



# RESEARCH UPDATES

For the latest in worldwide integrated cancer care

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**InspireHealth**  
INTEGRATED CANCER CARE

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*Research Updates* is produced once a month by InspireHealth to inform those interested of newly published articles in integrative cancer care. Authoritative articles are selected based on their evidence and their relevance to this area of medicine.

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## Breast

Lee, S-, J. H. Fowke, W. Lu, et al. **Cruciferous Vegetables, the GSTP1 Ile<sup>105</sup>Val Genetic Polymorphism, and Breast Cancer Risk.** *Am J Clin Nutr.* 2008 01 Mar; 87(3): 753-760. Background: Cruciferous vegetables are the primary source of isothiocyanates and other glucosinolate derivatives that are known to induce phase II detoxifying enzymes, including glutathione S-transferases (GSTs). Objective: We investigated the independent and combined effects of cruciferous vegetable intake and the GSTP1 Ile<sup>105</sup>Val genetic polymorphism on breast cancer risk. Design: Analyses included 3035 cases and 3037 population controls who were participating in the Shanghai Breast Cancer Study and for whom diet and genetic data were complete (87% of cases and 85% of controls). Results: With the use of multivariate logistic regression, the GSTP1 Val/Val genotype was significantly associated with greater breast cancer risk (OR = 1.50; 95% CI: 1.12, 1.99). The association was significantly greater in premenopausal women (OR = 1.69; 95% CI: 1.17, 2.43) than in postmenopausal women (OR = 1.20; 95% CI: 0.74, 1.92). Total cruciferous vegetable intake was not significantly associated with breast cancer risk, although subjects reporting greater turnip (P for trend < 0.001) and Chinese cabbage (P for trend = 0.049) intakes had a significantly lower postmenopausal breast cancer risk. Women with the GSTP1 Val/Val genotype and low cruciferous vegetable intake had a breast cancer risk 1.74-fold (95% CI: 1.13, 2.67) that of women with the Ile/Ile or Ile/Val genotype. This effect of low cruciferous vegetable intake and the Val/Val genotype was seen predominantly among premenopausal women (OR = 2.08; 95% CI = 1.20, 3.59). Conclusions: Cruciferous vegetable intake consistent with high isothiocyanate exposure may reduce breast cancer risk. Cruciferous vegetable intake also may ameliorate the effects of the GSTP1 genotype.

Abbas, S, J. Linseisen, T. Slanger, et al. **Serum 25-Hydroxyvitamin D and Risk of Post-Menopausal Breast Cancer - Results of a Large Case-Control Study.** *Carcinogenesis.* 2008 Jan; 29(1):93-99.

Various studies suggest that vitamin D may reduce breast cancer risk. Most studies assessed the effects of dietary intake only,

although endogenous production is an important source of vitamin D. Therefore, the measurement of serum 25-hydroxyvitamin D [25(OH)D] better indicates overall vitamin D status. To assess the association of 25(OH)D serum concentrations with post-menopausal breast cancer risk, we used a population-based case-control study in Germany, which recruited incident breast cancer patients aged 50-74 between 2002 and 2005. Information on sociodemographic and breast cancer risk factors was collected by personal interview. For this analysis, we included 1394 cases and 1365 controls, matched on year of birth and time of blood collection. Conditional logistic regression was used to calculate odds ratios (ORs) for breast cancer adjusted for potential confounders. Serum 25(OH)D concentration was significantly inversely associated with post-menopausal breast cancer risk. Compared with the lowest category (trend interaction < 0.0001). Our findings strongly suggest a protective effect for post-menopausal breast cancer through a better vitamin D supply as characterized by serum 25(OH)D measurement, with a stronger inverse association in women with low serum 25(OH)D concentrations (<50 nM).

Holick, CN, P. A. Newcomb, A. Trentham-Dietz, et al. **Physical Activity and Survival After Diagnosis of Invasive Breast Cancer.** *Cancer Epidemiology Biomarkers and Prevention.* 2008 01 Feb; 17(2): 379-386. Previous studies suggest that increased physical activity may lower the risk of breast cancer incidence, but less is known about whether levels of physical activity after breast cancer diagnosis can influence survival. We prospectively examined the relation between postdiagnosis recreational physical activity and risk of breast cancer death in women who had a previous invasive breast cancer diagnosed between 1988 and 2001 (at ages 20-79 years). All women completed a questionnaire on recent postdiagnosis physical activity and other lifestyle factors. Among 4,482 women without history of recurrence at the time of completing the questionnaire, 109 died from breast cancer within 6 years of enrollment. Physical activity was expressed as metabolic equivalent task-hours per week (MET-h/wk); hazard ratios (HR) and 95% confidence intervals (95% CI) were estimated using Cox proportional hazards regression. After adjusting for age at diagnosis, stage of disease, state of residence, interval

between diagnosis and physical activity assessment, body mass index, menopausal status, hormone therapy use, energy intake, education, family history of breast cancer, and treatment modality compared with women expending <2.8 MET-h/wk in physical activity, women who engaged in greater levels of activity had a significantly lower risk of dying from breast cancer (HR, 0.65; 95% CI, 0.39-1.08 for 2.8-7.9 MET-h/wk; HR, 0.59; 95% CI, 0.35-1.01 for 8.0-20.9 MET-h/wk; and HR, 0.51; 95% CI, 0.29-0.89 for [greater-than or equal to]21.0 MET-h/wk; P for trend = 0.05). Results were similar for overall survival (HR, 0.44; 95% CI, 0.32-0.60 for [greater-than or equal to]21.0 versus <2.8 MET-h/wk; P for trend <0.001) and were similar regardless of a woman's age, stage of disease, and body mass index. This study provides support for reduced overall mortality and mortality from breast cancer among women who engage in physical activity after breast cancer diagnosis.

## Prostate

Barnard, RJ **Prostate Cancer Prevention by Nutritional Means to Alleviate Metabolic Syndrome** *Am J Clin Nutr.* 2007 Sep; 863: s889-93.

In 1987 when Reaven introduced syndrome X (metabolic syndrome, or MS), we were studying skeletal muscle insulin resistance and found that when rodents were fed a high-fat, refined-sugar (HFS) diet, insulin resistance developed along with aspects of MS, including hyperinsulinemia, hypertension, hypertriglyceridemia, and obesity. MS was controlled in rodents by switching them to a low-fat, starch diet and was controlled in humans with a low-fat starch diet and daily exercise (Pritikin Program). Others reported inverse relations between serum insulin and sex hormone-binding globulin (SHBG). When subjects were placed on the Pritikin Program, insulin fell and SHBG rose and it was suggested that prostate cancer might also be an aspect of MS. A bioassay was developed with tumor cell lines grown in culture and stimulated with serum before and after a diet and exercise intervention. Diet and exercise altered serum factors that slowed the growth rate and induced apoptosis in androgen-dependent prostate cancer cells. Changes in serum with diet and exercise that might be important include reductions in insulin, estradiol, insulin-like growth factor-I (IGF-I), and free testosterone with increases in SHBG and IGF binding protein-1. Hyperinsulinemia stimulates liver production of IGF-I, plays a role in the promotion of prostate cancer, and thus is the cornerstone for both MS and prostate cancer. Adopting a low-fat starch diet with daily exercise controls MS and should reduce the risk of prostate cancer.

Stacewicz-Sapuntzakis, M, G. Borthakur, J. L. Burns and P. E. Bowen. **Correlations of Dietary Patterns with Prostate Health** *Molecular Nutrition & Food Research.* 2008 Jan; 521: 114-130. Both genetic and environmental influences may be involved in etiology of prostate health and prostate cancer. These include ethnic origin, family history, smoking, and diet. Adiposity and excess energy intake are potentially distinct risk factors and positive associations with prostate cancer risk for both were observed among case-control and cohort studies. Some epidemiological studies support an association between dietary fat, particularly saturated or animal fats, and prostate cancer risk. Of these, several suggest reduced risk with low-fat diets high in n-3 fatty acids and increased risk with high-fat diets rich in n-6 fatty acids. Others suggested association with higher meat intake, possibly due to heterocyclic amines and polycyclic aromatic hydrocarbons, produced during grilling or frying. Positive association of prostate cancer risk with dairy intake could involve alpha-methylacyl-CoA racemase activity (required for beta-oxidation of phytanic acid present in dairy products and red meat) or the suppression of vitamin D activity by calcium. Inverse associations were observed with dietary intake of plant foods. These include cereals, soy products, and fruit and vegetable

sources of carotenoids. Numerous plant constituents may act synergistically in the prevention and inhibition of prostate disorders. These diet-risk associations may lead to future individualized diet recommendations based upon genetic polymorphisms.

 Thank you to the **BC Foundation for Prostate Disease** for their generous support.  
[www.BCPROSTATECANCER.org](http://www.BCPROSTATECANCER.org)

## Skin

Gogas, H, M. Trakatelli, N. Dessypris, et al. **Melanoma Risk in Association with Serum Leptin Levels and Lifestyle Parameters: A Case-Control Study.** *Annals of Oncology.* 2008 Feb; 192: 384-389.

Background: Solar radiation has been identified as a principal factor for the causation of melanoma, whereas changing lifestyle patterns associated with obesity and diabetes might also contribute to the increasing incidence of the malignancy. No study has investigated the role of leptin, a hormone whose levels increase in obesity and which has also been related to cancer. Patients and methods: Fifty-five patients with incident melanomas and 165 age- and gender-matched healthy controls were interviewed on the basis of a questionnaire that covers phenotypic features, sociodemographic and medical history variables, lifestyle habits and frequency of consumption of major food groups. Anthropometrical measures were also recorded and blood samples were obtained for determination of serum leptin levels. Adjusted odds ratios (ORs) for melanoma risk were derived through multiple logistic regression analyses. Results: An excess melanoma risk was observed for sun sensitive individuals and those with high circulating levels of leptin (OR: 1.56, 95% confidence interval 1.07-2.28, P = 0.02), after controlling for obesity indices, diabetes mellitus and education. Increased physical exercise, lower alcohol consumption and plant food consumption seem to play a protective role against melanoma development. Conclusions: Melanoma risk was found to be positively associated with serum leptin levels and inversely with healthy lifestyle factors. The findings need to be confirmed in prospective studies.

## Lung

Yu, HM, Y. F. Liu, Y. F. Cheng, L. K. Hu and M. Hou. **Effects of Rhubarb Extract on Radiation Induced Lung Toxicity Via Decreasing Transforming Growth Factor-Beta-1 and Interleukin-6 in Lung Cancer Patients Treated with Radiotherapy.** *Lung Cancer.* 2008 Feb; 592: 219-226.

Background: Radiation induced lung toxicity (RILT) is the main adverse effect in the radiation therapy of lung cancer. However, the optimal management of RILT has not been defined. In this paper, we investigated the effects of rhubarb extract on RILT, pulmonary function (PF), transforming growth factor-beta-1 (TGF-beta1), and interleukin-6 (IL-6) in lung cancer patients treated with radiotherapy. Patients and methods: We conducted a randomized, double-blind, placebo-controlled trial. Eighty consecutive patients were randomly enrolled into two groups: trial group and control group. The trial group received three-dimensional conformal radiation therapy (3D-CRT) plus rhubarb (at a dose of 20 mg kg<sup>-1</sup> once a day) for 6 weeks. The control group received 3D-CRT plus a placebo containing starch for 6 weeks. Plasma TGF-beta1 and serum IL-6 were measured in all patients before, every 2 weeks during, and at 6 weeks after the completion of the treatment. RILT and PF were evaluated at 6 weeks and 6 months after the end of the treatment, respectively. The differences of TGF-beta1, IL-6, RILT, and PF between the two groups were analysed. Results: The incidence of RILT in the trial group was significantly lower than that in the control group at 6 weeks and 6 months after treatment (32.4% versus 56.7% at week 6, and 27.0% versus 52.8% at

month 6, both  $P < 0.05$ ). The plasma TGF-beta1 levels in the trial group were significantly lower than that in the control group during and after the treatment ( $P < 0.05$  or  $0.01$ , respectively). The serum IL-6 levels in the trial group were significantly lower than that in the control group during the treatment (all  $P < 0.01$ ). The forced vital capacity (FVC), forced expiratory volume at 1 s (FEV1) at 6 weeks and the diffusion capacity for carbon monoxide (DLCO) at 6 months in the trial group were significantly improved compared to the control group ( $P < 0.05$  or  $0.01$ , respectively). Conclusions: The rhubarb extract significantly attenuated RILT and improved PF, probably by decreasing the level of TGF-beta1 and IL-6. These results may be of value for the prophylaxis of RILT, but the exact mechanisms underlying these prophylactic effects remain to be further explored.

## Thyroid

Randi, G, M. Ferraroni, R. Talamini, et al. **Glycemic Index, Glycemic Load and Thyroid Cancer Risk.** *Annals of Oncology.* 2008 Feb; 192: 380-383.

Background: Risk of thyroid cancer has already been related to refined cereals and starch food, but the association has not been studied in terms of glycemic index (GI) and glycemic load (GL). Patients and methods: We analyzed data from a case-control study conducted in Italy from 1986 to 1992 and including 399 histologically confirmed and incident cases of thyroid cancer and 616 control subjects. Information on dietary habits was derived through a food-frequency questionnaire and multivariate odds ratios (ORs) for GI and GL levels were estimated with adjustment for age, education, sex, area of residence, history of diabetes, body mass index, smoking, alcohol consumption, intake of fruit and vegetables, and noncarbohydrate energy intake. Results: Compared with the lowest tertile, the ORs in subsequent tertiles were 1.68 and 1.73 for GI, and 1.76 and 2.17 for GL. The OR for highest tertile of GI compared with lowest one was 1.70 for papillary and 1.57 for follicular thyroid cancer. The ORs for GL were 2.17 for papillary and 3.33 for follicular thyroid cancer. Conclusion: Our study shows that high dietary levels of GI and GL are associated with thyroid cancer risk.

## Phytoestrogens

Cotterchio, M, B. A. Boucher, N. Kreiger, C. A. Mills and L. U. Thompson. **Dietary Phytoestrogen Intake - Lignans and Isoflavones - and Breast Cancer Risk (Canada).** *Cancer Causes and Control.* 2008 Apr; 193: 259-272.

Objective: To evaluate whether phytoestrogen intake is associated with reduced breast cancer risk, using a novel phytoestrogen database. Methods: Population-based breast cancer cases aged 25-74 years (diagnosed 2002-2003) were identified using Ontario Cancer Registry ( $n = 3,063$ ) and controls ( $n = 3,430$ ) were an age-stratified random sample of women identified through random digit dialing. An epidemiologic and Block food frequency questionnaire-expanded to include phytoestrogen-containing foods-was mailed to all subjects. The recently published Ontario phytoestrogen database was applied to FFQ responses to estimate intake. Multivariate logistic regression provided odds ratio (OR) estimates, while controlling for confounders. Results: Among all women, lignan intake was associated with a reduced breast cancer risk (Q5 vs. Q1 MVOR: 0.81, 95% CI: 0.65, 0.99); however, following stratification by BMI, this reduction in risk was statistically significant only among overweight (BMI > 25) women. Total phytoestrogen intake was also associated with a risk reduction among overweight women only. Among pre-menopausal women, total phytoestrogen intake was associated with a significant reduction in breast cancer risk among overweight women only (Q5 vs. Q1 MVOR: 0.51, 95% CI: 0.30, 0.87). Among post-menopausal women, no statistically significant association was observed between breast cancer risk and isoflavones or lignans. Conclusion:

Lignan intake may be associated with reduced breast cancer risk among pre-menopausal women, and our data suggest BMI modifies this association.

Wu, AH, M. C. Yu, C. C. Tseng and M. C. Pike. **Epidemiology of Soy Exposures and Breast Cancer Risk** *Br J Cancer.* 2008 Jan 15; 981: 9-14.

Most of the early studies published on soy and breast cancer were not designed to test the effect of soy; the assessment of soy intake was usually crude and few potential confounders were considered in the analysis. In this review, we focused on studies with relatively complete assessment of dietary soy exposure in the targeted populations and appropriate consideration for potential confounders in the statistical analysis of study data. Meta-analysis of the 8 (1 cohort, 7 case-control) studies conducted in high-soy-consuming Asians show a significant trend of decreasing risk with increasing soy food intake. Compared to the lowest level of soy food intake (or=20 mg isoflavones per day). In contrast, soy intake was unrelated to breast cancer risk in studies conducted in the 11 low-soy-consuming Western populations whose average highest and lowest soy isoflavone intake levels were around 0.8 and 0.15 mg per day, respectively. Thus, the evidence to date, based largely on case-control studies, suggest that soy food intake in the amount consumed in Asian populations may have protective effects against breast cancer.

## Antioxidants

Lin, LC, J. Que, K. L. Lin, H. W. Leung, C. L. Lu and C. H. Chang. **Effects of Zinc Supplementation on Clinical Outcomes in Patients Receiving Radiotherapy for Head and Neck Cancers: A Double-Blinded Randomized Study.** *Int J Radiat Oncol Biol Phys.* 2008 Feb 1; 702: 368-373.

PURPOSE: To evaluate the impact of zinc supplementation on the survival of patients after receiving radiotherapy for head and neck cancers. METHODS AND MATERIALS: Patients were randomly divided into two groups; experimental and control. Patients in the experimental group received a predetermined dose of a zinc supplement, and the control group, a placebo. The 50 patients in each group could be considered homogenous with respect to medical histories, tumor characteristics, and therapeutic details. RESULTS: Patients in both groups appeared to have similar results for 3-year overall, disease-free, and metastases-free survival rates ( $p = 0.19$ ,  $p = 0.54$ , and  $p = 0.35$ , respectively). However, patients in the experimental group had better 3-year local-free survival (LFS), although the difference was only marginal ( $p = 0.092$ ). Another difference was that patients in the experimental group with Stages III-IV disease had a much better 3-year LFS rate when they received concurrent chemoradiotherapy ( $p = 0.003$ ). CONCLUSIONS: One impact seen was that zinc supplementation improved LFS at 3 years after beginning treatment for patients with Stages III-IV disease. It is imperative that these patients be followed up for a longer period to draw a definite conclusion.

Moncayo, R, A. Kroiss, M. Oberwinkler, et al. **The Role of Selenium, Vitamin C, and Zinc in Benign Thyroid Diseases and of Selenium in Malignant Thyroid Diseases: Low Selenium Levels are found in Subacute and Silent Thyroiditis and in Papillary and Follicular Carcinoma.** *BMC Endocr Disord.* 2008 Jan 25; 82:

Background: Thyroid physiology is closely related to oxidative changes. The aim of this controlled study was to evaluate the levels of nutritional anti-oxidants such as vitamin C, zinc (Zn) and selenium (Se), and to investigate any association of them with parameters of thyroid function and pathology including benign and malignant thyroid diseases. Methods: This controlled evaluation of Se included a total of 1401 subjects (1186 adults and 215 children) distributed as follows: control group ( $n = 687$ ), benign thyroid disease (85 children and 465 adults); malignant thyroid disease (2 children and 79 adults). Clinical evaluation of patients with benign

thyroid disease included sonography, scintigraphy, as well as the determination of fT3, fT4, TSH, thyroid antibodies levels, Se, Zn, and vitamin C. Besides the routine oncological parameters (TG, TSH, fT4, ultrasound) Se was also determined in the cases of malignant disease. The local control groups for the evaluation of Se levels were taken from a general practice (WOMED) as well as from healthy active athletes. Blood samples were collected between 8:00 and 10:30 a.m. All patients lived in Innsbruck. Statistical analysis was done using SPSS 14.0. The Ho stated that there should be no differences in the levels of antioxidants between controls and thyroid disease patients. Results: Among the thyroid disease patients neither vitamin C, nor Zn nor Se correlated with any of the following parameters: age, sex, BMI, body weight, thyroid scintigraphy, ultrasound pattern, thyroid function, or thyroid antibodies. The proportion of patients with benign thyroid diseases having analyte concentrations below external reference cut off levels were 8.7% of cases for vitamin C; 7.8% for Zn, and 20.3% for Se. Low Se levels in the control group were found in 12%. Se levels were significantly decreased in cases of sub-acute and silent thyroiditis (66.4 +/- 23.1 mug/l and 59.3 +/- 20.1 mug/l, respectively) as well as in follicular and papillary thyroid carcinoma. The mean Se level in the control group was 90.5 +/- 20.8 mug/l. Conclusion: The Ho can be accepted for vitamin C and zinc levels whereas it has to be rejected for Se. Patients with benign or malignant thyroid diseases can present low Se levels as compared to controls. Low levels of vitamin C were found in all subgroups of patients. the current knowledge of the intake, bio-availability and metabolism of polyphenolics, their antioxidant effects, regulatory effects on signalling pathways, neuro-protective effects and regulatory effects on energy metabolism and gut health.

## Music

Ferrer, AJ **The Effect of Live Music on Decreasing Anxiety in Patients Undergoing Chemotherapy Treatment.** *J Music Ther.* 2007 443: 242-255.

The purpose of this study was to investigate the effects of familiar live music on the anxiety levels of patients undergoing chemotherapy treatment. Randomly selected patients were assigned to experimental (n = 25) and control (n = 25) conditions. Pre and posttests consisted of questionnaires and the recording of the patient's heart rate and blood pressures. Subjects in the experimental group received 20 minutes of familiar live music during their chemotherapy treatment. Subjects in the control group received standard chemotherapy. It was assumed that those patients receiving music intervention would: (a) lower their anxiety levels; (b) experience a decrease in heart rate and blood pressure; (c) improve their levels of negative reactions including fatigue, worry, and fear; and (d) improve their levels of positive reactions including comfort and relaxation. Results of the study showed statistically significant improvement for the experimental group on the measures of anxiety, fear, fatigue, relaxation, and diastolic blood pressure. No significant differences between groups were found for heart rate and systolic blood pressure. Descriptive values indicated that, on average, the experimental group was influenced positively by the music intervention, and participants improved their quality of life while undergoing chemotherapy treatment.

## CAM of the Month

Ingraham, BA, B. Bragdon and A. Nohe. **Molecular Basis of the Potential of Vitamin D to Prevent Cancer** *Current Medical Research & Opinion.* 2008 Jan; 241: 139-149.

OBJECTIVE: To review current research findings in cell biology, epidemiology, preclinical, and clinical trials on the protective effects of vitamin D against the development of cancers of the breast, colon, prostate, lung, and ovary. Current recommendations for optimal vitamin D status, the movement towards revision of standards, and reflections on healthy exposure to sunlight are also

reviewed. Search methodology: A literature search was conducted in April and updated in September 2007. The Medline and Web of Knowledge databases were searched for primary and review articles published between 1970 and 2007, using the search terms 'vitamin D', 'calcitriol', 'cancer', 'chemoprevention', 'nuclear receptor', 'vitamin D receptor', 'apoptosis', 'cell cycle', 'epidemiology', and 'cell adhesion molecule'. Articles that focused on epidemiological, preclinical, and clinical evidence for vitamin D's effects were selected and additional articles were obtained from reference lists of the retrieved articles. FINDINGS: An increasing body of research supports the hypothesis that the active form of vitamin D has significant, protective effects against the development of cancer. Epidemiological studies show an inverse association between sun exposure, serum levels of 25(OH)D, and intakes of vitamin D and risk of developing and/or surviving cancer. The protective effects of vitamin D result from its role as a nuclear transcription factor that regulates cell growth, differentiation, apoptosis and a wide range of cellular mechanisms central to the development of cancer. A significant number of individuals have serum vitamin D levels lower than what appears to protect against cancer, and the research community is currently revising the guidelines for optimal health. This will lead to improved public health policies and to reduced risk of cancer. CONCLUSIONS: Research strongly supports the view that efforts to improve vitamin D status would have significant protective effects against the development of cancer. The clinical research community is currently revising recommendations for optimal serum levels and for sensible levels of sun exposure, to levels greater than previously thought. Currently, most experts in the field believe that intakes of between 1000 and 4000 IU will lead to a more healthy level of serum 25(OH)D, at approximately 75 nmol/L that will offer significant protection effects against cancers of the breast, colon, prostate, ovary, lungs, and pancreas. The first randomized trial has shown significant protection against breast cancer, and other clinical trials will follow and ultimately lead to improved public health policies and significantly fewer cancers.

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