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InspireHealth
INTEGRATED CANCER CARE

In this issue

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

Abbas S, Linseisen J, Chang-Claude J. **Dietary vitamin D and calcium intake and premenopausal breast cancer risk in a German case-control study.** *Nutr Cancer* 2007;59(1):54-61.
Epidemiological studies and laboratory data suggest that vitamin D may protect against the development of cancer, including breast cancer. Vitamin D supply affects the bioavailability of dietary calcium, which might also have anticarcinogenic effects. However, few studies considered them jointly. We used a population-based case-control study in Germany to examine the independent and joint effects of dietary vitamin D and calcium on premenopausal breast cancer risk. Dietary information was assessed using a validated food frequency questionnaire from 278 premenopausal cases and 666 age-matched controls. Odds ratios (ORs) and 95% confidence intervals (CIs) were estimated using multivariate models adjusting vitamin D models for calcium intake and vice versa. Breast cancer risk was significantly inversely associated with vitamin D intake. The OR and 95% CI for the highest intake category ([greater-than or equal to]5 mug/day) was 0.50 (95% CI = 0.26-0.96) compared with the lowest ($_{trend}$ = 0.02). Dietary calcium intake was not associated with breast cancer (OR = 0.73, 95% CI = 0.41-1.29) for the highest ([greater-than or equal to]l,300 mg/day) versus the lowest category (= 0.02). Dietary calcium intake was not associated with breast cancer (OR = 0.73, 95% CI = 0.41-1.29) for the highest ([greater-than or equal to]l,300 mg/day) versus the lowest category ($_{trend}$ = 0.29). No statistically significant interaction between the 2 nutrients was observed. Our data support a protective effect of dietary vitamin D on premenopausal breast cancer risk independent of dietary calcium intake.

Hamner JB, Fleming MD. **Lymphedema therapy reduces the volume of edema and pain in patients with breast cancer.** *Annals of SurgicalOncology.*2007;14(6):1904-1908.
BACKGROUND: Despite recent advances in breast-conserving surgery, upper-extremity lymphedema remains a problem for patients after the treatment of breast cancer. This study examines the results of a protocol of therapy for lymphedema in breast cancer patients. METHODS: A total of 135 patients with lymphedema after breast cancer treatment were provided a protocol of complete decongestive therapy (CDT). This involved manual lymphatic drainage, compression garments, skin care, and range-of-motion exercises. Therapy was divided into an induction phase involving twice-weekly therapy for 8 weeks and maintenance therapy individualized to patient needs. Absolute volume and percentage of volume of lymphedema was compared before and after treatment. Also assessed was the degree of chronic pain and the need for pain medication. RESULTS: Mean initial lymphedema volume was 709 mL, and the percentage of lymphedema was 31%. The induction phase of CDT reduced this to 473 mL and 18%, respectively. Before therapy, 76 patients had chronic pain and 41 required oral pain medication. CDT reduced this to 20 and 11, respectively. The degree of pain was also assessed on a numerical scale from 0 to 10. Those patients with chronic pain initially rated their pain at an average of 6.9. After treatment, this was reduced to 1.1. CONCLUSIONS: Lymphedema continues to be a problem for patients with breast cancer. A program of lymphedema therapy can reduce the volume of edema and reduce pain in this population.

Montgomery GH, Bovbjerg DH, Schnur JB, et al. **A randomized clinical trial of a brief hypnosis intervention to control side effects in breast surgery patients.** *J Natl Cancer Inst.* 2007Sep5;99(17):1304-1312.
BACKGROUND: Breast cancer surgery is associated with side effects, including postsurgical pain, nausea, and fatigue. We carried out a randomized clinical trial to test the hypotheses that a brief presurgery hypnosis intervention would decrease intraoperative anesthesia and analgesic use and side effects associated with breast cancer surgery and that it would be cost effective. METHODS: We randomly assigned 200 patients who were scheduled to undergo excisional breast biopsy or lumpectomy (mean age 48.5 years) to a 15-minute presurgery hypnosis session conducted by a psychologist or nondirective empathic listening (attention control). Patients were not blinded to group assignment. Intraoperative anesthesia use (i.e., of the analgesics lidocaine and fentanyl and the sedatives propofol and midazolam) was assessed. Patient-reported pain and other side effects as measured on a

visual analog scale (0-100) were assessed at discharge, as was use of analgesics in the recovery room. Institutional costs and time in the operating room were assessed via chart review. RESULTS: Patients in the hypnosis group required less propofol (means = 64.01 versus 96.64 microg; difference = 32.63; 95% confidence interval [CI] = 3.95 to 61.30) and lidocaine (means = 24.23 versus 31.09 mL; difference = 6.86; 95% CI = 3.05 to 10.68) than patients in the control group. Patients in the hypnosis group also reported less pain intensity (means = 22.43 versus 47.83; difference = 25.40; 95% CI = 17.56 to 33.25), pain unpleasantness (means = 21.19 versus 39.05; difference = 17.86; 95% CI = 9.92 to 25.80), nausea (means = 6.57 versus 25.49; difference = 18.92; 95% CI = 12.98 to 24.87), fatigue (means = 29.47 versus 54.20; difference = 24.73; 95% CI = 16.64 to 32.83), discomfort (means = 23.01 versus 43.20; difference = 20.19; 95% CI = 12.36 to 28.02), and emotional upset (means = 8.67 versus 33.46; difference = 24.79; 95% CI = 18.56 to 31.03). No statistically significant differences were seen in the use of fentanyl, midazolam, or recovery room analgesics. Institutional costs for surgical breast cancer procedures were $8561 per patient at Mount Sinai School of Medicine. Patients in the hypnosis group cost the institution $772.71 less per patient than those in the control group (95% CI = 75.10 to 1469.89), mainly due to reduced surgical time. CONCLUSIONS: Hypnosis was superior to attention control regarding propofol and lidocaine use; pain, nausea, fatigue, discomfort, and emotional upset at discharge; and institutional cost. Overall, the present data support the use of hypnosis with breast cancer surgery patients.

Prostate

John EM, Koo J, Schwartz GG. **Sun exposure and prostate cancer risk: evidence for a protective effect of early-life exposure.** *Cancer Epidemiol Biomarkers Prev.* 2007 Jun;16(6):1283-1286.
Mounting experimental and epidemiologic evidence supports the hypothesis that vitamin D reduces the risk of prostate cancer. Some evidence suggests that prostate cancer risk may be influenced by sun exposure early in life. We analyzed data from the National Health and Nutrition Examination Survey I Epidemiologic Follow-up Study to examine associations of prostate cancer risk with early-life and adult residential sun exposure and adult sun exposures that were assessed through self-report, physician report, and dermatologic examination. We used solar radiation in the state of birth as a measure of sun exposure in early life. Follow-up from 1971 to 1975 (baseline) to 1992 identified 161 prostate cancer cases (102 nonfatal and 59 fatal) among non-Hispanic white men for whom sun exposure data were available. Significant inverse associations were found for men born in a region of high solar radiation (relative risk, 0.49, 95% confidence interval, 0.27-0.90 for high versus low solar radiation), with a slightly greater reduction for fatal than for nonfatal prostate cancer. Frequent recreational sun exposure in adulthood was associated with a significantly reduced risk of fatal prostate cancer only (relative risk, 0.47; 95% confidence interval, 0.23-0.99). These findings suggest that, in addition to sun exposure in adulthood, sun exposure in early life protects against prostate cancer.

Vaishampayan U, Hussain M, Banerjee M, et al. **Lycopene and soy isoflavones in the treatment of prostate cancer.** *Nutr Cancer.*2007;59(1):1-7.
Dietary intake of lycopene and soy has been associated with a lower risk of prostate cancer. In vitro studies with lycopene and genistein, a soy isoflavone, have shown induction of apoptosis and inhibition of cell growth in androgen-sensitive (LNCaP) and androgen-independent (PC3 and VeCaP) prostate cancer cell lines. In a previous Phase II clinical trial in prostate cancer patients, we observed prostate-specific antigen (PSA) stabilization with soy isoflavone intake. In this Phase II clinical trial, we investigated the efficacy of lycopene alone or in combination with soy isoflavones on serum PSA levels in men with prostate cancer. To be eligible for the study, men with prostate cancer had to have rising serum PSA following local therapy or while on hormone therapy. Study population included 71 eligible patients who had 3 successive rising PSA levels or a minimum PSA of 10 ng/ml at 2 successive evaluations prior to starting therapy. Subjects were randomly assigned to receive a tomato extract capsule containing 15 mg of lycopene alone (n = 38) or together with a capsule containing 40 mg of a soy isoflavone mixture (n = 33) twice daily orally for a maximum of 6 mo. One patient on the lycopene arm did not receive therapy due to his inability to ingest the study pill. There was no decline in serum PSA in either group qualifying for a partial or complete response. However, 35 of 37 (95%) evaluable patients in the lycopene group and 22 of 33 (67%) evaluable patients in the lycopene plus soy isoflavone group achieved stable disease described as stabilization in serum PSA level. The data suggest that lycopene and soy isoflavones have activity in prostate cancer patients with PSA relapse disease and may delay progression of both hormone-refractory and hormone-sensitive prostate cancer. However, there may not be an additive effect between the 2 compounds when taken together. Future studies are warranted to further investigate the efficacy of lycopene and soy isoflavones in prostate cancer as well as the mechanism of potential negative interaction between them.

Zhang J, Dhakal I, Stone A, et al. **Plasma carotenoids and prostate cancer: A population-based case-control study in arkansas.***NutrCancer.*2007;59(1):46-53.
Carotenoids possess antioxidant properties and thus may protect against prostate cancer. Epidemiological studies of dietary carotenoids and this malignancy were inconsistent, partially due to dietary assessment error. In this study, we aimed to investigate the relation between plasma concentrations of carotenoids and the risk of prostate cancer in a population-based case-control study in Arkansas. Cases (n = 193) were men with prostate cancer diagnosed in 3 major hospitals, and controls (n = 197) were matched to cases by age, race, and county of residence. After adjustment for confounders, plasma levels of lycopene, lutein/zeaxanthin, and beta-cryptoxanthin were inversely associated with prostate cancer risk. Subjects in the highest quartile of plasma lycopene (513.7 mug/l) had a 55% lower risk of prostate cancer than those in the lowest quartile (140.5 mug/l; P trend = 0.042). No apparent association was observed for plasma alpha-carotene and beta-carotene. Further adjustment for the other 4 carotenoids did not materially alter the risk estimates for plasma lycopene, lutein/zeaxanthin, and beta-cryptoxanthin but appeared to result in an elevated risk with high levels of plasma alpha-carotene and beta-carotene. The results of all analyses did not vary substantially by age, race, and smoking status. This study added to the emerging evidence that high circulating levels of lycopene, lutein/zeaxanthin, and beta-cryptoxanthin are associated with a low risk of prostate cancer.

Gastrointestinal

Kuchler T, Bestmann B, Rappat S, et al. **Impact of psychotherapeutic support for patients with gastrointestinal cancer undergoing surgery: 10-year survival results of a randomized trial**. *J Clin Oncol.* 2007 July 1;25(19):2702-2708.
Purpose: The impact of psychotherapeutic support on survival for patients with gastrointestinal cancer undergoing surgery was studied. *Methods*: A randomized controlled trial was conducted in cooperation with the Departments of General Surgery and Medical Psychology, University Hospital of Hamburg, Germany, from January 1991 to January 1993. Consenting patients (N = 271) with

a preliminary diagnosis of cancer of the esophagus, stomach, liver/gallbladder, pancreas, or colon/rectum were stratified by sex and randomly assigned to a control group that received standard care as provided on the surgical wards, or to an experimental group that received formal psychotherapeutic support in addition to routine care during the hospital stay. From June 2003 to December 2003, the 10-year follow-up was conducted. Survival status for all patients was determined from our own records and from three external sources: the Hamburg cancer registry, family doctors, and the general citizen registration offices. *Results*: Kaplan-Meier survival curves demonstrated better survival for the experimental group than the control group. The unadjusted significance level for group differences was P = .0006 for survival to 10 years. Cox regression models that took TNM staging or the residual tumor classification and tumor site into account also found significant differences at 10 years. Secondary analyses found that differences in favor of the experimental group occurred in patients with stomach, pancreatic, primary liver, or colorectal cancer. *Conclusion*: The results of this study indicate that patients with gastrointestinal cancer, who undergo surgery for stomach, pancreatic, primary liver, or colorectal cancer, benefit from a formal program of psychotherapeutic support during the inpatient hospital stay in terms of long-term survival.

Brain

Hardell L, Carlberg M, Soderqvist F, et al. **Long-term use of cellular phones and brain tumours: Increased risk associated with use for >=10 years.** *Occup Environ Med.* 2007 September 1;64(9):626-632.

Aim: To evaluate brain tumour risk among long-term users of cellular telephones. Methods: Two cohort studies and 16 casecontrol studies on this topic were identified. Data were scrutinised for use of mobile phone for [>=]10 years and ipsilateral exposure if presented. Results: The cohort study was of limited value due to methodological shortcomings in the study. Of the 16 casecontrol studies, 11 gave results for [>=]10 years' use or latency period. Most of these results were based on low numbers. An association with acoustic neuroma was found in four studies in the group with at least 10 years' use of a mobile phone. No risk was found in one study, but the tumour size was significantly larger among users. Six studies gave results for malignant brain tumours in that latency group. All gave increased odd ratios (OR), especially for ipsilateral exposure. In a meta-analysis, ipsilateral cell phone use for acoustic neuroma was OR = 2.4 (95% CI 1.1 to 5.3) and OR = 2.0, (1.2 to 3.4) for glioma using a tumour latency period of [>=]10 years. Conclusions: Results from present studies on use of mobile phones for [>=]10 years give a consistent pattern of increased risk for acoustic neuroma and glioma. The risk is highest for ipsilateral exposure.

Skin

Lehto US, Ojanen M, Dyba T, et al. **Baseline psychosocial predictors of survival in localized melanoma.** *J Psychosom Res.*2007Jul;63(1):9-15.

OBJECTIVE: There is no certainty about the contributing factors or the psychological processes involved in cancer progression. Many studies have suffered from poor theoretical basis, methodological flaws, and only one or few psychosocial factors investigated at a time. We examined the simultaneous contribution of several theory-based psychosocial elements to survival time in melanoma. METHODS: A consecutive sample of patients with localized (Clarke II-IV) melanoma (N=59) were evaluated with validated questionnaires on coping with cancer, anger expression, perceived social support, noncancer life stresses, and domains of quality of life (QOL) 3-4 months after diagnosis. Cox regression analyses were used to determine the predictors of survival time from the date of diagnosis to the date of death or the last follow-up. RESULTS: After controlling for age, gender, and Breslow depth for the tumor, the baseline psychological variables related to the cancer-prone Type C response pattern, namely, anger nonexpression (repression), hopelessness, and better single-item self-reported QOL predicted shorter survival. Before hopelessness was added to the model, the amount of depressive symptoms and heavy perceived impact of diagnosis were also predictive. In addition, longer survival was strongly predicted by Cognitive Escape-Avoidance coping, which included items close to the concept of denial/minimizing. CONCLUSION: Anger nonexpression, hopelessness, and overpositive reporting of QOL--all proposed to include in the Type C response style or reflect emotional nonexpression--seem to comprise a set of factors that reduce survival, whereas denial/minimizing response to the diagnosis as such predicts longer survival.

Multiple Myeloma

Hosgood III HD, Baris D, Zahm SH, et al. **Diet and risk of multiple myeloma in connecticut women.** *Cancer Causes and Control.* 2007Dec;18(10):1065-1076.

Multiple myeloma accounts for an estimated 19,900 incident cancer cases per year in the United States. A population-based case-control study, consisting of 179 incident cases and 691 controls, was conducted to examine the impact of diet on multiple myeloma risk. Diet was assessed using a food frequency questionnaire and odds ratios, 95% confidence intervals, and P-trends were calculated across quartiles of consumption. After controlling for potential confounders, we observed inverse associations for cooked tomatoes (P-trend = 0.002), cruciferous vegetables (P-trend = 0.01), fresh fish (P-trend < 0.001), alcohol (P-trend < 0.001), and vitamin A (P-trend < 0.001) with multiple myeloma risk. In contrast, consumption of cream soups (P-trend = 0.01), jello (P-trend = 0.01), ice cream (P-trend = 0.01), and pudding (P-trend < 0.001) were positively associated with multiple myeloma. Furthermore, there was a suggestion that carbohydrate intake may be positively associated, whereas vitamin D and calcium intake may be inversely associated, with multiple myeloma risk. Despite very limited data on dietary factors in relation to multiple myeloma, the findings from this study concur with previously published studies, suggesting an inverse association for consumption of fish, cruciferous vegetables and green vegetables, and a positive association for some dairy products.

Nutrition

Chan J, Wang F, Holly E. **Whole grains and risk of pancreatic cancer in a large population-based case-control study in the San Francisco bay area, California.** *Am J Epidemiol.* 2007 September18.

Epidemiologic data suggest that consumption of whole-grain products may be inversely associated with risk of pancreatic cancer. Grain intake was examined in a population-based case-control study of pancreatic cancer in the San Francisco Bay Area (19951999). A 131-item semiquantitative food frequency questionnaire was administered to 532 cases and 1,701 controls. Odds ratios and 95% confidence intervals were computed as estimates of relative risk. Persons who consumed [≥]2 servings of whole grains daily had a lower risk of pancreatic cancer than persons who consumed <1 serving/day (odds ratio (OR) = 0.60, 95% confidence interval (CI): 0.31, 1.2; trend-p = 0.04). Similar results were observed for brown rice (OR = 0.72, 95% CI: 0.44, 1.2; trend-p = 0.01) and tortillas (OR = 0.56, 95% CI: 0.35, 0.89; trend-p = 0.02). Consumption of doughnuts ([≥]2 servings/week vs. <1 serving/month) conferred increased risk (OR = 1.8, 95% CI: 1.2, 2.7; trend-p = 0.003). Consumption of cooked breakfast cereals ([≥]2 servings/week vs. <1 serving/month) was positively associated with risk (for oatmeal/oat bran, OR = 1.3, 95% CI: 1.0, 1.7; for other cooked breakfast cereals, OR = 2.1, 95% CI: 1.4,

3.3). Dietary fiber was inversely associated with risk (for highest quartile vs. lowest, OR = 0.65, 95% CI: 0.47, 0.89; trend-p = 0.02). These data provide some support for the hypothesis that consuming more whole-grain or high-fiber foods may reduce the risk of pancreatic cancer. Refined grains were not associated with risk.

Yang G, Shu XO, Li H, et al. **Prospective cohort study of green tea consumption and colorectal cancer risk in women.** *Cancer Epidemiol Biomarkers Prev.* 2007 Jun;16(6):1219-1223. Tea and its constituents have shown anticarcinogenic activities in in vitro and animal studies. Epidemiologic studies, however, have been inconsistent. We prospectively evaluated the association between green tea consumption and colorectal cancer (CRC) risk in a cohort of 69,710 Chinese women aged 40 to 70 years. Information on tea consumption was assessed through in-person interviews at baseline and reassessed 2 to 3 years later in a follow-up survey. During 6 years of follow-up, 256 incident cases of CRC were identified. The multivariate relative risk of CRC was 0.63 (95% confidence interval, 0.45-0.88) for women who reported drinking green tea regularly at baseline compared with nonregular tea drinkers. A significant dose-response relationship was found for both the amount of tea consumed (Ptrend = 0.01) and duration in years of lifetime tea consumption (Ptrend = 0.006). The reduction in risk was most evident among those who consistently reported to drink tea regularly at both the baseline and follow-up surveys (relative risk, 0.43; 95% confidence interval, 0.24-0.77). The inverse association with regular tea drinking was observed for both colon and rectal cancers. This study suggests that regular consumption of green tea may reduce CRC risk in women.

Linseisen J, Rohrmann S, Miller AB, et al. **Fruit and vegetable consumption and lung cancer risk: Updated information from the European Prospective Investigation into Cancer and nutrition (EPIC).** *Int J Cancer.* 2007 Sep 1;121(5):1103-1114. The association of fruit and vegetable consumption and lung cancer incidence was evaluated using the most recent data from the European Prospective Investigation into Cancer and Nutrition (EPIC), applying a refined statistical approach (calibration) to account for measurement error potentially introduced by using food frequency questionnaire data. Between 1992 and 2000, detailed information on diet and life-style of 478,590 individuals participating in EPIC was collected. During a median follow-up of 6.4 years, 1,126 lung cancer cases were observed. Multivariate Cox proportional hazard models were applied for statistical evaluation. In the whole study population, fruit consumption was significantly inversely associated with lung cancer risk while no association was found for vegetable consumption. In current smokers, however, lung cancer risk significantly decreased with higher vegetable consumption; this association became more pronounced after calibration, the hazard ratio (HR) being 0.78 (95% CI 0.62-0.98) per 100 g increase in daily vegetable consumption. In comparison, the HR per 100 g fruit was 0.92 (0.85-0.99) in the entire cohort and 0.90 (0.81-0.99) in smokers. Exclusion of cases diagnosed during the first 2 years of follow-up strengthened these associations, the HR being 0.71 (0.55-0.94) for vegetables (smokers) and 0.86 (0.78-0.95) for fruit (entire cohort). Cancer incidence decreased with higher consumption of apples and pears (entire cohort) as well as root vegetables (smokers). In addition to an overall inverse association with fruit intake, the results of this evaluation add evidence for a significant inverse association of vegetable consumption and lung cancer incidence in smokers.

Supplements

Meyer F, Bairati I, Jobin E, et al. **Acute adverse effects of radiation therapy and local recurrence in relation to dietary and plasma beta carotene and alpha tocopherol in head and neck cancer patients.** *Nutr Cancer.* 2007;59(1):29-35. There is a debate concerning the effects of antioxidant vitamins during radiation therapy: Can they reduce the adverse effects of therapy without reducing treatment efficacy? We examined whether dietary and plasma beta carotene and alpha tocopherol were related to severe acute adverse effects of radiation therapy and to cancer local recurrence. We conducted a prospective study of 540 head and neck cancer patients treated by radiation therapy. Dietary intakes of beta carotene and alpha tocopherol were measured by a validated food frequency questionnaire and plasma levels were determined. Acute adverse effects of radiation therapy and local recurrence were documented. A higher beta carotene dietary intake was associated with fewer severe acute adverse effects: odds ratio (OR) = 0.61 [95% confidence interval (CI) = 0.40-0.93]. There was a tendency for a similar effect for plasma beta carotene: OR = 0.73 (95% CI = 0.48-1.11). Participants with higher plasma beta carotene had a significantly lower rate of local recurrence (hazard ratio = 0.67; 95% CI = 0.45-0.99). Alpha tocopherol was not related to severe adverse effects or to cancer recurrence. This study suggests that a higher usual dietary beta carotene intake can reduce the occurrence of severe adverse effects of radiation therapy and decrease local cancer recurrence.

CAM of the Month

Molassiotis A, Helin AM, Dabbour R, et al. **The effects of P6 acupressure in the prophylaxis of chemotherapy-related nausea and vomiting in breast cancer patients.** *Complement TherMed.*200703;15(1):3-12.

BACKGROUND: Nausea, and to a lesser extend vomiting, remain significant clinical problems after the administration of chemotherapy, with up to 60% of patients reporting nausea despite use of antiemetics. Combining antiemetics with other non-pharmacological treatments may prove more effective in decreasing nausea than antiemetics alone. Hence, the aim of the current study was to evaluate the effectiveness of using acupressure in Pericardium 6 (Neiguan) acu-point in managing chemotherapy-induced nausea and vomiting. METHODS: This was a randomised controlled trial. Acupressure was applied using wristbands (Sea-Band) which patients in the experimental group had to wear for the 5 days following the chemotherapy administration. Assessments of nausea, retching and vomiting were obtained from all patients daily for 5 days. Thirty-six patients completed the study from two centres in the UK, with 19 patients allocated to the control arm and 17 to the experimental arm. RESULTS: It was found that nausea and retching experience, and nausea, vomiting and retching occurrence and distress were all significantly lower in the experimental group compared to the control group ($P<0.05$). The only exception was with the vomiting experience, which was close to significance ($P=0.06$). DISCUSSION: Results highlight the important role of safe and convenient non-pharmacological complementary therapies, such as acupressure, in the management of the complex symptoms of chemotherapy-related nausea and vomiting.