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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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Vitamin C and Chemotherapy: Looking at the Evidence

As a result of a recently published study¹, there was concern expressed in the media regarding the use of vitamin C during chemotherapy. As many cancer patients take vitamins and supplements, this is an important issue. In order to ensure that patients are not unduly frightened by conclusions drawn from a single study, it is important that these results be understood within the larger context of the broader evidence. This is important for two reasons. First, because the form of vitamin C used in the reported study is not the form of vitamin C taken by cancer patients, and second, because there is a much larger body of evidence that indicates that the form of vitamin C that is taken by cancer patients is not harmful in conjunction with chemotherapy and may, in fact, be helpful.

Ascorbic acid, the commonly used form of vitamin C, is beneficial for health because of its antioxidant effects. The form of vitamin C used in the recently published study is the oxidized form of vitamin C (dehydroascorbic acid) which does not have antioxidant properties. This oxidized form of vitamin C, which is not available in the marketplace, has pro-oxidant qualities and therefore might reasonably be expected to have the opposite effects to ascorbic acid, the commonly used form of vitamin C. In fact, numerous studies of the use of regular vitamin C (i.e., ascorbic acid) in conjunction with chemotherapy have found that vitamin C does not interfere with chemotherapy and may, in fact, be helpful in this context. As is universally understood in medical research, clinical research in people is of far greater importance than studies in laboratory dishes or mice, such as the one by Heaney reported recently. There are two randomized trials in humans^{2 3} (i.e., the highest standard of research) that found that vitamin C (as ascorbic acid) does not interfere with chemotherapy. In addition, there are over 20 published research studies⁴⁻²⁶ in laboratory dishes and mice demonstrating that vitamin C (as ascorbic acid) can improve the response to chemotherapy, help make it work when cancer cells are resistant to it, and even help to increase survival. The only negative study is the one using the oxidized form of vitamin C, reported

recently. Unfortunately, the lack of context in the recent media reports of this negative study may have unduly frightened cancer patients. More research needs to be done, but the weight of the current evidence does not suggest that the commonly used form of vitamin C, ascorbic acid, is harmful in the context of chemotherapy. In fact, the weight of the preliminary evidence suggests that it may be helpful.

It is also important to note that research shows that patients with cancer may have a greater need for vitamin C than people who don't have cancer – vitamin C levels in their blood are lower. More research in this important area is needed. However, it is important not to make decisions based on one negative paper with a form of vitamin C not used by the public when the overwhelming majority of information (including human use with the form of vitamin C used by the public) shows no harmful effects and the possibility to help.

Breast

Alem, M and MSC Gurgel. **Acupuncture in the Rehabilitation of Women After Breast Cancer Surgery -- a Case Series** *ACUPUNCTURE MED.* 2008 06; 262: 86-93. Objective To evaluate the effect of acupuncture on rehabilitation of motor function, reduction in lymphoedema and improvement in perceived heaviness and tightness in the arms of women who had undergone breast cancer surgery. Subjects and Methods Twenty nine women who had had mastectomy or segmentectomy with axillary dissection, presenting with lymphoedema and/or a decrease in movement amplitude of the upper limb ipsilateral to surgery were studied. The patients underwent 24 acupuncture sessions once a week from February to December 2004. The movement amplitude of shoulder flexion and abduction and circumferential measurements of the arm, forearm and wrist were evaluated before and after one, three and six months of treatment. Statistical analysis was performed by Friedman's test. Results Significant improvements in range of movement of shoulder flexion and abduction (P<0.001), degree of lymphoedema (P=0.016), and sense of heaviness and tightening (P<0.001) in the affected limb after six months of therapy were observed. For circumferential measurements of the arm, forearm and wrist, no significant

improvement between the different periods of treatment was observed. Conclusions Acupuncture in rehabilitation after breast cancer surgery was shown to be associated with improvements in movement amplitude of the shoulder, symptoms of heaviness and tightness in the arm, and the degree of lymphoedema. However, controlled trials should be performed to ascertain whether the results were due to the natural history of the complaint or the acupuncture treatment.

Messina, MJ and C. E. Wood. **Soy Isoflavones, Estrogen Therapy, and Breast Cancer Risk: Analysis and Commentary** *Nutrition Journal*. 2008 717.

There has been considerable investigation of the potential for soyfoods to reduce risk of cancer, and in particular cancer of the breast. Most interest in this relationship is because soyfoods are essentially a unique dietary source of isoflavones, compounds which bind to estrogen receptors and exhibit weak estrogen-like effects under certain experimental conditions. In recent years the relationship between soyfoods and breast cancer has become controversial because of concerns--based mostly on in vitro and rodent data--that isoflavones may stimulate the growth of existing estrogen-sensitive breast tumors. This controversy carries considerable public health significance because of the increasing popularity of soyfoods and the commercial availability of isoflavone supplements. In this analysis and commentary we attempt to outline current concerns regarding the estrogen-like effects of isoflavones in the breast focusing primarily on the clinical trial data and place these concerns in the context of recent evidence regarding estrogen therapy use in postmenopausal women. Overall, there is little clinical evidence to suggest that isoflavones will increase breast cancer risk in healthy women or worsen the prognosis of breast cancer patients. Although relatively limited research has been conducted, and the clinical trials often involved small numbers of subjects, there is no evidence that isoflavone intake increases breast tissue density in pre- or postmenopausal women or increases breast cell proliferation in postmenopausal women with or without a history of breast cancer. The epidemiologic data are generally consistent with the clinical data, showing no indication of increased risk. Furthermore, these clinical and epidemiologic data are consistent with what appears to be a low overall breast cancer risk associated with pharmacologic unopposed estrogen exposure in postmenopausal women. While more research is required to definitively allay concerns, the existing data should provide some degree of assurance that isoflavone exposure at levels consistent with historical Asian soyfood intake does not result in adverse stimulatory effects on breast tissue. [References: 136]

Prostate

Ma, J, Haojie Li, Ed Giovannucci, et al. **Prediagnostic Body-Mass Index, Plasma C-Peptide Concentration, and Prostate Cancer-Specific Mortality in Men with Prostate Cancer: A Long-Term Survival Analysis** *The Lancet Oncology*,. In Press, Corrected Proof

Background: Excess body-mass index (BMI) has been associated with adverse outcomes in prostate cancer, and hyperinsulinaemia is a candidate mediator, but prospective data are sparse. We assessed the effect of prediagnostic BMI and plasma C-peptide concentration (reflecting insulin secretion) on prostate cancer-specific mortality after diagnosis. **Methods:** This study involved men diagnosed with prostate cancer during the 24 years of follow-up in the Physicians' Health Study. BMI measurements were available at baseline in 1982 and eight years later in 1990 for 2546 men who developed prostate cancer. Baseline C-peptide concentration was available in 827 men. We used Cox proportional hazards regression models controlling for age, smoking, time between BMI measurement and prostate cancer diagnosis, and competing causes of death to assess the risk of prostate cancer-specific mortality according to BMI and C-peptide concentration. **Findings:** Of the 2546 men diagnosed with prostate cancer during the follow-up period, 989 (38.8%) were overweight (BMI 25.0–29.9

kg/m²) and 87 (3.4%) were obese (BMI ≥30 kg/m²). 281 men (11%) died from prostate cancer during this follow-up period. Compared with men of a healthy weight (BMI <25 kg/m²) at baseline, overweight men and obese men had a significantly higher risk of prostate cancer mortality (proportional hazard ratio [HR] 1.47 [95% CI 1.16–1.88] for overweight men and 2.66 [1.62–4.39] for obese men; p_{trend}<0.0001). The trend remained significant after controlling for clinical stage and Gleason grade and was stronger for prostate cancer diagnosed during the PSA screening era (1991–2007) compared with during the pre-PSA screening era (1982–1990) or when using BMI measurements obtained in 1990 compared with those obtained in 1982. Of the 827 men with data available for baseline C-peptide concentration, 117 (14%) died from prostate cancer. Men with C-peptide concentrations in the highest quartile (high) versus the lowest quartile (low) had a higher risk of prostate cancer mortality (HR 2.38 [95% CI 1.31–4.30]; p_{trend}=0.008). Compared with men with a BMI less than 25 kg/m² and low C-peptide concentrations, those with a BMI of 25 kg/m² or more and high C-peptide concentrations had a four-times higher risk of mortality (4.12 [1.97–8.61]; p_{interaction}=0.001) independent of clinical predictors. **Interpretation:** Excess bodyweight and a high plasma concentration of C-peptide both predispose men with a subsequent diagnosis of prostate cancer to an increased likelihood of dying of their disease. Patients with both factors have the worst outcome. Further studies are now needed to confirm these findings.

Galvao, DA, K. Nosaka, D. R. Taaffe, et al. **Endocrine and Immune Responses to Resistance Training in Prostate Cancer Patients.** *Prostate Cancer & Prostatic Diseases*. 2008 112: 160-165.

This study examined the effect of 20 weeks resistance training on a range of serum hormones and inflammatory markers at rest, and following acute bouts of exercise in prostate cancer patients undergoing androgen deprivation. Ten patients exercised twice weekly at high intensity for several upper and lower-body muscle groups. Neither testosterone nor prostate-specific antigen changed at rest or following an acute bout of exercise. However, serum growth hormone (GH), dehydroepiandrosterone (DHEA), interleukin-6, tumor necrosis factor-alpha and differential blood leukocyte counts increased (P < 0.05) following acute exercise. Resistance exercise does not appear to compromise testosterone suppression, and acute elevations in serum GH and DHEA may partly underlie improvements observed in physical function.

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

Pot, GK, A. Geelen, E. M. van Heijningen, C. L. Siezen, H. J. van Kranen and E. Kampman. **Opposing Associations of Serum n-3 and n-6 Polyunsaturated Fatty Acids with Colorectal Adenoma Risk: An Endoscopy-Based Case-Control Study.** *International Journal of Cancer*. 2008 Oct 15; 1238: 1974-1977. Several human and animal studies have shown that n-3 polyunsaturated fatty acids (PUFA) might be associated with a decreased risk, whereas other studies showed that n-6 PUFA may be associated with an increased risk of colorectal cancer. However, results from these studies are not consistent. We evaluated the associations between serum n-3 and n-6 PUFA levels and colorectal adenoma risk in an endoscopy-based case-control study, conducted in The Netherlands between 1997 and 2002. We included 363 cases of colorectal adenomas and 498 adenoma-free controls. Serum fatty acids were measured in cholesteryl esters. Logistic regression models were used to calculate odds ratios (OR), which were adjusted for age, gender and alcohol intake. Total serum n-3 PUFA levels were inversely associated with colorectal adenoma risk, the OR comparing the third tertile with the

first tertile was 0.67 [95% confidence interval (CI) 0.46-0.96, p for trend = 0.03]. Serum eicosapentaenoic acid (EPA; C20:5n-3) and docosahexaenoic acid (DHA; C22:6n-3) and the n-3/n-6 ratio were inversely associated with colorectal adenoma risk, but these were not statistically significant. In contrast, the risk of colorectal adenomas was increased by total n-6 PUFA with an OR of 1.68 (95% CI, 1.17-2.42, p for trend = 0.006) and by linoleic acid (LA; C18:2n-6) with an OR of 1.65 (95% CI, 1.15-2.38, p for trend = 0.007). This is the first observational study that simultaneously finds an inverse association of serum n-3 PUFA and a positive association of n-6 PUFA with colorectal adenoma risk.

Lymphoma

Ebrahim, MA, M. A. -H Salah-Eldin, M. I. Esmaeel, M. Abdallah, S. M. Mosaad and W. El-Sankary. **Study of Selenium Concentration in Patients with Newly Diagnosed Non-Hodgkin's Lymphoma.** *Journal of Medical Sciences.* 2008 15 Feb; 82: 125-130.

This study was designed to examine selenium concentrations in patients with newly diagnosed Non-Hodgkin's Lymphoma (NHL) and the possible association between the levels of this trace element with clinical features of the disease. Also, to test the hypothesis that selenium concentration at presentation would predict for response to treatment. This study was carried out on fifty-patients with newly diagnosed NHL and 25 control subjects, blood samples were taken for measurement of selenium by spectrometry. In comparison to the control subjects the serum selenium level was significantly lower with NHL with a mean of 0.033 (SD, 0.1) vs 0.81 (SD, 0.05), $p < 0.001$. The mean serum selenium was significantly lower in patients with poorer performance status ($p = 0.03$) and in patients with advanced stage ($p = 0.02$), but there was no significant relation to the aggressiveness of the disease. Serum albumin was the only parameter that showed a significant positive correlation with serum selenium. There was a trend for serum selenium level to be higher in patients who achieved CR, but the difference was not statistically significant ($p = 0.1$). Selenium may play a role in the pathogenesis and prognosis of patients with NHL. In this study; the level of selenium was found inversely associated with the clinical stage of the disease and the performance status and may predict for the response to treatment in aggressive lymphoma. The possible utility of measuring serum selenium in NHL deserves further evaluation in clinical trials.

Vitamin D

Melamed, ML, E. D. Michos, W. Post and B. Astor. **25-Hydroxyvitamin D Levels and the Risk of Mortality in the General Population.** *Arch Intern Med.* 2008 Aug 11; 16815: 1629-1637.

BACKGROUND: In patients undergoing dialysis, therapy with calcitriol or paricalcitol or other vitamin D agents is associated with reduced mortality. Observational data suggests that low 25-hydroxyvitamin D levels (25[OH]D) are associated with diabetes mellitus, hypertension, and cancers. However, whether low serum 25(OH)D levels are associated with mortality in the general population is unknown. **METHODS:** We tested the association of low 25(OH)D levels with all-cause, cancer, and cardiovascular disease (CVD) mortality in 13 331 nationally representative adults 20 years or older from the Third National Health and Nutrition Examination Survey (NHANES III) linked mortality files. Participant vitamin D levels were collected from 1988 through 1994, and individuals were passively followed for mortality through 2000. **RESULTS:** In cross-sectional multivariate analyses, increasing age, female sex, nonwhite race/ethnicity, diabetes, current smoking, and higher body mass index were all independently associated with higher odds of 25(OH)D deficiency (lowest quartile of 25(OH)D level, < 17.8 ng/mL [to convert to nanomoles per liter, multiply by 2.496]), while greater physical activity, vitamin D supplementation, and nonwinter season were inversely associated.

During a median 8.7 years of follow-up, there were 1806 deaths, including 777 from CVD. In multivariate models (adjusted for baseline demographics, season, and traditional and novel CVD risk factors), compared with the highest quartile, being in the lowest quartile (25[OH]D levels < 17.8 ng/mL) was associated with a 26% increased rate of all-cause mortality (mortality rate ratio, 1.26; 95% CI, 1.08-1.46) and a population attributable risk of 3.1%. The adjusted models of CVD and cancer mortality revealed a higher risk, which was not statistically significant. **CONCLUSION:** The lowest quartile of 25(OH)D level (< 17.8 ng/mL) is independently associated with all-cause mortality in the general population.

Psychosocial

Chida, Y, M. Hamer, J. Wardle and A. Steptoe. **Do Stress-Related Psychosocial Factors Contribute to Cancer Incidence and Survival?** *Nature Clinical Practice Oncology.* 2008 Aug; 58: 466-475.

A substantial body of research has investigated the associations between stress-related psychosocial factors and cancer outcomes. Previous narrative reviews have been inconclusive. In this Review, we evaluated longitudinal associations between stress and cancer using meta-analytic methods. The results of 165 studies indicate that stress-related psychosocial factors are associated with higher cancer incidence in initially healthy populations ($P = 0.005$); in addition, poorer survival in patients with diagnosed cancer was noted in 330 studies ($P < 0.001$), and higher cancer mortality was seen in 53 studies ($P < 0.001$). Subgroup meta-analyses demonstrate that stressful life experiences are related to poorer cancer survival and higher mortality but not to an increased incidence. Stress-prone personality or unfavorable coping styles and negative emotional responses or poor quality of life were related to higher cancer incidence, poorer cancer survival and higher cancer mortality. Site-specific analyses indicate that psychosocial factors are associated with a higher incidence of lung cancer and poorer survival in patients with breast, lung, head and neck, hepatobiliary, and lymphoid or hematopoietic cancers. These analyses suggest that stress-related psychosocial factors have an adverse effect on cancer incidence and survival, although there is evidence of publication bias and results should be interpreted with caution. [References: 36]

Kieviet-Stijnen, A, A. Visser, B. Garsen and W. Hudig. **Mindfulness-Based Stress Reduction Training for Oncology Patients: Patients' Appraisal and Changes in Well-being.** *Patient Educ Couns.* 2008 Sep; 723: 436-442.

Objective: This study explores satisfaction and changes in well-being in cancer patients following mindfulness-based stress reduction training. **Method:** Data were collected in 47 cancer patients before and after the training, and also 1 year later. Standardized questionnaires were used to measure quality of life, joy in life, mood disturbances (depression, anger, vigor, fatigue, and tension), meaning in life and physical symptoms. **Results:** Participants were highly satisfied and said they had reached their goals with the training. The results show that directly after the training patients reported a better quality of life, more joy in life, less tension, and fewer physical symptoms. These effects appeared even stronger at follow-up. A year after the training a decrease was also found in depression, anger, vigor and total mood disturbance. No changes could be established for meaning in life and fatigue. Effect sizes varied between 0.28 and 0.60, indicating small-to-moderate changes. **Conclusion:** Mindfulness training potentially supports cancer patients in handling the stress due to their life-threatening disease and increases their well-being. Several suggestions for further research are discussed. **Practice implications:** Mindfulness training provides cancer patients with tools to deal with their limitations and worries, both during and after their treatment. copyright 2008 Elsevier Ireland Ltd. All rights reserved.

CAM / Integrative Medicine

Verhoef, MJ, M. S. Rose, M. White and L. G. Balneaves. **Declining Conventional Cancer Treatment and using Complementary and Alternative Medicine: A Problem Or a Challenge?** *Curr Oncol.* 2008 Aug; 15 Supp 2101-106.

BACKGROUND: Several studies have shown that a small but significant percentage of cancer patients decline one or more conventional cancer treatments and use complementary and alternative medicine (cam) instead. **OBJECTIVES:** Here, drawing on the literature and on our own ongoing research, we describe why cancer patients decide to decline conventional cancer treatments, who those patients are, and the response by physicians to patients who make such decisions. **RESULTS:** Poor doctor-patient communication, the emotional impact of the cancer diagnosis, perceived severity of conventional treatment side effects, a high need for decision-making control, and strong beliefs in holistic healing appear to affect the decision by patients to decline some or all conventional cancer treatments. Many patients indicate that they value ongoing follow-up care from their oncologists provided that the oncologists respect their beliefs. Patients declining conventional treatments have a strong sense of internal control and prefer to make the final treatment decisions after considering the opinions of their doctors. Few studies have looked at the response by physicians to patients making such a decision. Where research has been done, it found that a tendency by doctors to dichotomize patient decisions as rational or irrational may interfere with the ability of the doctors to respond with sensitivity and understanding. **CONCLUSIONS:** Declining conventional treatment is not necessarily an indicator of distrust of the medical system, but rather a reflection of many personal factors. Accepting and respecting such decisions may be instrumental in "keeping the door open."

Remen, RN **Practicing a Medicine of the Whole Person: An Opportunity for Healing** *Hematology/Oncology Clinics of North America.* 2008 8; 224: 767-773.

Integrative medicine has been defined in several ways. For some it is a discipline that combines such approaches to the resolution of disease as acupuncture and homeopathy, meditation and imagery with more familiar and accepted health practices, such as surgery, pediatrics, and oncology. For others it is about cultivating awareness and sensitivity beyond symptoms to the mental, emotional, and spiritual needs of the patient. But, integrative medicine is more than the weaving together of techniques, or understanding the intimate interaction of the mental, emotional, and spiritual dimensions of human experience. It is about rethinking the task of medicine and the infrastructure of relationships and beliefs that have limited its power to serve all people.

Parabens

Darbre, PD and P. W. Harvey. **Paraben Esters: Review of Recent Studies of Endocrine Toxicity, Absorption, Esterase and Human Exposure, and Discussion of Potential Human Health Risks** *Journal of Applied Toxicology.* 2008 Jul; 285: 561-578.

This toxicology update reviews research over the past four years since publication in 2004 of the first measurement of intact esters of p-hydroxybenzoic acid (parabens) in human breast cancer tissues, and the suggestion that their presence in the human body might originate from topical application of bodycare cosmetics. The presence of intact paraben esters in human body tissues has now been confirmed by independent measurements in human urine, and the ability of parabens to penetrate human skin intact without breakdown by esterases and to be absorbed systemically has been demonstrated through studies not only in vitro but also in vivo using healthy human subjects. Using a wide variety of assay systems in vitro and in vivo, the oestrogen agonist properties of parabens together with their common metabolite (p-hydroxybenzoic acid) have been extensively documented, and, in addition, the parabens

have now also been shown to possess androgen antagonist activity, to act as inhibitors of sulfotransferase enzymes and to possess genotoxic activity. With the continued use of parabens in the majority of bodycare cosmetics, there is a need to carry out detailed evaluation of the potential for parabens, together with other oestrogenic and genotoxic co-formulants of bodycare cosmetics, to increase female breast cancer incidence, to interfere with male reproductive functions and to influence development of malignant melanoma which has also recently been shown to be influenced by oestrogenic stimulation. 2008 John Wiley & Sons, Ltd [References: 180]

CAM of the Month

Sanatani, M, G. Schreier and L. Stitt. **Level and Direction of Hope in Cancer Patients: An Exploratory Longitudinal Study.** *Supportive Care in Cancer.* 2008 May; 165: 493-499.

GOALS: Hope is an important factor to consider when caring for cancer patients as a key component of coping with adversity. The aim of our study was to address the following questions: Is there a difference in level of hope between those patients being curatively and those palliatively treated, and how does this change over time? What are patients' most important hopes? Better understanding of patients' hopes may promote more effective patient-centered care. **MATERIALS AND METHODS:** Outpatients referred to medical oncology or pain and symptom clinics at the London Regional Cancer Program were surveyed before consultation. The Herth Hope Index (HHI) questionnaire was administered to assess level of hope, and the patients were asked to indicate their highest priority hopes. Qualitative thematic analysis was performed on the responses, and comparison was made between patients treated with curative vs those treated with palliative intent. This survey was repeated 4 months after initial assessment. **RESULTS:** Fifty patients were surveyed (29 curative-intent; 21 palliative). Highest priority initial hopes were categorized as follows: cure, other positive health outcomes, emotional well-being, life achievements/return to normalcy, interpersonal goals, other. There was no association noted between treatment intent and choice of highest-priority hope. Follow-up assessments after 4 months revealed no significant differences in the distribution pattern of hopes. There was a statistically significant increase in the HHI over time in curatively treated patients, but none in the combined analysis. **DISCUSSION AND CONCLUSION:** Our study indicates that patients receiving palliative therapy have a HHI score not significantly different from patients being treated for cure. The hope deemed most important is also similar between groups. Over time, overall hope was maintained or increased even in the presence of a trend towards fewer patients hoping for a cure. These results remind oncologists to explore the experience of hope with all patients to ensure that the subjective needs and goals of the patients are met by the proposed therapies.

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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