



RESEARCH UPDATES

For the latest in worldwide integrated cancer care

April 2009



InspireHealth
INTEGRATED CANCER CARE

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Breast

Larsson, SC, L. Bergkvist and A. Wolk. **Folate Intake and Risk of Breast Cancer by Estrogen and Progesterone Receptor Status in a Swedish Cohort.** *Cancer Epidemiology, Biomarkers & Prevention.* 2008 Dec; 17(12): 3444-3449. **BACKGROUND:** Folate is a B vitamin involved in one-carbon metabolism and has been postulated to influence the risk of breast cancer. However, epidemiologic studies of folate intake in relation to breast cancer risk are inconclusive. We examined the association between dietary folate intake and the risk of breast cancer by estrogen receptor (ER) and progesterone receptor (PR) status of the breast tumor in the Swedish Mammography Cohort. **METHODS:** Our study population consisted of 61,433 women who completed a food frequency questionnaire at baseline (1987-1990) and again in 1997. Cox proportional hazards models were used to estimate rate ratios (RR) with 95% confidence intervals (95% CI). **RESULTS:** During an average of 17.4 years of follow-up, 2,952 incident cases of invasive breast cancer were ascertained. We observed no association between dietary folate intake and risk of total breast cancer or ER+/PR+ or ER-/PR- tumors. The multivariate RR of total breast cancer comparing extreme quintiles of folate intake was 1.01 (95% CI, 0.90-1.13; P(trend) = 0.84). However, folate intake was inversely associated with risk of ER+/PR- breast cancer (n = 417 cases; RR for highest versus lowest quintile, 0.79; 95% CI, 0.59-1.07; P(trend) = 0.01). Results did not vary by alcohol intake or menopausal status. **CONCLUSIONS:** These findings do not support an overall association between folate intake and risk of breast cancer but suggest that folate intake may be inversely associated with ER+/PR- tumors.

Larsson, SC, L. Bergkvist and A. Wolk. **Long-Term Dietary Calcium Intake and Breast Cancer Risk in a Prospective Cohort of Women.** *Am J Clin Nutr.* 2009 Jan; 89(1): 277-282. **BACKGROUND:** Calcium may potentially influence the risk of breast cancer because of

its role in regulating cell proliferation, differentiation, and apoptosis. However, prospective studies of calcium intake in relation to breast cancer incidence are sparse. **OBJECTIVE:** The objective of this study was to prospectively examine and show the association, if any, of dietary calcium intake with risk of breast cancer by estrogen receptor (ER) and progesterone receptor (PR) status of the tumor. **DESIGN:** The Swedish Mammography Cohort is a population-based prospective cohort of 61,433 women who were cancer-free at enrollment in 1987-1990. Dietary calcium intake was assessed with a food-frequency questionnaire at baseline and again in 1997. Cox proportional hazards models were used to estimate rate ratios (RRs) and 95% CIs, adjusted for breast cancer risk factors. **RESULTS:** During an average of 17.4 y of follow-up, 2,952 incident cases of invasive breast cancer were ascertained. Dietary calcium intake was not associated with risk of overall breast cancer; the multivariate RR for the highest compared with the lowest quintile of calcium intake was 0.97 (95% CI: 0.87, 1.09; P for trend: 0.49). There was a statistically significant inverse trend for ER-negative/PR-negative (ER-/PR-) breast cancer (P for trend: 0.02); the multivariate RR for the comparison of extreme quintiles of calcium intake was 0.66 (95% CI: 0.44, 0.99). Calcium intake was not associated with ER-positive/PR-positive (ER+/PR+) or ER+/PR- tumors. **CONCLUSIONS:** Our findings do not support an association between dietary calcium intake and overall breast cancer risk. The inverse relation between calcium intake and ER-/PR- breast cancer requires confirmation in other studies.

Shin, A, C. E. Matthews, X. -O Shu, et al. **Joint Effects of Body Size, Energy Intake, and Physical Activity on Breast Cancer Risk.** *Breast Cancer Res Treat.* 2009 January; 113(1): 153-161. To evaluate the joint effect of body size, energy intake, and physical activity on breast cancer risk, we analyzed information on body weight history, energy intake, anthropometric measurements, and physical activity patterns in a population based case-control study.

Included in this analysis were 3,458 incidence breast cancer cases and 3,474 age-frequency matched controls from the Shanghai Breast Cancer Study. High weight, height, body mass index, waist-to-hip ratio, and weight gain showed stronger associations with breast cancer risk in postmenopausal women than premenopausal women. High total physical activity was inversely associated with postmenopausal breast cancer risk (p for trend = 0.026) and premenopausal breast cancer (p for trend = 0.059). The odds ratios for women with a high waist-to-hip ratio (≥ 0.84) and low total physical activity (≤ 10.9 MET-h/day) had the highest risk for breast cancer (OR = 2.7, 95% CI: 1.4-4.9 for postmenopausal women, OR = 2.1, 95% CI: 1.5-3.1 for premenopausal women) compared to their counterpart with low waist-to-hip ratio (20.5 MET-h/day). We did not find a statistically significant multiplicative interaction between body size, caloric intake and total physical activity on breast cancer risk. copyright 2008 Springer Science+Business Media, LLC.

Wen, W, X. O. Shu, H. Li, et al. **Dietary Carbohydrates, Fiber, and Breast Cancer Risk in Chinese Women.** *Am J Clin Nutr.* 2009 Jan; 891: 283-289.

BACKGROUND: Few studies have investigated the association of dietary carbohydrate and fiber intake with breast cancer risk in women in China, where carbohydrate intake is traditionally high. **OBJECTIVE:** The objective was to prospectively evaluate the association of dietary carbohydrates, glycemic index, glycemic load, and dietary fiber with breast cancer risk and to determine whether the effect of these dietary intakes is modified by age and selected insulin- or estrogen-related risk factors. **DESIGN:** A total of 74,942 women aged 40-70 y were recruited into the Shanghai Women's Health Study, a population-based cohort study. Dietary intake was assessed by in-person interviews. A Cox proportional hazards regression model was used to evaluate associations. **RESULTS:** During an average of 7.35 y of follow-up, 616 incident breast cancer cases were documented. A higher carbohydrate intake was associated with a higher risk of premenopausal breast cancer (P for trend = 0.002). Compared with the lowest quintile, the hazard ratios (and 95% CIs) were 1.47 (1.00, 2.32) and 2.01 (1.26, 3.19) for the fourth and fifth quintiles, respectively. A similar pattern was found for glycemic load. The association between carbohydrate intake and breast cancer was significantly modified by age; the increased breast cancer risk associated with carbohydrate intake was restricted to women who were younger than 50 y. No significant association of breast cancer risk with glycemic index or dietary fiber intake was found. **CONCLUSION:** Our data suggest that a high carbohydrate intake and a diet with a high glycemic load may be associated with breast cancer risk in premenopausal women or women <50 y.

Prostate

Kurahashi, N, M. Iwasaki, M. Inoue, S. Sasazuki and S. Tsugane. **Plasma Isoflavones and Subsequent Risk of Prostate Cancer in a Nested Case-Control Study: The Japan Public Health Center.** *Journal of Clinical Oncology.* 2008 20 Dec; 2636: 5923-5929.

Purpose: The incidence of prostate cancer is much lower in Japanese than Western populations. Given the preventive effects of isoflavones on carcinogenesis in the prostate in many nonhuman studies and the high consumption of isoflavones in Japanese, this low incidence may be partly due to the effects of soy. **Patients and Methods:** We conducted a nested case-control study within the Japan Public Health Center-based Prospective Study. A total of 14,203 men aged 40 to 69 years who had returned the baseline questionnaire and provided

blood samples were observed from 1990 to 2005. During a mean of 12.8 years of follow-up, 201 newly diagnosed prostate cancers were identified. Two matched controls for each case were selected from the cohort. Conditional logistic regression model was used to estimate the odds ratios (ORs) and 95% CIs for prostate cancer in relation to plasma levels of isoflavone. **Results:** Plasma genistein level tended to be inversely associated with the risk of total prostate cancer. Although plasma daidzein showed no association, the highest tertile for plasma equol, a metabolite of daidzein, was significantly associated with a decreased risk of total prostate cancer (OR = 0.60; 95% CI, 0.36 to 0.99; $P_{\text{trend}} = .04$). These inverse associations were strengthened after analysis was confined to localized cases, with ORs in the highest group of plasma genistein and equol compared with the lowest of 0.54 (95% CI, 0.29 to 1.01; $P_{\text{trend}} = .03$) and 0.43 (95% CI, 0.22 to 0.82; $P_{\text{trend}} = .02$), respectively. Plasma isoflavone levels were not statistically significantly associated with the risk of advanced prostate cancer. **Conclusion:** Isoflavones may prevent the development of prostate cancer. copyright 2008 by American Society of Clinical Oncology.

Segal, RJ, R. D. Reid, K. S. Courneya, et al. **Randomized Controlled Trial of Resistance Or Aerobic Exercise in Men Receiving Radiation Therapy for Prostate Cancer.** *Journal of Clinical Oncology.* 2009 Jan 20; 273: 344-351.

PURPOSE: Radiotherapy for prostate cancer (PCa) may cause unfavorable changes in fatigue, quality of life (QOL), and physical fitness. We report results from the Prostate Cancer Radiotherapy and Exercise Versus Normal Treatment study examining the effects of 24 weeks of resistance or aerobic training versus usual care on fatigue, QOL, physical fitness, body composition, prostate-specific antigen, testosterone, hemoglobin, and lipid levels in men with PCa receiving radiotherapy. **PATIENTS AND METHODS:** Between 2003 and 2006, we conducted a randomized controlled trial in Ottawa, Canada, where 121 PCa patients initiating radiotherapy with or without androgen deprivation therapy were randomly assigned to usual care ($n = 41$), resistance ($n = 40$), or aerobic exercise ($n = 40$) for 24 weeks. Our primary end point was fatigue assessed by the Functional Assessment of Cancer Therapy-Fatigue scale. **RESULTS:** The follow-up assessment rate for our primary end point of fatigue was 92.6%. Median adherence to prescribed exercise was 85.5%. Mixed-model repeated measures analyses indicated both resistance ($P = .010$) and aerobic exercise ($P = .004$) mitigated fatigue over the short term. Resistance exercise also produced longer-term improvements ($P = .002$). Compared with usual care, resistance training improved QOL ($P = .015$), aerobic fitness ($P = .041$), upper- ($P < .001$) and lower-body ($P < .001$) strength, and triglycerides ($P = .036$), while preventing an increase in body fat ($P = .049$). Aerobic training also improved fitness ($P = .052$). One serious adverse event occurred in the group that performed aerobic exercise. **CONCLUSION:** In the short term, both resistance and aerobic exercise mitigated fatigue in men with PCa receiving radiotherapy. Resistance exercise generated longer-term improvements and additional benefits for QOL, strength, triglycerides, and body fat.

 Thank you to the **BC Foundation for Prostate Disease** for their generous support.
www.BCPROSTATECANCER.org

Colorectal

Jaszewski, R, S. Misra, M. Tobi, et al. **Folic Acid Supplementation Inhibits Recurrence of Colorectal Adenomas: A Randomized Chemoprevention Trial.** *World Journal of Gastroenterology.* 2008 28 Jul; 1428: 4492-4498. Aim: To determine whether folic acid supplementation will reduce the recurrence of colorectal adenomas, the precursors of colorectal cancer, we performed a double-blind placebo-controlled trial in patients with adenomatous polyps. Methods: In the current double-blind, placebo-controlled trial at this VA Medical Center, patients with colorectal adenomas were randomly assigned to receive either a daily 5 mg dose of folic acid or a matched identical placebo for 3 years. All polyps were removed at baseline colonoscopy and each patient had a follow up colonoscopy at 3 years. The primary endpoint was a reduction in the number of recurrent adenomas at 3 years. Results: Of 137 subjects, who were eligible after confirmation of polyp histology and run-in period to conform compliance, 94 completed the study; 49 in folic acid group and 45 in placebo group. Recurrence of adenomas at 3-year was compared between the two groups. The mean number of recurrent polyps at 3-year was 0.36 (SD, 0.69) for folic acid treated patients compared to 0.82 (SD, 1.17) for placebo treated subjects, resulting in a 3-fold increase in polyp recurrence in the placebo group. Patients below 70 years of age and those with left-sided colonic adenomas or advanced adenomas responded better to folic acid supplementation. Conclusion: High dose folic acid supplementation is associated with a significant reduction in the recurrence of colonic adenomas suggesting that folic acid may be an effective chemopreventive agent for colorectal neoplasia. copyright 2008 The WJG Press. All rights reserved.

Ovarian

Kolahdooz, F, T. I. Ibiebele, J. C. van der Pols and P. M. Webb. **Dietary Patterns and Ovarian Cancer Risk.** *Am J Clin Nutr.* 2009 Jan; 891: 297-304. BACKGROUND: Evidence for a role of individual foods and nutrients in the causation of ovarian cancer is inconclusive. To date, few studies have considered dietary patterns in relation to ovarian cancer risk. OBJECTIVE: We conducted a population-based case-control study in Australia to identify and analyze dietary patterns in relation to ovarian cancer risk. DESIGN: Principal components analysis of 40 food groups was performed to identify eating patterns in 683 women with epithelial ovarian cancer and in 777 control women aged 18-79 y. Detailed information on risk factors was obtained through face-to-face interviews, whereas dietary information was obtained by administering a semiquantitative food-frequency questionnaire for subjects to complete themselves. Multivariable-adjusted odds ratios (ORs) for ovarian cancer risk were estimated with logistic regression modeling. RESULTS: Three major eating patterns were identified: "snacks and alcohol," "fruit and vegetable," and "meat and fat." A significant inverse association between the snacks and alcohol pattern and ovarian cancer risk (highest compared with lowest group, multivariable-adjusted OR: 0.59; 95% CI: 0.43, 0.82; P for trend: 0.001) was attenuated after further adjustment for white or red wine intake. The fruit and vegetable pattern was not associated with risk. The meat and fat pattern was associated with an increased risk of ovarian cancer (highest compared with lowest group, multivariable-adjusted OR: 2.49; 95% CI: 1.75, 3.55; P for trend < 0.0001). Further adjustment for body mass index strengthened this association. CONCLUSIONS: A diet characterized by high meat and fat intake may increase the risk of epithelial ovarian cancer. A diet high in fruit and vegetables

was not associated with reduced risk.

Nutrition

Biondo, PD, D. N. Brindley, M. B. Sawyer and C. J. Field. **The Potential for Treatment with Dietary Long-Chain Polyunsaturated n-3 Fatty Acids during Chemotherapy** *J Nutr Biochem.* 2008 Dec; 1912: 787-796. Dietary intake of long-chain omega-3 (or n-3) polyunsaturated fatty acids (PUFA), eicosapentaenoic acid (EPA), and docosahexaenoic acid (DHA) can affect numerous processes in the body, including cardiovascular, neurological and immune functions, as well as cancer. Studies on human cancer cell lines, animal models and preliminary trials with human subjects suggest that administration of EPA and DHA, found naturally in our diet in fatty fish, can alter toxicities and/or activity of many drugs used to treat cancer. Multiple mechanisms are proposed to explain how n-3 PUFA modulate the tumor cell response to chemotherapeutic drugs. n-3 PUFA are readily incorporated into cell membranes and lipid rafts, and their incorporation may affect membrane-associated signaling proteins such as Ras, Akt and Her-2/neu. Due to their high susceptibility to oxidation, it has also been proposed that n-3 PUFA may cause irreversible tumor cell damage through increased lipid peroxidation. n-3 PUFA may increase tumor cell susceptibility to apoptosis by altering expression or function of apoptotic proteins, or by modulating activity of survival-related transcription factors such as nuclear factor-kappaB. Some studies suggest n-3 PUFA may increase drug uptake or even enhance drug activation (e.g., in the case of some nucleoside analogue drugs). Further research is warranted to identify specific mechanisms by which n-3 PUFA increase chemotherapy efficacy and to determine the optimal cellular/membrane levels of n-3 PUFA required to promote these mechanisms, such that these fatty acids may be prescribed as adjuvants to chemotherapy. [References: 137]

Supplements

Li, GY, X. M. Yu, H. W. Zhang, et al. **Haishengsu as an Adjunct Therapy to Conventional Chemotherapy in Patients with Non-Small Cell Lung Cancer: A Pilot Randomized and Placebo-Controlled Clinical Trial.** *Complement Ther Med.* 2009 Jan; 171: 51-55. OBJECTIVE: To investigate the effect of Haishengsu, an extract from *Tegillarca granosa*, on non-small cell lung cancer as an adjunct to conventional chemotherapy. DESIGNS/SETTINGS: Randomized, double-blind, placebo-controlled trial was conducted in 83 patients. The Haishengsu (n=42, 2.4mg Haishengsu in 250ml normal saline, iv, for 15 days) and the placebo group (n=41, 250ml normal saline, iv) were also treated with two cycles (28 days for each cycle) of conventional chemotherapy consisting mitomycin, vindesine and cisplatin. RESULTS: The curative effect of conventional chemotherapy was observed in 62% of Haishengsu group patients and in 39% in of the placebo group patients (P=0.04, RR 1.59, 95% CI: 1.01-2.49). Improvement in Karnofsky performance status scores was seen in 66.7% of Haishengsu group patients and in 17.1% of the placebo group patients (P<0.01, RR 3.63, 95%CI: 1.77-7.41). The ratio of patients with no or only mild gastrointestinal reaction in the Haishengsu and the placebo group was 83.3% and 39.0%, respectively (P<0.01, RR 2.13, 95% CI: 1.42-3.20). CONCLUSIONS: This study suggests that Haishengsu may be an effective adjunct therapy to the conventional chemotherapy for non-small cell lung cancer. The short-term therapeutic effect of chemotherapy may be improved and the chemotherapy-induced nausea or vomiting may be reduced by concurrent Haishengsu administration.

Sachdanandam, P **Antiangiogenic and Hypolipidemic Activity of Coenzyme Q10 Supplementation to Breast Cancer Patients Undergoing Tamoxifen Therapy.** *Biofactors.* 2008 321-4: 151-159.

Tamoxifen, a non-steroidal anti-estrogen is now widely used and has led to an increase in both disease-free and overall survival of women after primary surgery. Tamoxifen therapy is found to cause hypertriglyceridemia by reducing activity of lipolytic enzymes on triglycerides, and thereby increasing the risk of cardiovascular disease. Angiogenesis promotes local tumour progression and invasion and enables tumour cell dissemination and metastasis formation. Our study has found that co-administration of Coenzyme Q10 (100 mg) along with tamoxifen (10 mg, twice a day) to breast cancer patients reduced the level of angiogenesis markers and lipid levels. copyright 2008 - IUBMB/IOS Press and the authors. All rights reserved.

Psychosocial

Park, CL, D. Edmondson, J. R. Fenster and T. O. Blank. **Positive and Negative Health Behavior Changes in Cancer Survivors: A Stress and Coping Perspective.** *Journal of Health Psychology.* 2008 Nov; 138: 1198-1206. Cancer survivors often make health behavior changes in response to their increased risk for subsequent health problems. However, little is known about the mechanisms underlying these changes or whether they differ for positive and negative changes. This cross-sectional study applied a stress and coping model to examine both positive and negative health behavior changes in 250 middle-aged cancer survivors. A structural equation model showed that social support, sense of control over illness course, life meaning, and approach coping were related to positive health behavior changes; a lack of life meaning and avoidance coping were related to negative health behavior changes.

Rao, MR, N. Raghuram, H. R. Nagendra, et al. **Anxiolytic Effects of a Yoga Program in Early Breast Cancer Patients Undergoing Conventional Treatment: A Randomized Controlled Trial.** *Complement Ther Med.* 2009 January; 171: 1-8.

Objectives: This study compares the anxiolytic effects of a yoga program and supportive therapy in breast cancer outpatients undergoing conventional treatment at a cancer centre. Methods: Ninety-eight stage II and III breast cancer outpatients were randomly assigned to receive yoga (n = 45) or brief supportive therapy (n = 53) prior to their primary treatment i.e., surgery. Only those subjects who received surgery followed by adjuvant radiotherapy and six cycles of chemotherapy were chosen for analysis following intervention (yoga, n = 18, control, n = 20). Intervention consisted of yoga sessions lasting 60 min daily while the control group was imparted supportive therapy during their hospital visits as a part of routine care. Assessments included Spielberger's State Trait Anxiety Inventory and symptom checklist. Assessments were done at baseline, after surgery, before, during, and after radiotherapy and chemotherapy. Results: A GLM-repeated measures ANOVA showed overall decrease in both self-reported state anxiety (p < 0.001) and trait anxiety (p = 0.005) in yoga group as compared to controls. There was a positive correlation between anxiety states and traits with symptom severity and distress during conventional treatment intervals. Conclusion: The results suggest that yoga can be used for managing treatment-related symptoms and anxiety in breast cancer outpatients. copyright 2008.

CAM of the Month

Yang, Y-, J. -Z Ge, Y. Wu, et al. **Cohort Study on the Effect of a Combined Treatment of Traditional Chinese Medicine and Western Medicine on the Relapse and Metastasis of 222 Patients with Stage II and III Colorectal Cancer After Radical Operation.** *Chinese Journal of Integrative Medicine.* 2008 December; 144: 251-256.

Objective: To evaluate the effectiveness of a comprehensive therapy of traditional Chinese medicine (TCM) in reducing the relapse and metastasis of stage II and III colorectal cancer based on conventional Western medicine (WM) therapy. Methods: Two hundred and twenty-two patients in total, diagnosed as stage II and III colorectal cancer from February 2000 to March 2006, were recruited from Xiyuan Hospital, China Academy of Chinese Medical Sciences and the General Hospital of Beijing Military Area. They were followed-up once every 3-6 months. Twenty cases dropped out from the cohort. The remaining 202 patients were all treated with routine WM treatment [including R0 radical operation, or chemotherapy or/and radiotherapy according to national comprehensive cancer network (NCCN) clinical guidelines]. These patients were assigned to two groups based on whether or not they were additionally treated with TCM comprehensive therapy (orally administered with a decoction according to syndrome differentiation, combined with a traditional patent drug over one year). Ninety-eight patients from Xiyuan Hospital were treated with WM and TCM (combined group), and 104 patients from the General Hospital of Beijing Military Area were treated with WM alone (WM group). The demographic data at baseline were comparable, including the operation times, age, sex, TNM staging, and pathological types. The patients were followed-up for one to five years. Up to now, there are 98, 98, 77, 64, and 47 patients with 1, 2, 3, 4, and 5 years of follow-up in the combined group, respectively; and 104, 104, 97, 81, and 55 patients in the WM group, respectively. The results of the 5-year follow-up of all the patients will be available in 2011. Results: The relapse/metastasis rate of 1-, 2-, 3-, 4-, and 5-year were 0 (0/98), 2.04% (2/98), 11.69% (9/77), 14.06% (9/64), and 21.28% (10/47) in the combined group, and were 4.80% (5/104), 16.35% (17/104), 21.65% (21/97), 25.93% (21/81), and 38.18% (21/55) in the WM group, respectively. A significant difference was found in the second year between the two groups (chi2=12.117, P=0.000). Median relapse/ metastasis time was 26.5 months in the combined group and 16.0 months in the WM group. Conclusion: The combined therapy of TCM and WM may have great clinical value and a potential for decreasing the relapse or metastasis rate in stage II and III colorectal cancer after conventional WM therapy.

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Megan Wiebe, Clinical Librarian, compiles Research Updates under the supervision of the editorial board. She has a Master's degree in Library and Information Studies and a Bachelor's degree in Psychology from the University of British Columbia, and has worked in a variety of medical library settings. Megan can be contacted at mwiebe@inspirehealth.ca or 604-734-7125, ext 238.