.49-2.54; P < 0.00001) as well as 1-year survival rate (28.4 vs. 52.2%; RR = 1.90; 95% CI, 1.28-2.83; P = 0.001), and dramatically decreased radiochemotherapy-related side effects including thrombocytopenia (19.7 vs. 2.2%; RR = 0.13; 95% CI, 0.06-0.28; P < 0.00001), neurotoxicity (15.2 vs. 2.5%; RR = 0.19; 95% CI, 0.09-0.40; P < 0.0001), and fatigue (49.1 vs. 17.2%; RR = 0.37; 95% CI, 0.28-0.48; P < 0.00001). Effects were consistent across different types of cancer. No severe adverse events were reported. **CONCLUSIONS:** Melatonin as an adjuvant therapy for cancer led to substantial improvements in tumor remission, 1-year survival, and alleviation of radiochemotherapy-related side effects.

**INSPIREHEALTH'S INTERPRETATION:** There is significant interest in the role that the antioxidant and immunomodulatory hormone melatonin may have in cancer treatment, particularly as an adjuvant in addition to chemotherapy and radiation treatment. Although some studies have shown that melatonin can prevent tumour initiation, promotion and progression, there

are also concerns that as an antioxidant, it may reduce the effectiveness of chemotherapy and/or radiation. In this 2011 meta-analysis, Wang et al. included only randomized controlled trials (RCTs) whose subjects had pathology confirmed malignancy, and that included data on tumour remission or 1 year survival, and chemotherapy side effects. In all studies, participants were randomized to receive standard chemotherapy/radiation therapy plus 20mg melatonin (intervention group) or chemotherapy/radiation therapy alone (control group).

A relatively small (for a meta-analysis) total sample of 761 participants was analyzed and although the studies were RCTs, none used “placebo melatonin” for their control groups. Therefore study participants weren’t blinded to their treatment and results may have been affected by the “placebo effect”. Of the 8 trials included, 7 were performed in Italy (6 at the same centre, with the same lead author) and 1 was performed in China. Overall, the meta-analysis showed that subjects who took 20mg of melatonin per day in addition to standard treatment had improved 1-year survival rate, tumour remission, and fewer radiochemotherapy-related side effects such as fatigue, low platelets and nerve toxicity. Although the results of this well designed meta-analysis support the use of melatonin in the setting of chemotherapy and/or radiation therapy, the noted limitations of the studies included may decrease the validity and weight of the findings. The authors conclude that larger, international, multicenter randomized placebo controlled trials are needed to more certainly determine melatonin’s efficacy and safety before clinicians can confidently and routinely add it to a chemo-radiation cancer treatment regimen.

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