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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**


BACKGROUND: Reactive oxygen species (ROS) such as superoxide anion, hydrogen peroxide (H2O2), hydroxyl radical have been implicated in pathogenesis of various diseases including cancer and metastasis. Tamoxifen (TAM) is a non-steroidal anti-estrogen drug most widely used as an adjuvant hormonal therapy in breast cancer. TAM also has estrogenic activity on liver and endometrium causing severe oxidative stress and hypertriglyceridemia. Coenzyme Q(10) (CoQ(10)), Niacin and Riboflavin are well-known potent antioxidants and protective agents against many diseases including cancer. In this context, this study was undertaken to find if co-administration of CoQ(10), Niacin and Riboflavin along with TAM could augment the antioxidant (AO) status in postmenopausal women with breast cancer.

METHODS: The vitamin supplementation with Tamoxifen was given for a period of 90 days. Blood samples were collected at the base line, 45th and 90th day during the course of treatment. Plasma lipids, lipid peroxides and various circulating enzymatic and non-enzymatic antioxidants were estimated in 78 untreated, sole TAM treated and combinatorial treated group along with 46 age- and sex-matched controls.

RESULTS: Enhanced oxidative stress as evidenced by increased lipids and lipid peroxides with decreased AO levels in untreated breast cancer patients was observed. Adjuvant TAM-treated group had a limited impact on the increased oxidative stress with decreased AO status. Severe hypertriglyceridemia was observed in TAM-treated group when compared to untreated and control subjects. Combinatorial therapy (CT) of CoQ(10), Niacin and Riboflavin along with TAM decreased the oxidative stress and increased the AO status.

CONCLUSION: The antioxidant defense system is compromised in breast cancer patients. There is a shift in the oxidant / antioxidant balance in favor of lipid peroxidation (LPO), which could lead to tumour promotion observed in the disease. CT of CoQ(10), Niacin and Riboflavin along with TAM significantly increased the AO status, while decreasing lipid and lipid peroxides. The results suggest the necessity of therapeutic co-administration of antioxidants along with conventional drug to such patients. However, due to limited number of cases included in this study, more studies may be required to substantiate the results and arrive at a definitive conclusion, in terms of safety and efficacy of adding an AO therapy in treatment of breast cancer.


Tumour angiogenesis is a complex mechanism consisting of multi-step events including secretion or activation of angiogenic factors by tumour cells, activation of proteolytic enzymes, proliferation, migration and differentiation of endothelial cells. Both primary and metastatic tumours in the breast are dependent on angiogenesis. In the present study, 84 breast cancer patients were randomized to receive a daily supplement of CoQ10 100 mg, riboflavin 10 mg and niacin 50 mg (CoRN), one dosage per day along with tamoxifen (TAM) 10 mg twice a day. Serum pro-angiogenic levels were elevated in untreated breast cancer patients (Group II) and their levels were found to be reduced in breast cancer patients undergoing TAM therapy for more than 1 year (Group III). When these group III breast cancer patients were supplemented with CoRN for 45 days (Group IV) and 90 days (Group V) along with TAM, a further significant reduction in pro-angiogenic marker levels were observed. Supplemeting CoRN to breast cancer patients has found to decrease the levels of pro-angiogenic factors and increase the levels of anti-angiogenic factors. A reduction in pro-angiogenic marker levels attributes to reduction in tumour burden and may suggest good prognosis and efficacy of the treatment, and might even offer protection from cancer metastases and recurrence.

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**Prostate**

Simko J, Shinozaka K, Haqq CM, Carroll PR. Changes in Prostate Gene Expression in Men Undergoing an Intensive Nutrition and Lifestyle Intervention. Proc Natl Acad Sci U S A. 2008 Jun 17; 105(24): 8369-8374. Epidemiological and prospective studies indicate that comprehensive lifestyle changes may modify the progression of prostate cancer. However, the molecular mechanisms by which improvements in diet and lifestyle might affect the prostate microenvironment are poorly understood. We conducted a pilot study to examine changes in prostate gene expression in a unique population of men with low-risk prostate cancer who declined immediate surgery, hormonal therapy, or radiation and participated in an intensive nutrition and lifestyle intervention while undergoing careful surveillance for tumor progression. Consistent with previous studies, significant improvements in weight, abdominal obesity, blood pressure, and lipid profile were observed (all P < 0.05), and surveillance of low-risk patients was safe. Gene expression profiles were obtained from 30 participants, pairing RNA samples from control prostate needle biopsy taken before intervention to RNA from the same patient's 3-month postintervention biopsy. Quantitative real-time PCR was used to validate array observations for selected transcripts. Two-class paired analysis of global gene expression using significance analysis of microarrays detected 48 up-regulated and 453 down-regulated transcripts after the intervention. Pathway analysis identified significant modulation of biological processes that have critical roles in tumorigenesis, including protein metabolism and modification, intracellular protein traffic, and protein phosphorylation (all P < 0.05). Intensive nutrition and lifestyle changes may modulate gene expression in the prostate. Understanding the prostate molecular response to comprehensive lifestyle changes may strengthen efforts to develop effective prevention and treatment. Larger clinical trials are warranted to confirm the results of this pilot study.

Thank you to the BC Foundation for Prostate Disease for their generous support.

www.BCPROSTATECANCER.org

Vitamin D
Rosso, S. F. Sera, N. Segnan and R. Zanetti. Sun Exposure Prior to Diagnosis is Associated with Improved Survival in Melanoma Patients: Results from a Long-Term Follow-Up Study of Italian Patients. Eur J Cancer. 2008 Jun; 44: 1275-1281. We followed up 260 melanoma patients included in a population-based case-control study in Turin, Italy. We collected information on host factors and sun exposure history, and analysed their relative survival. Intermittent sun exposure was inversely associated with the risk of death (hazard ratios, HR = 0.41 95% confidence interval, CI = 0.17-0.98). Outdoor work was not associated with an increased risk of death. Multivariate models including anatomic site, melanoma thickness and histology, showed that intermittent sun exposure had a tendency to be inversely associated with the risk of death from melanoma with a HR of 0.60 (95%CI = 0.24-1.5) in the patients with 1 to 59 weeks and a HR of 0.54 (95%CI = 0.23-1.2) in patients with more than 60 weeks spent on the beach during their lifetime. This study, with similar methods and a longer follow-up, confirms the finding that sun exposure prior to diagnosis of melanoma is associated with improved survival.

Ng, K. J. A. Meyerhardt, K. Wu, et al. Circulating 25-Hydroxyvitamin D Levels and Survival in Patients with Colorectal Cancer Journal of Clinical Oncology. 2008 Jun 20; 26:18: 2984-2991. PURPOSE: Higher plasma 25-hydroxyvitamin D(3) (25(OH)D) levels are associated with a decreased incidence of colorectal cancer, but the influence of plasma 25(OH)D on the outcome of patients with established colorectal cancer is unknown. PATIENTS AND METHODS: We prospectively examined the association between prediagnosis 25(OH)D levels and mortality among 304 participants in the Nurses’ Health Study (NHS) and the Health Professionals Follow-Up Study (HPFS) who were diagnosed with colorectal cancer from 1991 to 2002. Participants diagnosed within 2 years of blood collection were excluded. Patients were observed until death, June 2005 (NHS), or January 2005 (HPFS), whichever came first. The primary end point was overall mortality. Cox proportional hazards models were used to calculate hazard ratios (HR) adjusted for other risk factors for cancer survival. RESULTS: Higher plasma 25(OH)D levels were associated with a significant reduction in overall mortality (P for trend = .02). Compared with the lowest quartile, participants in the highest quartile had an adjusted HR of 0.52 (95% CI, 0.29 to 0.94) for overall mortality. A trend toward improved colorectal cancer-specific mortality was also seen (HR = 0.61; 95% CI, 0.31 to 1.19). The results remained unchanged after excluding patients diagnosed within 5 years of blood collection (P for trend = .04); the multivariate HR for overall mortality comparing extreme quartiles was 0.45 (95% CI, 0.19 to 1.09). CONCLUSION: Among patients with colorectal cancer, higher prediagnosis plasma 25(OH)D levels were associated with a significant improvement in overall survival. Further study of the vitamin D pathway and its influence on colorectal carcinogenesis and cancer progression is warranted.

Mistletoe
Horneber, MA, G. Bueschel, R. Huber, K. Linde and M. Rostock. Mistletoe Therapy in Oncology Cochrane Database Syst Rev. 2008 06; 2: Background Mistletoe extracts are commonly used in cancer patients. It is claimed that they improve survival and quality of life (QOL) in cancer patients. Objectives To determine the effectiveness, tolerability and safety of mistletoe extracts given either as monotherapy or adjunct therapy for patients with cancer. Search strategy Search sources included the Cochrane Central Register of Controlled Trials (CENTRAL, Issue 3, 2007) Cochrane Complementary Medicine Field Registry of randomized clinical trials (RCTs) and controlled clinical trials, MEDLINE, EMBASE, HEALTHSTAR, INT. HEALTH TECHNOLOGY ASSESSMENT, SOMED, AMED, BIOETHICSLINE, BIOSIS, CancerLit, CATLINE, CISCOM (August 2007). For the search the Standard Operating Procedures of the Information System in Health Economics at the German Institute for Medical Documentation and Information (DIMDI) were utilized. Reference lists of relevant articles and authors extensive files were searched for additional studies. Manufacturers of mistletoe preparations were contacted. Selection criteria We included RCTs of adults with cancer of any type. The interventions were mistletoe extracts as sole treatments or given concomitantly with chemo- or radiotherapy. The outcome measures were survival times, tumor response, QOL, psychological distress, adverse effects from antineoplastic treatment and safety of mistletoe extracts. Data collection and analysis Three review authors independently assessed trials for inclusion in the review. All review authors independently took part in the extraction of data and assessment of study quality and clinical relevance. Disagreements were resolved by consensus. Study authors were contacted where information was unclear. Methodological quality was narratively described and additionally assessed with the Delphi list and the Jadad score. High methodological quality was defined if six out of nine Delphi criteria, or four out of five Jadad criteria were fulfilled. Results were presented qualitatively. Main results Eighty studies were identified. Fifty-eight were excluded for various reasons, usually as there was no prospective trial design with randomised treatment allocation. Of the 21 included studies 13 provided data on survival, 7 on tumour response, 16 on measures of QOL or psychological outcomes, or prevalence of chemotherapy-related adverse effects and 12 on side effects of mistletoe treatment; overall comprising 3484 randomised cancer patients. Interventions evaluated were 5 preparations of mistletoe extracts from 5 manufacturers and one
commercially not available preparation. The general reporting of RCTs was poor. Of the 13 trials investigating survival, 6 showed some evidence of a benefit, but none of them was of high methodological quality. The results of two trials in patients with melanoma and head and neck cancer gave some evidence that the used mistletoe extracts are not effective for improving survival. Of the 16 trials investigating the efficacy of mistletoe extracts for either improving QOL, psychological measures, performance index, symptom scales or the reduction of adverse effects of chemotherapy, 14 showed some evidence of a benefit, but only 2 of them including breast cancer patients during chemotherapy were of higher methodological quality. Data on side effects indicated that, depending on the dose, mistletoe extracts were usually well tolerated and had few side effects. Authors' conclusions The evidence from RCTs to support the view that the application of mistletoe extracts has impact on survival or leads to an improved ability to fight cancer or to withstand anticancer treatments is weak. Nevertheless, there is some evidence that mistletoe extracts may offer benefits on measures of QOL during chemotherapy for breast cancer, but these results need replication. Overall, more high quality, independent clinical research is needed to truly assess the safety and effectiveness of mistletoe extracts. Patients receiving mistletoe therapy should be encouraged to take part in future trials.

Diet & Nutrition

Krishnawamy, K Traditional Indian Spices and their Health Significance Asia Pac J Clin Nutr. 2008 17Suppl 1: 265-268. India has been recognized all over the world for spices and medicinal plants. Both exhibit a wide range of physiological and pharmacological properties. Current biomedical efforts are focused on their scientific merits, to provide science-based evidence for the traditional uses and to develop either functional foods or nutraceuticals. The Indian traditional medical systems use turmeric for wound healing, rheumatic disorders, gastrointestinal symptoms, deworming, rhinitis and as a cosmetic. Studies in India have explored its anti-inflammatory, cholekinetic and anti-oxidant potentials with the recent investigations focusing on its preventive effect on precarcinogenic, anti-inflammatory and anti-atherosclerotic effects in biological systems both under in vitro and in vivo conditions in animals and humans. Both turmeric and curcumin were found to increase detoxifying enzymes, prevent DNA damage, improve DNA repair, decrease mutations and tumour formation and exhibit antioxidative potential in animals. Limited clinical studies suggest that turmeric can significantly impact excretion of mutagens in urine in smokers and regress precancerous palatal lesions. It reduces DNA adducts and micronuclei in oral epithelial cells. It prevents formation of nitroso compounds both in vivo and in vitro. It delays induced cataract in diabetes and reduces hyperlipidemia in obese rats. Recently several molecular targets have been identified for therapeutic / preventive effects of turmeric. Fenugreek seeds, a rich source of soluble fiber used in Indian cuisine reduces blood glucose and lipids and can be used as a food adjuvant in diabetics. Similarly garlic, onions, and ginger have been found to modulate favourably the process of carcinogenesis. [References: 19]

Simopoulos, AP The Importance of the Omega-6/omega-3 Fatty Acid Ratio in Cardiovascular Disease and Other Chronic Diseases Experimental Biology & Medicine. 2008 Jun; 2336: 674-688. Several sources of information suggest that human beings evolved on a diet with a ratio of omega-6 to omega-3 essential fatty acids (EFA) of approximately 1 whereas in Western diets the ratio is 15/1-16.7/1. Western diets are deficient in omega-3 fatty acids, and have excessive amounts of omega-6 fatty acids compared with the diet on which human beings evolved and their genetic patterns were established. Excessive amounts of omega-6 polyunsaturated fatty acids (PUFA) and a very high omega-6/omega-3 ratio, as is found in today's Western diets, promote the pathogenesis of many diseases, including cardiovascular disease, cancer, and inflammatory and autoimmune diseases, whereas increased levels of omega-3 PUFA (a lower omega-6/omega-3 ratio), exert suppressive effects. In the secondary prevention of cardiovascular disease, a ratio of 4/1 was associated with a 70% decrease in total mortality. A ratio of 2.5/1 reduced rectal cell proliferation in patients with colorectal cancer, whereas a ratio of 4/1 with the same amount of omega-3 PUFA had no effect. The lower omega-6/omega-3 ratio in women with breast cancer was associated with decreased risk. A ratio of 2-3/1 suppressed inflammation in patients with rheumatoid arthritis, and a ratio of 5/1 had a beneficial effect on patients with asthma, whereas a ratio of 10/1 had adverse consequences. These studies indicate that the optimal ratio may vary with the disease under consideration. This is consistent with the fact that chronic diseases are multigenic and multifactorial. Therefore, it is quite possible that the therapeutic dose of omega-3 fatty acids will depend on the degree of severity of disease resulting from the genetic predisposition. A lower ratio of omega-6/omega-3 fatty acids is more desirable in reducing the risk of many of the chronic diseases of high prevalence in Western societies, as well as in the developing countries. [References: 134]

Hogervorst, JG, L. J. Schouten, E. J. Konings, R. A. Goldbohm and P. A. van den Brandt. Dietary Acrylamide Intake and the Risk of Renal Cell, Bladder, and Prostate Cancer. Am J Clin Nutr. 2008 May; 875: 1428-1438. BACKGROUND: Acrylamide, a probable human carcinogen, was recently detected in various heat-treated carbohydrate-rich foods. Epidemiologic studies on the relation with cancer have been few and largely negative. OBJECTIVE: We aimed to prospectively examine the association between dietary acrylamide intake and renal cell, bladder, and prostate cancers. DESIGN: The Netherlands Cohort Study on diet and cancer includes 120,852 men and women aged 55-69 y. At baseline (1986), a random subcohort of 5000 participants was selected for a case-cohort analysis approach using Cox proportional hazards analysis. Acrylamide intake was assessed with a food-frequency questionnaire at baseline and was based on chemical analysis of all relevant Dutch foods. RESULTS: After 13.3 y of follow-up, 339, 1210, and 2246 cases of renal cell, bladder, and prostate cancer, respectively, were available for analysis. Compared with the lowest quintile of acrylamide intake (mean intake: 9.5 microg/d), multivariable-adjusted hazard rates for renal cell, bladder, and prostate cancer in the highest quintile (mean intake: 40.8 microg/d) were 1.59 (95% CI: 1.09, 2.30; P for trend = 0.04), 0.91 (95% CI: 0.73, 1.15; P for trend = 0.60), and 1.06 (95% CI: 0.87, 1.30; P for trend = 0.69), respectively. There was an inverse nonsignificant trend for advanced prostate cancer in never smokers. CONCLUSIONS: We found some indications for a positive association between dietary acrylamide and renal cancer risk. There were no positive associations with bladder and prostate cancer risk.

Exercise

Cramp, F and J. Daniel. Exercise for the Management of Cancer-Related Fatigue in Adults Cochrane Database of Systematic Reviews. 2008 2: 006145. BACKGROUND: Cancer-related fatigue is now recognised as an important symptom associated with cancer and its treatment. A number of studies have investigated the effects of physical activity in reducing cancer-related fatigue with no definitive conclusions regarding its effectiveness. OBJECTIVES: To evaluate the effect of exercise on cancer-related fatigue both during and after cancer treatment. SEARCH STRATEGY: The Cochrane Controlled Trials Register (CENTRAL/ CCTR), MEDLINE (1966 to July 2007), EMBASE (1980 to July 2007), CINAHL (1982 to July 2007), AMED (1985 to July 2007), SIGLE (1980 to July 2007), and Dissertation Abstracts International (1861 to July 2007) were all searched using key words. Reference lists of all studies identified for inclusion and relevant reviews were also searched. In addition, relevant journals
were hand searched and experts in the field of cancer-related fatigue were contacted. SELECTION CRITERIA: Randomised controlled trials (RCTs) that investigated the effect of exercise on cancer-related fatigue in adults were included. DATA COLLECTION AND ANALYSIS: Two review authors independently assessed the methodological quality of studies and extracted data based upon predefined criteria. Where data were available meta-analyses were performed for fatigue using a random-effects model. MAIN RESULTS: Twenty-eight studies were identified for inclusion (n = 2083 participants), with the majority carried out on participants with breast cancer (n = 16 studies; n = 1172 participants). A meta-analysis of all fatigue data, incorporating 22 comparisons provided data for 920 participants who received an exercise intervention and 742 control participants. At the end of the intervention period exercise was statistically more effective than the control intervention (SMD -0.23, 95% Confidence Interval (CIs) -0.33 to -0.13). AUTHORS’ CONCLUSIONS: Exercise can be regarded as beneficial for individuals with cancer-related fatigue during and post cancer therapy. Further research is required to determine the optimal type, intensity and timing of an exercise intervention. [References: 74]


Within a population-based cohort study, 40 708 men aged 45-79 years followed from 1998 to 2004. After adjusting for potential confounders, we observed a strong inverse linear association between total daily physical activity (PA) and death from cancer (n=1153). For each increment of 4 metabolic equivalent (MET)-h day \(^{-1}\) of total PA (approximately 1 h daily of moderate effort) cancer mortality decreased significantly by 12% (95% confidence interval -0.23, 95% Confidence Interval (CIs) -0.33 to -0.13). AUTHORS’ CONCLUSIONS: Exercise can be regarded as beneficial for individuals with cancer-related fatigue during and post cancer therapy. Further research is required to determine the optimal type, intensity and timing of an exercise intervention. [References: 74]

Qigong


Quality of life (QOL) of cancer patients is often diminished due to the side effects of treatment and symptoms of the disease itself. Medical Qigong (coordination of gentle exercise and relaxation through meditation and breathing exercise based on Chinese medicine theory of energy channels) may be an effective therapy for improving QOL, symptoms and side effects, and longevity of cancer patients. In this pilot study, the feasibility, acceptability, and impact of Medical Qigong (MQ) were evaluated on outcomes in cancer patients. Thirty patients diagnosed with heterogeneous cancers, were randomly assigned to two groups: a control group that received usual medical care and an intervention group who participated in a MQ program for 8 weeks in addition to receiving usual medical care. Randomization was stratified by completion of cancer treatment (n = 14) or under chemotherapy (n = 16). Patients completed measures before and after the program. Quality of life and symptoms were measured by the EORTC QLQ-C 30 and progress of disease by the inflammation biomarker (CRP: c-reactive protein) via a blood test was assessed. The MQ intervention group reported clinically significant improved global QOL scores pre- and post-intervention. The MQ intervention also reduced the symptoms of side effects of cancer treatment and inflammation biomarker (CRP) compared to the control group. Due to the small sample size, however, the results were not statistically significant between treatment and the control groups. Data from the pilot study suggest that MQ with usual medical treatment can enhance the QOL of cancer patients and reduce inflammation. This study needs a further investigation with a larger sample size.

CAM of the Month


BACKGROUND: Mind-body practices that elicit the relaxation response (RR) have been used worldwide for millennia to prevent and treat disease. The RR is characterized by decreased oxygen consumption, increased exhaled nitric oxide, and reduced psychological distress. It is believed to be the counterpart of the stress response that exhibits a distinct pattern of physiology and transcriptional profile. We hypothesized that RR elicitation results in characteristic gene expression changes that can be used to measure physiological responses elicited by the RR in an unbiased fashion. METHODS/PRINCIPAL FINDINGS: We assessed whole blood transcriptional profiles in 19 healthy, long-term practitioners of daily RR practice (group M), 19 healthy controls (group N(1)), and 20 N(1) individuals who completed 8 weeks of RR training (group N(2)). 2209 genes were differentially expressed in group M relative to group N(1) (p<0.05) and 1561 genes in group N(2) compared to group N(1) (p<0.05). Importantly, 433 (p<10(-10)) of 2209 and 1561 differentially expressed genes were shared among long-term (M) and short-term practitioners (N(2)). Gene ontology and gene set enrichment analyses revealed significant alterations in cellular metabolism, oxidative phosphorylation, generation of reactive oxygen species and response to oxidative stress in long-term and short-term practitioners of daily RR practice that may counteract cellular damage related to chronic psychological stress. A significant number of genes and pathways were confirmed in an independent validation set containing 5 N(1) controls, 5 N(2) short-term and 6 M long-term practitioners.

CONCLUSIONS/SIGNIFICANCE: This study provides the first compelling evidence that the RR elicits specific gene expression changes in short-term and long-term practitioners. Our results suggest consistent and constitutive changes in gene expression resulting from RR may relate to long term physiological effects. Our study may stimulate new investigations into applying transcriptional profiling for accurately measuring RR and stress related responses in multiple disease settings.

InspireHealth provides an integrated whole person approach to health for individuals living with cancer. Our medical doctors guide patients to explore and learn about a variety of wellness approaches to health and healing in addition to conventional cancer treatment. This integrated medical model, which engages people in their own care, improves quality of life and reduces the likelihood of cancer recurrence. The editorial board includes: Dr. Hal Gunn, CEO and Co-founder, Dr. Janice Wright, Dr. Teresa Clarke, Dr. Ron Puhky, and Dr. Walter Lemmo, ND.

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