



RESEARCH UPDATES MARCH 2014

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FOR THE LATEST IN WORLDWIDE INTEGRATIVE CANCER CARE

IN THIS ISSUE: Our new format introduced last month met with success and positive feedback, so we are going to continue with the expanded InspireHealth's Interpretation section. This month features some very interesting articles: Ko and colleagues found that women who consumed soy-containing foods on a regular basis were less likely to develop gastric cancer than women who ate less of those foods. Interestingly, the same association was not seen in men. Sieri et al. examined the relationships between glycemic index and glycemic load on breast cancer risk in a Mediterranean population. They found that a high glycemic load diet is associated with the development of breast cancer. Timperi and associates observed that breast cancer survivors who worked for at least a few hours per week had higher perceived quality of life and functional well-being than those who did not work at all. It is important to note that this is not a causal relationship. Kim and colleagues noted improvements in fatigue, anxiety, quality of life, and emotional faculties in women with breast cancer following a broad intervention that included aspects of meditation, physical activity, and positive thinking. Vincent and associates examined the cardio-protective role of dietary and supplemental antioxidants during chemotherapy treatment. Though the conclusion is that more research is needed, this was a very informative overview of the current knowledge of antioxidants and cardiotoxicity. In their meta-analysis, Bristow et al. found that over a four year period, calcium supplements administered without vitamin D did not have an effect on cancer risk.

NUTRITION

Ko, KP, S. K. Park, J. J. Yang, et al.

Intake of Soy Products and Other Foods and Gastric Cancer Risk: A Prospective Study.

Journal of Epidemiology. 2013 Sep 5; 235: 337-343.

BACKGROUND: Gastric cancer, the most common cancer in the world, is affected by some foods or food groups. We examined the relationship between dietary intake and stomach cancer risk in the Korean Multi-Center Cancer Cohort (KMCC).

METHODS: The KMCC included 19 688 Korean men and women who were enrolled from 1993 to 2004. Of those subjects, 9724 completed a brief 14-food frequency questionnaire at baseline. Through record linkage with the Korean Central Cancer Registry and National Death Certificate databases, we documented 166 gastric cancer cases as of December 31, 2008. Cox proportional hazard models were used to estimate relative risks (RRs) and 95% CIs. **RESULTS:** Frequent intake of soybean/tofu was significantly associated with reduced risk of gastric cancer, after adjustment for age, sex, cigarette smoking, body mass index, alcohol consumption, and area of residence (P for trend = 0.036). We found a significant inverse association between soybean/tofu intake and gastric cancer risk among women (RR = 0.41, 95% CI: 0.22-0.78). Men with a high soybean/tofu intake had a lower risk of gastric cancer, but the reduction was not statistically significant (RR = 0.77, 95% CI: 0.52-1.13). There was no interaction between soybean/tofu intake and cigarette smoking in relation to gastric cancer risk (P for interaction = 0.268). **CONCLUSIONS:** Frequent soybean/tofu intake was associated with lower risk of gastric cancer.

INSPIREHEALTH'S INTERPRETATION: This was a well-designed, prospective Korean study examining the association between soy food intake and gastric cancer risk. A food frequency questionnaire was used to quantify the amount and type of specific soy-containing foods in each subject's diet. Many studies that use a food frequency questionnaire are retrospective in nature; participants are asked about their eating habits from a previous time period, sometimes years before the questionnaire is administered. As can be expected, this methodology leaves a lot of room for error and reporting bias – a misrepresentation of the foods actually eaten during the time period in question.

The current study was prospective in nature; subjects filled out the questionnaire as they ate. This method is much more reliable because memory is taken out of the equation. Another benefit of the prospective design is that all subjects began the study without cancer and were followed for an average of 8.5 years. Female participants with high levels of soybean/tofu intake

were 59% less likely to develop gastric cancer over the course of the study compared to female participants who had low intake levels. Interestingly, the same relationship was not seen in male participants. A possible reason for this is the estrogen-like activity of phytoestrogens in soy-containing foods. Phytoestrogens work in the human body like endogenous estrogen does, however, they are not as potent. In people with high estrogen levels, phytoestrogens will compete for binding sites with endogenous estrogen and as a result, lower the overall estrogenic activity in the body. In people with very low or deficient estrogen levels, phytoestrogens will attach to the open binding sites and increase the overall estrogenic activity. In women, both of these scenarios are beneficial because estrogen levels move towards or maintain the normal physiological range. However, because men normally have low circulating estrogen levels, dietary phytoestrogens will only act to increase overall estrogenic activity. In men, increasing estrogenic activity doesn't provide the same benefit as it does to women. It is important to note that soy-containing foods did not have a negative effect on the men in the study, their consumption simply did not result in the benefits women received.

NUTRITION

Sieri, S, V. Pala, F. Brighenti, et al.

High Glycemic Diet and Breast Cancer Occurrence in the Italian EPIC Cohort.

Nutrition Metabolism & Cardiovascular Diseases. 2013 Jul; 237: 628-634.

BACKGROUND AND AIMS: There are theoretical reasons for suspecting that a high glycemic index (GI) or glycemic load (GL) diet may increase breast cancer risk, perhaps via an effect on the insulin-like growth factor (IGF) axis. However observational studies have produced inconsistent findings and it is controversial whether breast cancer risk is influenced by the carbohydrate characteristics of the diet. We prospectively investigated the association between dietary GI and GL and breast cancer in the Italian section of the European Prospective Investigation into Cancer and Nutrition (EPIC). **METHODS AND RESULTS:** Women were recruited from 1993 to 1998 at five centers: Varese and Turin (north Italy), Florence (central Italy), and Ragusa and Naples (south Italy). Participants completed validated food frequency questionnaires from which GI and GL were estimated. Multivariable Cox proportional hazard regression models quantified the association between breast cancer risk and total carbohydrate intake, GI, and GL. During 11 years of follow-up, 879 breast cancer (797 invasive and 82 in situ) cases were identified. High dietary GL was associated with increased breast cancer risk (RR 1.45, 95% CI = 1.06-1.99; highest vs. lowest quintile; p-trend 0.029), whereas dietary GI and total carbohydrate had no influence. The association was not modified by menopausal status or body mass index. **CONCLUSION:** Our data indicate that, in a Mediterranean population characterized by traditionally high and varied carbohydrate intake, a diet high in GL plays a role in the development of breast cancer.

INSPIREHEALTH'S INTERPRETATION: Concerns that a carbohydrate rich diet may increase breast cancer risk have been present since the 1990's, however, data from observational studies have produced conflicting results. This well designed and very large European Prospective Investigation into Cancer and Nutrition (EPIC) study involved 10 European countries and collected data from 1993-1998. Over 47,000 volunteers were recruited for EPIC Italy, the Italian section of the EPIC trial. Baseline information regarding lifestyle, diet, body habitus and lab values was obtained and participants followed for the development of cancer. Food frequency questionnaires were used to gather dietary patterns. Because dietary carbohydrates have such variable effects on blood glucose levels, two different indices have been developed for quantification of blood glucose changes and classification of food. Glycemic Index (GI) measures how quickly blood sugar (glucose) levels rise after eating a particular food. Glycemic Load (GL) estimates the amount blood glucose will rise after eating a certain food. GL is calculated by multiplying the amount of carbohydrate in the serving of food by its GI and then dividing by 100. Watermelon, for example, has a high GI and a low GL because it contains such a high percentage of water, and a low total amount of carbohydrate. Typical high GI foods include white bread, white rice, many breakfast cereals, and simple sugars (glucose, fructose, and maltose). Low GI foods include beans, nuts, seeds, most vegetables and many fruits. To further clarify: one piece of white bread has a high GI and will raise your blood glucose quickly, eating 4 pieces of white bread will both raise your blood glucose quickly and by a large amount (high GL).

The authors found that a high dietary GL (but not high GI or total carbohydrate intake) was associated with increased risk of breast cancer. This association remained even when the results were statistically adjusted to control for potential confounding factors such as smoking status, alcohol intake, body mass index, and physical activity. In particular, this adverse association of GL with breast cancer risk was present in normal and overweight women and in pre- and post-menopausal women. In summary, consuming large quantities of high glycemic index foods (a high GL diet) is associated with increased breast cancer risk. The delicious and nutritious whole food diet recommended by InspireHealth nutritionists and practitioners provides healthy carbohydrate quality and quantity.

QUALITY OF LIFE

Timperi, AW, I. J. Ergas, D. H. Rehkopf, et al.

Employment Status and Quality of Life in Recently Diagnosed Breast Cancer Survivors.

Psychooncology. 2013 Jun; 22(6): 1411-1420.

BACKGROUND: Breast cancer survivors are less likely to be employed than similar healthy women, yet effects of employment on the well being of survivors are largely unknown. In a prospective cohort study of 2013 women diagnosed from 2006 to 2011 with invasive breast cancer in Kaiser Permanente Northern California, we describe associations between hours worked per week and change in employment with quality of life (QOL) from diagnosis through active treatment. **METHODS:** Participants completed information on employment status and QOL approximately 2 and 8 months post-diagnosis. QOL was assessed by the Functional Assessment of Cancer Therapy--Breast Cancer. Multivariable linear regression models were adjusted for potential confounders including demographic, diagnostic, and medical care factors to examine associations between employment and QOL. **RESULTS:** At baseline, overall well being was higher for women who worked at least some hours per week compared with women who were not working. Women working 1-19 h/week at baseline also had higher functional well being compared with women who were not working. There was a significant, positive association between hours worked per week and physical and social well being. At the 6-month follow-up, women working at least 20 h/week had higher physical and functional well being than those who were not working. Lower scores for physical and functional well being were observed among women who stopped working during the 6-month follow-up period. **CONCLUSIONS:** Continuing to work after a breast cancer diagnosis may be beneficial to multiple areas of QOL. Strategies to help women continue working through treatment should be explored.

INSPIREHEALTH'S INTERPRETATION: This study investigated possible associations between employment status and quality of life following a cancer diagnosis. Women who were recently diagnosed with breast cancer filled out two questionnaires at approximately 2 months and 8 months post-diagnosis. The questionnaires assessed the number of hours worked per week, if at all, as well as five quality of life variables: physical well-being, functional well-being, emotional well-being, social/family well-being, and breast cancer specific concerns. Women who worked at least a few hours per week generally had greater overall well-being than women who did not. Interestingly, working greater than 20 hours per week was not associated with high functional well-being. Women who worked 1-19 hours per week had the greatest breast cancer concern scores yet reported high physical well-being. These data suggest that working some hours may be beneficial but too much can be overwhelming. The authors suggest that the workplace may provide enhanced social support through colleagues and friends and thus enhance social well-being.

While women with a better prognosis may be expected to work more often, this study provides some evidence for a therapeutic effect from employment. However, these results should be interpreted with caution since changes in employment status were not considered. For example, women who had reduced hours after 6 months compared to their initial workload at baseline reported lower physical and functional well-being compared to when they were working more hours. Additionally, an observational study of this design cannot determine causality, which is whether a change in well-being caused a change in employment status or vice versa. Other variables that were not measured (e.g., household income, familial support, physical activity) may also affect well-being and employment status.

QUALITY OF LIFE

Kim, YH, H. J. Kim, S. D. Ahn, et al.

Effects of Meditation on Anxiety, Depression, Fatigue, and Quality of Life of Women Undergoing Radiation Therapy for Breast Cancer.

Complement Ther Med. 2013 Aug; 21(4): 379-387.

OBJECTIVE: To investigate the effects of meditation on anxiety, depression, fatigue, and quality of life in women who are receiving radiation therapy for breast cancer. **DESIGN:** Randomized, non-program controlled, parallel intervention clinical trial. **SETTING:** The ASAN Cancer Center located in Seoul, Korea. **INTERVENTION:** The subjects of this study included 102 female breast cancer patients who had undergone breast-conserving surgery; these female patients were randomized into equally assigned meditation control groups, with each group consisting of 51 patients. The test group received a total of 12 meditation therapy sessions during their 6-week radiation therapy period, and the control group underwent only a conventional radiation therapy. **OUTCOME:** The tools used to evaluate the effects of meditation were Hospital Anxiety and Depression scale, Revised Piper Fatigue scale, and European Organization for Research and Treatment of Cancer-Quality of Life Core-30. The results were analyzed based on the principles of intention-to-treat analysis, and, as a corollary analysis, per-protocol analysis was conducted. **RESULTS:** The breast cancer patients who received meditation therapy compared with the non-intervention group saw improvements in reduction of anxiety ($p=.032$), fatigue ($p=.030$), and improvement in global quality of life ($p=.028$).

CONCLUSIONS: Based on the results of this study, an affirmation can be made that meditation can be used as a non-invasive intervention treatment for improving fatigue, anxiety, quality of life, and emotional faculties of women with breast cancer.

INSPIREHEALTH'S INTERPRETATION: This interesting Korean study examined the effects of a technique called Brain Wave Vibration Meditation on anxiety, depression, fatigue, and quality of life. The authors state that Brain Wave Vibration Meditation is based on the Korean traditional exercise "Danhak." Neither the meditation technique nor the Danhak technique is explained in explicit detail in the article. Of the 102 female subjects undergoing radiotherapy for breast cancer, half were randomized into the control group and half into the intervention group. The intervention group attended two 60 minute classes per week which included a combination of the following: physical movement, positive self-talk and mental encouragement, visualizations, relieving negative thoughts, and music. Each week, the class was different. Outcome measures were evaluated using three separate questionnaires. By including so many different practices in the 'meditation' class, and by changing the class each week, it is impossible to know which practices were associated with the resulting benefits. InspireHealth supports meditation, physical activity, music, and positive thinking, and there certainly is research that supports the benefit of these practices. This study, however, was too broad in its intervention to confidently conclude that meditation improves fatigue, anxiety, quality of life, and emotional faculties of women with breast cancer.

ANTIOXIDANTS

Vincent, DT, Y. F. Ibrahim, M. G. Espey, et al.

The Role of Antioxidants in the Era of Cardio-Oncology.

Cancer Chemotherapy & Pharmacology. 2013 Dec; 726: 1157-1168.

Although most chemotherapeutic drugs have the potential to exert cardiotoxicity, these drugs have been chosen for use in cancer treatment because survival and curability benefits outweigh the risk of these complications. Anthracyclines, for example, are a powerful class of chemotherapeutic agents; however, their use is restricted by dose-related cardiotoxicity. Experimental evidence strongly supports the role of reactive oxygen species in this process, suggesting that antioxidants may be effective in protecting the heart from toxicity. Clinical use of antioxidants to protect the heart during anthracycline chemotherapy has been controversial due to the potential for reduced cytotoxic efficacy toward cancer cells. Results from randomized clinical trials addressing whether antioxidants either reduce the incidence of clinical heart failure among patients undergoing anthracycline-based chemotherapy or reduce the response rates to anthracycline-based chemotherapy have been unclear. While anthracyclines are by far the most well-studied antitumor agents with cardiotoxic properties, evidence now shows that reactive oxygen species may play roles in cardiotoxicity induced by other chemotherapeutic agents such as cyclophosphamide, cisplatin, 5-fluorouracil, and trastuzumab. Thus, in the new era of combination therapy and long-term survival of cancer patients, the use of antioxidants to support cancer therapy should be revisited.

INSPIREHEALTH'S INTERPRETATION: Many chemotherapeutic drugs have the potential to damage the heart by influencing heart rhythm or causing heart pumping problems; this has led many researchers to study ways to mitigate this serious complication. Anthracycline agents (eg. Doxorubicin or Adriamycin), for example, are powerful chemotherapeutic drugs, but their dose must be monitored carefully to lessen potential cardiotoxic effects. Although this toxicity is caused in part by reactive oxygen species (chemically unstable molecules containing oxygen that can damage cells), and could possibly be reduced by dietary or pharmacologic antioxidants, such compounds may also reduce the ability of chemotherapeutic drugs to cause cancer cell death. In other words, controversy exists because the mechanisms underlying chemotherapy's benefits and toxicities may be the same.

The authors of this review article summarize the need for cardiologists and oncologists to work collaboratively (a discipline they term cardio-oncology) to research optimal cancer treatments that minimize cardiotoxicity. They review current research into the mechanisms of cardiotoxicity by various chemotherapeutic agents and summarize human clinical trials using antioxidants such as N-acetylcysteine, L-carnitine, Coenzyme Q10, melatonin and a novel pharmaceutical dexrazoxane to protect against cardiotoxicity. Although some of these agents did reduce cardiotoxicity, many studies didn't collect data on tumour response rates between control (chemotherapy only) and intervention (chemotherapy + antioxidant) groups. For dexrazoxane, studies examining tumour response showed no significant difference between control and intervention groups in terms of overall survival. On the other hand, quality of life scores improved for those in the intervention groups and diminished efficacy of chemotherapy was not found. The authors also reviewed the results of a 250 subject Italian study (as discussed in our LIFE Program), that melatonin may have some promise when used together with chemotherapy, to both mitigate side effects such as cardiotoxicity and improve survival. In summary the authors state that larger multicenter trials must be designed to examine whether dietary or pharmacologic antioxidant therapy provides overall benefit during and after chemotherapy treatment.

CALCIUM

Bristow, SM, M. J. Bolland, G. S. MacLennan, et al.

Calcium Supplements and Cancer Risk: A Meta-Analysis of Randomised Controlled Trials.

Br J Nutr. 2013 Oct; 1108: 1384-1393.

Some evidence suggests that calcium (Ca) and vitamin D supplements affect cancer risk; however, it is uncertain whether the effects are due to Ca, vitamin D or the combination. We investigated the effect of Ca supplements without co-administered vitamin D on cancer risk. Medline, Embase and the Cochrane Central Register of Controlled Trials, reference lists of meta-analyses and two clinical trial registries were searched for randomised, placebo-controlled trials of Ca supplements (≥ 500 mg/d), with ≥ 100 participants and duration >1 year. The lead authors of eligible trials supplied data on cancer outcomes. Trial-level data were analysed using random-effects meta-analyses and patient-level data using Cox proportional hazards models. A total of sixteen trials were eligible, six had no data available, ten provided trial-level data (n 10,496, mean duration 3.9 years), and of these, four provided patient-level data (n 7221, median duration 3.5 years). In the meta-analysis of trial-level data, allocation to Ca did not alter the risk of total cancer (relative risk 0.95, 95% CI 0.76, 1.18, $P=0.63$), colorectal cancer (relative risk 1.38, 95% CI 0.89, 2.15, $P=0.15$), breast cancer (relative risk 1.01, 95% CI 0.64, 1.59, $P=0.97$) or cancer-related mortality (relative risk 0.96, 95% CI 0.74, 1.24, $P=0.75$), but reduced the risk of prostate cancer (relative risk 0.54, 95% CI 0.30, 0.96, $P=0.03$), although there were few events. The meta-analysis of patient-level data showed similar results, with no effect of Ca on the risk of total cancer (hazard ratio 1.07, 95% CI 0.89, 1.28, $P=0.50$). Ca supplements without co-administered vitamin D did not alter total cancer risk over 4 years, although the meta-analysis lacked power to detect very small effects, or those with a longer latency.

INSPIREHEALTH'S INTERPRETATION: The authors of this meta-analysis pooled data from 10 randomized placebo controlled trials involving 10,500 participants to examine whether calcium supplements without co-administered Vitamin D were associated with cancer risk. Though trials analyzed for this study provided cancer outcome data, they were typically designed to evaluate fracture outcomes (re: osteoporosis). Many studies have shown reduced cancer risk with calcium and/or Vitamin D making it difficult to determine if calcium supplements on their own can impact cancer risk. Results of the meta-analysis showed that calcium monotherapy (typical dose was 1000mg/d) neither increased nor decreased the risk of developing total cancer, colorectal cancer, breast cancer or cancer mortality. While there was a reduction in prostate cancer risk with calcium supplementation, the actual number of prostate cancer cases was small, making a robust association very difficult. The authors suggest that future trials examining calcium supplementation and cancer incidence would need to be very large and of longer duration for meaningful associations to be found. Until such time as we have better and more consistent evidence regarding calcium supplementation, it is reasonable to recommend that calcium be obtained from food sources such as beans, dark leafy greens, organic dairy products, and nuts and seeds.

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