

RESEARCH UPDATES

For the latest in world-wide integrated cancer care research

June 2007

Breast

Garland CF, Gorham ED, Mohr SB, et al. **Vitamin D and prevention of breast cancer: pooled analysis.** *J Steroid Biochem Mol Biol* 2007;103(3-5):708-11.

Background: Inadequate photosynthesis or oral intake of Vitamin D are associated with high incidence and mortality rates of breast cancer in ecological and observational studies, but the dose-response relationship in individuals has not been adequately studied. Methods: A literature search for all studies that reported risk by of breast cancer by quantiles of 25(OH)D identified two studies with 1760 individuals. Data were pooled to assess the dose-response association between serum 25(OH)D and risk of breast cancer. Results: The medians of the pooled quintiles of serum 25(OH)D were 6, 18, 29, 37 and 48 ng/ml. Pooled odds ratios for breast cancer from lowest to highest quintile, were 1.00, 0.90, 0.70, 0.70 and 0.50 (p trend < 0.001). According to the pooled analysis, individuals with serum 25(OH)D of approximately 52 ng/ml had 50% lower risk of breast cancer than those with serum <13 ng/ml. This serum level corresponds to intake of 4000 IU/day. This exceeds the National Academy of Sciences upper limit of 2000 IU/day. A 25(OH)D level of 52 ng/ml could be maintained by intake of 2000 IU/day and, when appropriate, about 12 min/day in the sun, equivalent to oral intake of 3000 IU of Vitamin D3. Conclusions: Intake of 2000 IU/day of Vitamin D3, and, when possible, very moderate exposure to sunlight, could raise serum 25(OH)D to 52 ng/ml, a level associated with reduction by 50% in incidence of breast cancer, according to observational studies.

Schultz PE, Haberman M, Nichols J, et al. **Down-regulated lymphocyte NF- κ B activation in breast cancer survivors following yoga participation.** *FASEB J* 2007;21:765-7.

The purpose of the study was to examine lymphocyte NF- κ B activation in female breast cancer survivors who participated in eight weeks of yoga. Survivors (Stages I-IV, age 61+7.4 yr, mean+SD) were randomly assigned to yoga (Y, n = 10) or waitlisted (WL, n = 9) groups. Iyengar yoga practice included two 90-minute classes per week plus one home practice. Demands of Illness (DOI) and lymphocyte NF- κ B activation were evaluated pre- (T1) and post-yoga (T2). Lymphocyte NF-

activation (Y, n = 5; WL, n = 4) was determined by EMSA following stimulation by phorbol 12-myristate 13-acetate, phytohemagglutinin and ionomycin. These data were initially analyzed by Mann-Whitney U test and Spearman Rank Order Correlation test. Results indicated that DOI significantly declined (p = 0.038) from T1 to T2 with yoga. The change in NF- κ B activation from T1 (Y = 2563+1076, WL = 2029+1456, integrated density value/ μ g protein/ 10^6 cells) to T2 (Y = 1439 + 1142, WL = 2359+443) was significantly different (p = 0.039) between groups. Linear regression analysis of DOI and log transformed NF- κ B activation data revealed a significant association between variables (r = 0.75, p = 0.01) in yoga participants only. These findings lend support to the hypothesis that yoga participation by breast cancer survivors can attenuate illness-related stressors and alter lymphocyte NF- κ B regulation.

Knight JA, Lesosky M, Barnett H, et al. **Vitamin D and reduced risk of breast cancer: A population-based case-control study.** *Cancer Epidemiol Biomark Prev* 2007;16(3):422-9. Background: Vitamin D, antiproliferative and proapoptotic in breast cancer cell lines, can reduce the development of mammary tumors in carcinogen-exposed rats. Current evidence in humans is limited with some suggestion that vitamin D-related factors may reduce the risk of breast cancer. We conducted a population-based case-control study to assess the evidence for a relationship between sources of vitamin D and breast cancer risk. Methods: Women with newly diagnosed invasive breast cancer were identified from the Ontario Cancer Registry. Women without breast cancer were identified through randomly selected residential telephone numbers. Telephone interviews were completed for 972 cases and 1,135 controls. Odds ratios (OR) and 95% confidence intervals (CI) for vitamin D-related variables were estimated using unconditional logistic regression with adjustment for potential confounders. Results: Reduced breast cancer risks were associated with increasing sun exposure from ages 10 to 19 (e.g., OR, 0.65; 95% CI, 0.50-0.85 for the highest quartile of outdoor activities versus the lowest; P for trend = 0.0006). Reduced risk was also associated with cod liver oil use (OR, 0.76; 95% CI, 0.62-0.92) and increasing milk consumption (OR, 0.62 95% CI 0.45-0.86 for \geq 10 glasses per week versus none; P for trend = 0.0004). There was weaker evidence for associations from ages 20 to 29 and no evidence for ages 45 to 54. Conclusion: We found strong



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evidence to support the hypothesis that vitamin D could help prevent breast cancer. However, our results suggest that exposure earlier in life, particularly during breast development, may be most relevant. These results should be confirmed.

Molassiotis A. **The effects of P6 acupressure in the prophylaxis of chemotherapy-related nausea and vomiting in breast cancer patients.** *Comp Ther Med* 2007;15 (1): 3-12.

BACKGROUND: Nausea, and to a lesser extent 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.

Prostate

Li H, Stampfer MJ, Hollis JBW, et al. **A prospective study of plasma vitamin D metabolites, vitamin D receptor polymorphisms, and prostate cancer.** *Plos Med* 2007; 4(3):562-571.


Background: Vitamin D insufficiency is a common public health problem nationwide. Circulating 25-hydroxyvitamin D3 (25[OH]D), the most commonly used index of vitamin D status, is converted to the active hormone 1,25 dihydroxyvitamin D3 (1,25[OH] $<inf>2</inf>$ D), which, operating through the vitamin D receptor (VDR), inhibits in vitro cell proliferation, induces differentiation and apoptosis, and may protect against prostate cancer. Despite intriguing results from laboratory studies, previous epidemiological studies showed inconsistent associations of circulating levels of 25(OH)D, 1,25(OH) 2D, and several VDR polymorphisms with prostate cancer risk. Few studies have explored the joint association of circulating vitamin D levels with VDR polymorphisms. **Methods and Findings:** During 18 y of follow-up of 14,916 men initially free of diagnosed cancer, we identified 1,066 men with incident prostate cancer (including 496 with aggressive disease, defined as stage C or D, Gleason 7-10, metastatic, and fatal prostate cancer) and 1,618 cancer-free, age- and smoking-matched control participants in the Physicians' Health Study. We examined the associations of prediagnostic plasma levels of 25(OH)D and 1,25(OH) 2 D, individually and jointly, with total and aggressive disease, and explored whether relations between vitamin D metabolites and prostate cancer were modified by the functional VDR FokI polymorphism, using conditional logistic regression. Among these US physicians,

the median plasma 25(OH)D levels were 25 ng/ml in the blood samples collected during the winter or spring and 32 ng/ml in samples collected during the summer or fall. Nearly 13% (summer/fall) to 36% (winter/spring) of the control participants were deficient in 25(OH)D (<20 ng/ml) and 51% (summer/fall) and 77% (winter/spring) had insufficient plasma 25(OH)D levels (<32 ng/ml). Plasma levels of 1,25(OH) $<inf>2</inf>$ D did not vary by season. Men whose levels for both 25(OH)D and 1,25(OH) 2D were below (versus above) the median had a significantly increased risk of aggressive prostate cancer (odds ratio [OR] = 2.1, 95% confidence interval [CI] 1.2-3.4), although the interaction between the two vitamin D metabolites was not statistically significant (p interaction = 0.23). We observed a significant interaction between circulating 25(OH)D levels and the VDR FokI genotype (p interaction < 0.05). Compared with those with plasma 25(OH)D levels above the median and with the FokI FF or Ff genotype, men who had low 25(OH)D levels and the less functional FokI ff genotype had increased risks of total (OR=1.9, 95% CI 1.1-3.3) and aggressive prostate cancer (OR=2.5, 95% CI 1.1-5.8). Among men with plasma 25(OH)D levels above the median, the ff genotype was no longer associated with risk. Conversely, among men with the ff genotype, high plasma 25(OH)D level (above versus below the median) was related to significant 60%-70% lower risks of total and aggressive prostate cancer. **Conclusions:** Our data suggest that a large proportion of the US men had suboptimal vitamin D status (especially during the winter/spring season), and both 25(OH)D and 1,25(OH) 2 D may play an important role in preventing prostate cancer progression. Moreover, vitamin D status, measured by 25(OH)D in plasma, interacts with the VDR FokI polymorphism and modifies prostate cancer risk. Men with the less functional FokI ff genotype (14% in the European-descent population of this cohort) are more susceptible to this cancer in the presence of low 25(OH)D status.

Calton BA, Chang SC, Wright ME, et al. **History of diabetes mellitus and subsequent prostate cancer risk in the NIH-AARP Diet and Health Study.** *Cancer Causes Control* 2007;18(5):493-503.

Objective: A history of diabetes has been hypothesized to decrease prostate cancer risk, but studies have not always considered confounding or effect modification by dietary or lifestyle factors. **Methods:** We examined the association between diabetes history and subsequent prostate cancer risk in 328,316 men enrolled in the NIH-AARP Diet and Health Study. Participants were ages 50-71 years and without a prostate cancer diagnosis at baseline in 1995. A prior history of physician-diagnosed diabetes was assessed using a self-administered mailed questionnaire. Cases of prostate cancer were ascertained by matching the cohort to state cancer registries. Multivariable relative risks (RR) and 95% confidence intervals (CI) of prostate cancer were estimated using Cox regression. **Results:** During 5 years and 1,432,676 person-years of follow-up, 11,193 prostate cancer cases were ascertained. The age-adjusted and multivariable RRs of prostate cancer comparing men with diabetes to those without diabetes were 0.69 (95% CI = 0.64, 0.74) and 0.71 (95% CI = 0.66, 0.76), respectively, indicating no important confounding. The inverse association between diabetes and prostate cancer was particularly strong among men in the highest category of routine physical activity at work or home (RR = 0.41; 95% CI = 0.23, 0.74; p value for test of interaction = 0.03). Findings were similar for organ-confined and advanced prostate cancer. **Conclusion:** Results from this large prospective study suggest that a history of diabetes is associated with a decreased risk of prostate cancer. The relationship strengthened with high levels of routine

physical activity. Because increased physical activity is associated with lower circulating levels of insulin and testosterone, our findings support a role of hypoinsulinemia and low androgenicity linking diabetes to decreased prostate cancer risk.

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Thank you for your generous support!

Colorectal

Mai PL, Sullivan-Halley J, Ursin G, et al. **Physical activity and colon cancer risk among women in the California Teachers Study.** *Cancer Epidemiol Biomark Prev* 2007;16(3):517-25.

Background: Existing data suggest that physical activity reduces colon cancer risk, but the association is not consistently observed in women. One potential explanation for this inconsistency is that hormone therapy, which is associated with lower colon cancer risk, acts as a modifier of the physical activity/colon cancer relationship. Methods: Participants in the California Teachers Study (N = 120,147), a prospective cohort of female teachers and administrators residing in California, ages 22 to 84 years at baseline and with no prior history of colon cancer were eligible for study. Between 1996 and 2002, 395 patients were diagnosed with invasive colon cancer. The relative risks (RR) associated with lifetime (high school through age 54 years or current age) and recent (past 3 years) strenuous and moderate recreational physical activity were estimated using Cox proportional hazards regression models. Results: Combined lifetime moderate and strenuous recreational physical activity was only modestly associated with colon cancer risk in the cohort [≥ 4 versus ≤ 0.5 h/wk/y: RR, 0.75; 95% confidence interval, 0.57-1.00; Ptrend = 0.23]. Lifetime physical activity reduced colon cancer risk among postmenopausal women who had never taken hormone therapy (≥ 4 versus ≤ 0.5 h/wk/y: RR, 0.51; 95% confidence interval, 0.31-0.85; Ptrend = 0.02). Postmenopausal women with histories of hormone therapy use had lower colon cancer risk, but their risk was not associated with physical activity. The likelihood ratio test for interaction between hormone use and lifetime moderate plus strenuous physical activity was of borderline statistical significance (P = 0.05). We observed no effect modification by age, body mass index, smoking status, menopausal status, or folate intake. Conclusions: Lifetime recreational physical activity may protect against colon cancer among postmenopausal women who have never used hormone therapy. Among hormone therapy users, who have lower risk of colon cancer, recreational physical activity does not seem to provide any additional benefit. With declining rates of hormone therapy use, physical activity offers one possible means for reducing women's colon cancer risk.

Lee KJ, Inoue M, Otani T, et al. **Coffee consumption and risk of colorectal cancer in a population-based prospective cohort of Japanese men and women.** *Int J Cancer* 2007; epub ahead of print.

We prospectively examined the association between coffee consumption and the risk of developing colorectal cancer in a large population-based cohort study (the JPHC Study) of Japanese men and women. Data were analyzed from a population-based cohort of 96,162 subjects (46,023 men and 50,139 women). A total of 1,163 incident colorectal cancers

were identified during the follow-up period, including 763 cases of colon cancer and 400 of rectal cancer. We observed a significant inverse association between coffee consumption and the risk of developing invasive colon cancer among women. Compared with those who almost never consumed coffee, women who regularly consumed 3 or more cups of coffee per day had a RR of 0.44 (95% CI = 0.19-1.04; p for trend = 0.04) after adjustment for potential confounding factors. However, no significant association was found for rectal cancer in women. In men, no significant decrease was observed in any colorectal cancer site. Further, additional analyses on the association of green tea consumption with colorectal cancer risk found no significant association in men or women. These findings suggest that coffee consumption may lower the risk of colon cancer among Japanese women.

Supplements

Kienle GS, Kiene H. **Complementary cancer therapy: A systematic review of prospective clinical trials on anthroposophic mistletoe extracts.** *Eur J Med Res* 2007;12(3):103-19.

Background: Anthroposophic Mistletoe therapy is a widely used complementary cancer treatment. Objective: To evaluate prospective clinical trials on the effectiveness of anthroposophic mistletoe therapy for cancer. Design: Systematic review. Material and Methods: Search of 9 electronic databases, reference lists and extensive expert consultations. Criteria-based assessment of methodological study quality. Results: 16 randomized (RCT) and 9 non-randomized (N-RCT) controlled trials were identified that investigated mistletoe treatment of malignant diseases. Statistically significant benefit for survival was reported in 8 of 17 trials (in 5 of 10 RCTs), for disease-free survival and tumour recurrence in none of 2 RCTs, for remission of tumour and malignant effusion in 1 RCT and 1 N-RCT of 4 controlled trials, for quality of life (QoL) in 3 of 5 RCTs, and for QoL and reduction of side effects of cytoreductive therapies (chemotherapy, radiation or surgery) in 5 of 7 trials (3 of 5 RCTs). Methodological quality of the controlled trials differed substantially; some had major limitations while others were reasonably well conducted. 12 single-arm cohort studies were identified. 5 of 7 studies found substantial tumour remission in various cancers, one study reported remission of CIN, and 4 studies remission of malignant pleural effusion or ascites. Quality of reporting in cohort studies was mostly reasonably good. Mistletoe application was well tolerated. Conclusions: Regarding quality of studies and consistency of results, the best evidence for efficacy of mistletoe therapy exists for improvement of QoL and reduction of side effects of cytotoxic therapies (chemotherapy, radiation). Survival benefit has been shown but not beyond critique. Tumour remissions are described in cohort studies that investigate the application of high dose or local mistletoe extracts. As several reasonably well-conducted studies indicate beneficial effects, further properly designed trials should be encouraged to investigate clinical efficacy and its possible dependency on the mode of application.

Yeom CH, Jung GC, Song KJ. **Changes of terminal cancer patients' health-related quality of life after high dose vitamin C administration.** *J Korean Med Sci* 2007;22(1):7-11.

Over the years there has been a great deal of controversy on the effect of vitamin C on cancer. To investigate the effects of vitamin C on cancer patients' health-related quality of life, we prospectively studied 39 terminal cancer patients. All patients were given an intravenous administration of 10 g vitamin C

twice with a 3-day interval and an oral intake of 4 g vitamin C daily for a week. And then we investigated demographic data and assessed changes in patients' quality of life after administration of vitamin C. Quality of life was assessed with EORTC QLQ-C30. In the global health/quality of life scale, health score improved from 36+/-18 to 55+/-16 after administration of vitamin C (p=0.001). In functional scale, the patients reported significantly higher scores for physical, role, emotional, and cognitive function after administration of vitamin C (p<0.05). In symptom scale, the patients reported significantly lower scores for fatigue, nausea/vomiting, pain, and appetite loss after administration of vitamin C (p<0.005). The other function and symptom scales were not significantly changed after administration of vitamin C. In terminal cancer patients, the quality of life is as important as cure. Although there is still controversy regarding anticancer effects of vitamin C, the use of vitamin C is considered a safe and effective therapy to improve the quality of life of terminal cancer patients.

Reichrath J. **Sunlight, skin cancer and vitamin D: What are the conclusions of recent findings that protection against solar ultraviolet (UV) radiation causes 25-hydroxyvitamin D deficiency in solid organ-transplant recipients, xeroderma pigmentosum, and other risk groups?.** *J Steroid Biochem Mol Biol* 2007;103(3-5):664-7.

A connection between vitamin D deficiency and severe health problems including various types of cancer has been demonstrated. We have shown that patients that have to protect themselves against solar UV radiation for medical reasons, including patients with xeroderma pigmentosum (XP), basal cell nevus syndrome (BCNS), lupus erythematosus (LE) or transplant recipients, are at risk to develop vitamin D deficiency. We conclude that 25-hydroxyvitamin D serum levels as a measure of vitamin D status have to be analyzed in patients that have to protect themselves against solar UV radiation for medical reasons. Suboptimal vitamin D status has to be substituted (e.g. via oral treatment) to protect against serious vitamin D deficiency-related health problems without increasing the risk to develop solar UV-induced skin cancer. Our finding that protection against solar UV radiation causes vitamin D deficiency underlines the need for re-defining dermatological recommendations for solar UV protection in skin cancer prevention programs.

Nutrition

Austin GL, Adair LS, Galanko JA, et al. **A diet high in fruits and low in meats reduces the risk of colorectal adenomas.** *J Nutr* 2007;137(4):999-1004.

Recent evidence suggests overall dietary patterns, rather than specific dietary components, may be a better predictor of colorectal adenomas or cancers. Using cluster analysis, we aimed to assess the association between dietary patterns and colorectal adenomas and whether adjusting for total energy consumption prior to creating clusters affects this relation. Data from a case-control study of 725 individuals undergoing a colonoscopy were utilized. Cases (n = 203) had ≥ 1 adenoma on colonoscopy, and controls (n = 522) were those who had no adenomas. Dietary data were obtained from an FFQ. Daily intake for 18 different food groups was calculated. The values were transformed into Z-scores. Participants were first clustered without energy adjustment, then again based on their consumption per 1000 kcal (4187 kJ). There was no association between dietary patterns and colorectal adenomas

without energy adjustment prior to creating dietary clusters, as clusters formed as a by-product of energy consumption. After adjusting for energy consumption, 3 distinct clusters emerged: 1) high fruit-low meat cluster; 2) high vegetable-moderate meat cluster; and 3) high meat cluster. After adjusting for potential confounders, the high vegetable-moderate meat cluster (odds ratio [OR] 2.17: [95% CI] 1.20-3.90) and high meat cluster (OR 1.70: [95% CI] 1.04-2.80) were at significantly increased odds of having had an adenoma compared with the high fruit-low meat cluster. A high-fruit, low-meat diet appears to be protective against colorectal adenomas compared with a dietary pattern of increased vegetable and meat consumption.

CAM of the Month

Lopez MaL, Iglesias JM, Del Valle MaO, et al. **Impact of a primary care intervention on smoking, drinking, diet, weight, sun exposure, and work risk in families with cancer experience.** *Cancer Causes Control* 2007;18(5):525-35.

Background: Modifying multiple behavior risks is a promising approach to reduce cancer risk. Primary prevention advices of the European Code against Cancer were included in an educational intervention (EI) using social cognitive theories for motivating families with cancer experiences to adopt six cancer prevention behaviors. Methods: A randomized clinical controlled trial recruited 3,031 patients from Primary Care among cancer patients' relatives. The experimental group (EG) received four EI, one EI every six months, focused on tobacco, alcohol, diet, weight, sun and work, and based on social cognitive models. The impact of the first three EI was calculated measuring at baseline and 18 months later: (a) The percentage of people with each risk behavior; (b) The score reached in a Total Cancer Behavioral Risk (TCBR) indicator; (c) The Odds Ratios at the post-test. Results: Five risk behaviors decreased significantly more (p < 0.01) in the EG than in the CG: Smoking (OR = 0.662), drinking (OR = 0.504), diet (OR = 0.542), weight (OR = 0.698), and sun (OR = 0.389). The TCBR indicator also decreased an average of nearly 5 points (28.42 vs. 23.82), significantly more (p < 0.001) in the EG. Conclusion: Families with cancer experiences changed five cancer risk behaviors when approached in Primary Care with interventions based on social cognitive models.

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, and Dr. Teresa Clarke.

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