



RESEARCH UPDATES

For the latest in worldwide integrated cancer care

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InspireHealth
INTEGRATED CANCER CARE

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Research Updates is produced once a month by InspireHealth to inform those interested of newly published articles in integrative cancer care. Authoritative articles are selected based on their evidence and their relevance to this area of medicine.

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Breast

Formelli, F, E. Meneghini, E. Cavadini, et al. **Plasma Retinol and Prognosis of Postmenopausal Breast Cancer Patients.**

Cancer Epidemiology Biomarkers and Prevention. 2009 January; 181: 42-48. Background: The role of retinol (vitamin A) in breast cancer prognosis has never been investigated in postmenopausal women. We prospectively assessed the long-term prognostic role of retinol plasma levels in a cohort of postmenopausal breast cancer patients. Patients and Methods: We investigated 208 women self-reported as postmenopausal operated on for T1-2N0M0 breast cancer who participated in a chemoprevention trial as controls and never received chemotherapy or hormone therapy. Plasma samples were collected 3 months (median) after surgery and assayed within 3 weeks for retinol. Minimum and median potential follow-up were 12 and 15 years, respectively. The main analyses were on all women and on a subgroup ages [greater-than or equal to]55 years, assumed too old to be in perimenopause. The main end point was breast cancer death. Breast cancer survival was estimated by the Kaplan-Meier method. The hazard ratios of breast cancer death by retinol level were estimated by Cox models stratified for age, where relevant, and recruitment period, and adjusted for tumor size and histology. Results: At 12 years, patients with low retinol (<2.08 $\mu\text{mol/L}$, median of distribution) had lower breast cancer survival than those with high retinol (log-rank $P = 0.052$); the difference was significant for women [greater-than or equal to]55 years (log-rank $P = 0.006$). The adjusted hazard ratios for low versus high retinol were 2.11 (95% confidence interval, 1.08-4.14) for all women and 3.58 (95% confidence interval, 1.50-8.57) for those [greater-than or equal to]55 years. Conclusions: Low plasma retinol strongly predicts poorer prognosis in postmenopausal breast cancer patients. Retinol levels should be determined as part of the prognostic workup. Copyright copyright 2009 American Association for Cancer Research.

Irwin, ML, K. Varma, M. Alvarez-Reeves, et al. **Randomized Controlled Trial of Aerobic Exercise on Insulin and Insulin-Like Growth Factors in Breast Cancer Survivors: The Yale Exercise and Survivorship Study.** *Cancer Epidemiology Biomarkers and Prevention*. 2009 January; 181: 306-313.

Background: High insulin and insulin-like growth factor-I (IGF-I) levels may be associated with an increased breast cancer risk and/or death. Given the need to identify modifiable factors that decrease insulin, IGF-I, and breast cancer risk and death, we investigated the effects of a 6-month randomized controlled aerobic exercise intervention versus usual care on fasting insulin, IGF-I, and its binding protein (IGFBP-3) in postmenopausal breast cancer survivors. Methods: Seventy-five postmenopausal breast cancer survivors were identified from the Yale-New Haven Hospital Tumor Registry and randomly assigned to an exercise ($n = 37$) or usual care ($n = 38$) group. The exercise group participated in 150 minutes per week of moderate-intensity aerobic exercise. The usual care group was instructed to maintain their current physical activity level. A fasting blood sample was collected on each study participant at baseline and 6 months. Blood levels of insulin and IGF were measured with ELISA. Results: On average, exercisers increased aerobic exercise by 129 minutes per week compared with 45 minutes per week among usual care participants ($P < 0.001$). Women randomized to exercise experienced decreases in insulin, IGF-I, and IGFBP-3, whereas women randomized to usual care had increases in these hormones. Between-group differences in insulin, IGF-I, and IGFBP-3 were 20.7% ($P = 0.089$), 8.9% ($P = 0.026$), and 7.9% ($P = 0.006$), respectively. Conclusions: Moderate-intensity aerobic exercise, such as brisk walking, decreases IGF-I and IGFBP-3. The exercise-induced decreases in IGF may mediate the observed association between higher levels of physical activity and improved survival in women diagnosed with breast cancer. Copyright copyright 2009 American Association for Cancer Research.

Zhang, M, J. Huang, X. Xie and C. D. Holman. **Dietary Intakes of Mushrooms and Green Tea Combine to Reduce the Risk of Breast Cancer in Chinese Women.** *International Journal of Cancer.* 2009 Mar 15; 1246: 1404-1408.

To investigate effects of dietary mushrooms and joint effects of mushrooms and green tea on breast cancer, a case-control study was conducted in southeast China in 2004-2005. The incident cases were 1,009 female patients aged 20-87 years with histologically confirmed breast cancer. The 1,009 age-matched controls were healthy women randomly recruited from outpatient breast clinics. Information on frequency and quantity of dietary intake of mushrooms and tea consumption, usual diet, and lifestyle were collected by face-to-face interview using a validated and reliable questionnaire. Compared with nonconsumers, the Odds ratios (Ors) were 0.36 (95% CI = 0.25-0.51) and 0.53 (0.38-0.73) for daily intake of ≥ 10 g fresh mushrooms and ≥ 4 g dried mushrooms, based on multivariate logistic regression analysis adjusting for established and potential confounders. There were dose-response relationships with significant tests for trend ($p = 1.05$ g dried green tea leaves per day). The corresponding linear trends were statistically significant for joint effect ($p < 0.001$). We conclude that higher dietary intake of mushrooms decreased breast cancer risk in pre- and postmenopausal Chinese women and an additional decreased risk of breast cancer from joint effect of mushrooms and green tea was observed. More research is warranted to examine the effects of dietary mushrooms and mechanism of joint effects of phytochemicals on breast cancer.

Prostate

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.

Tretli, S, E. Hernes, J. P. Berg, U. E. Hestvik and T. E. Røksahm. **Association between Serum 25(OH)D and Death from Prostate Cancer.** *Br J Cancer.* 2009 Feb 10; 1003: 450-454.

Based on observations that for certain cancers, mortality varies according to sun exposure, vitamin D has been proposed to influence on disease progression. This study aims to investigate whether serum levels of 25(OH)D are associated with prognosis in patients with prostate cancer. In total, 160 patients with a serum sample in the JANUS serum bank were included. For 123 patients a pre-treatment serum sample was taken, whereas 37 of the patients had received hormone therapy prior to the blood collection. The serum level of 25(OH)D was classified as low (80 nmol l⁻¹). A Cox proportional hazard regression model was used to assess the association between serum 25(OH)D and cancer mortality. During follow-up, 61 deaths occurred, of whom 52 died of prostate cancer. The median time of follow-up was 44.0 months (range, 1.2-154.6). Serum 25(OH)D at medium or high levels were significantly related to better prognosis (RR 0.33; 95% CI 0.14-0.77, RR 0.16; 95% CI 0.05-0.43) compared with the low level. Analysis restricted to patients receiving hormone therapy gave a stronger association. The serum level of 25(OH)D may be involved in disease progression and is a potential marker of prognosis in patients with prostate cancer.

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

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 ($\chi^2=12.117$, $P=0.000$). 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 11 and M colorectal cancer after conventional WM therapy.

Fakih, MG, D. L. Trump, C. S. Johnson, L. Tian, J. Muindi and A. Y. Sunga. **Chemotherapy is Linked to Severe Vitamin D Deficiency in Patients with Colorectal Cancer.** *Int J Colorectal Dis.* 2009 242: 219-224.

Background: Preclinical and clinical evidence support an association between vitamin D deficiency and an increased risk of colorectal cancer. Normal vitamin D status has been linked to favorable health outcomes ranging from decreased risk of osteoporosis to improved cancer mortality. We performed a retrospective study to assess the impact of metastatic disease and chemotherapy treatment on vitamin D status in patients with colorectal cancer residing in Western New York. Materials and methods: Patients, 315, with colorectal cancer treated in a single institute were assayed for 25-OH vitamin D. The association of age, gender, primary disease site and stage, body mass index, and chemotherapy with vitamin D status was investigated. Results: Vitamin D deficiency was common among participants with a median 25-OH vitamin D level of 21.3 ng/ml (optimal range 32-100 ng/ml). Primary site of disease and chemotherapy status were associated with very low 25-OH vitamin D levels (≤ 15 ng/ml) on multivariate analysis. Patients receiving chemotherapy and patients with a rectal primary were 3.7 and 2.6-fold more likely to have severe vitamin D deficiency on multivariate analysis than nonchemotherapy patients and colon cancer primary patients, respectively. Conclusions: Chemotherapy is associated with a significant increase in the risk of severe vitamin D deficiency. Patients with colorectal cancer, especially those receiving chemotherapy, should be considered for aggressive vitamin D replacement strategies. copyright Springer-Verlag 2008. was not associated with reduced risk.

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.

Bladder

Kurahashi, N, M. Inoue, M. Iwasaki, S. Sasazuki and S. Tsugane. **Coffee, Green Tea, and Caffeine Consumption and Subsequent Risk of Bladder Cancer in Relation to Smoking Status: A Prospective Study in Japan.** *Cancer Science.* 2009 1002: 284-291.

Coffee and caffeine consumption are thought to increase the risk of bladder cancer. However, few studies have stratified this risk by smoking status, which is a potential confounder. Here, we investigated the association between coffee, green tea (another major source of caffeine), and bladder cancer incidence in relation to smoking status. We conducted a population-based prospective study in a cohort of Japanese, comprising a total of 49,566 men and 54,874 women aged 40-69 years who reported their coffee and green tea consumption at baseline. During follow-up from 1990 through 2005, 164 men and 42 women were newly diagnosed with bladder cancer. Cigarette smoking was associated with an increased risk of bladder cancer, with a strong dose-response relationship. Coffee was positively associated with bladder cancer risk in men, without statistical significance. When stratified by smoking status, coffee and caffeine consumption were associated with an increased risk of bladder cancer in never- or former-smoking men, with hazard ratios (95% confidence interval) in the highest categories of coffee (one or more cups per day) and caffeine consumption compared with the lowest of 2.24 (95% CI = 1.21-4.16) and 2.05 (95% CI = 1.15-3.66), respectively. In conclusion, cigarette smoking was confirmed as a risk factor for bladder cancer. Coffee and caffeine may be associated with an increased bladder cancer risk in never or former smokers among Japanese men. copyright 2009 Japanese Cancer Association.

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]

Tram, KL, A. J. Cross, D. Consonni, et al. **Intakes of Red Meat, Processed Meat, and Meat Mutagens Increase Lung Cancer Risk.** *Cancer Res.* 2009 01 Feb; 693: 932-939. Red and processed meat intake may increase lung cancer risk. However, the epidemiologic evidence is inconsistent and few studies have evaluated the role of meat mutagens formed during high cooking temperatures. We investigated the association of red meat, processed meat, and meat mutagen intake with lung cancer risk in Environment And Genetics in Lung cancer Etiology, a population-based case-control study. Primary lung cancer cases (n = 2,101) were recruited from 13 hospitals within the Lombardy region of Italy examining [similar to]80% of the cases from the area. Noncancer population controls (n = 2,120), matched to cases on gender, residence, and age, were randomly selected from the same catchment area. Diet was assessed in 1,903 cases and 2,073 controls and used in conjunction with a meat mutagen database to estimate intake of heterocyclic amines (HCA) and benzo(a)-pyrene (BaP). Multivariable odds ratios (OR) and 95% confidence intervals (95% CI) for sex-specific tertiles of intake were calculated using unconditional logistic regression. Red and processed meat were positively associated with lung cancer risk (highest-versus-lowest tertile: OR, 1.8; 95% CI, 1.5-2.2; P trend < 0.001 and OR, 1.7; 95% CI, 1.4-2.1; P trend < 0.001, respectively); the risks were strongest among never smokers (OR, 2.4; 95% CI, 1.4-4.0; P trend = 0.001 and OR, 2.5; 95% CI, 1.5-4.2; P trend = 0.001, respectively). HCAs and BaP were significantly associated with increased risk of lung cancer. When separated by histology, significant positive associations for both meat groups were restricted to adenocarcinoma and squamous cell carcinoma but not small cell carcinoma of the lung. In summary, red meat, processed meat, and meat mutagens were independently associated with increased risk of lung cancer. copyright2009 American Association for Cancer Research.

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.

Collinge, W, J. Kahn, P. Yarnold, S. Bauer-Wu and R. McCorkle. **Couples and Cancer: Feasibility of Brief Instruction in Massage and Touch Therapy to Build Caregiver Efficacy.** *Journal Of The Society For Integrative Oncology.* 2007 54: 147-154. This study examined the feasibility of brief instruction in massage and touch therapy for caregivers ("partners") to provide comfort to cancer patients. Fifty partners and 49 patients participated. A longitudinal, within-subjects, repeated measures, control and intervention phases design used self-report instruments to assess feasibility via change in frequency, duration, partner-perceived self-efficacy, and patient-perceived helpfulness over a 90-day follow-up. Exploratory data were collected on psychosocial and quality of life variables. Focus groups provided qualitative data. A structured 6-hour workshop taught basic manual techniques for comfort and relaxation, followed by home practice. Significant increases in frequency (1.2 vs 2.7 times per week) and duration (4.7 vs 12.2 minutes) of massage, both p < .001, were sustained through the 3-month follow-up. Partners' perceived self-efficacy in massage and patients' ratings of its helpfulness more than doubled. Classification tree analysis found caregiver burden, relationship quality, and frequency and duration of practice to predict individual responses. Inhibitions about touch in cancer caregiving may lead to unnecessary physical and emotional distancing at a time when patients need touch the most. Brief instruction may be a feasible intervention to increase caregiver efficacy, patient satisfaction, quality of life, and quality of the relationship.

CAM of the Month

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.

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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.