RESEARCH UPDATES

For the latest in worldwide integrated cancer care

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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

Milne, HM, K. E. Wallman, S. Gordon and K. S. Courneya. **Impact of a Combined Resistance and Aerobic Exercise Program on Motivational Variables in Breast Cancer Survivors: A Randomized Controlled Trial**. *Annals of Behavioral Medicine.Springer New York LLC.* 2008 October; 362: 158-166. Background: Short term exercise interventions have been shown to be beneficial for breast cancer survivors soon after treatments but longer term adherence is needed. Purpose: To examine the effects of a supervised exercise program on motivational variables in breast cancer survivors using Self-Determination Theory (SDT). Method: Sixty breast cancer survivors were randomized in a cross-over design to either an immediate exercise group (IEG; n = 30) that exercised from baseline to week 12 or a delayed exercise group (DEG; n = 30) that exercised from week 12 to 24. SDT variables were assessed at baseline, 6, 12, 18 and 24 weeks using the Behavioral Regulation for Exercise Questionniare-2 and the Basic Psychological Needs Satisfaction Scale. Results: Fifty-eight participants completed the follow-up assessments and achieved a 61.3% adherence rate. Analyses of variance revealed significant time by group interactions for almost all psychological needs and motivations that favored the exercise intervention time periods. For example, autonomy increased in the IEG from baseline to 12 weeks by 2.0 points compared to the DEG where scores decreased by 0.1 points (mean group difference = 2.0, $p < 0.001$). The cross-over results further supported the main findings. Conclusion: Supervised exercise soon after breast cancer treatments may help to develop a positive exercise motivational profile among breast cancer survivors that could portend longer term adherence. copyright 2008 The Society of Behavioral Medicine.

Kwan, ML, C. B. Ambrosone, M. M. Lee, et al. **The Pathways Study: A Prospective Study of Breast Cancer Survivorship within Kaiser Permanente Northern California.** *Cancer Causes and Control.* 2008 December; 1910: 1065-1076. Objective: With 2.3 million breast cancer survivors in the US today, identification of modifiable factors associated with breast cancer recurrence and survival is increasingly important. Only recently new studies have been designed to examine the impact of lifestyle factors on prognosis, including Pathways, a prospective study of women with breast cancer in Kaiser Permanente Northern California (KPNC). Methods: Pathways aims to examine the effect on recurrence and survival of (1) lifestyle factors such as diet, physical activity, quality of life, and use of alternative therapies and (2) molecular factors such as genetic polymorphisms involved in metabolism of chemotherapeutic agents. Eligibility includes any woman diagnosed with invasive breast cancer within KPNC, no previous diagnosis of other invasive cancer, age 21 years or older, and ability to speak English, Spanish, Cantonese, or Mandarin. Newly diagnosed patients are identified daily from electronic pathology records and are enrolled within two months of diagnosis. An extensive baseline interview is conducted, blood and saliva samples are collected, and body measurements are taken. Women are followed for lifestyle updates, treatment, and outcomes by self-report and query of KPNC databases. Results: Recruitment began in 9 January, 2006, and as of 16 January, 2008, 1,539 women have been enrolled along with collection of 1,323 blood samples (86%) and 1,398 saliva samples (91%). Conclusions: The Pathways Study will become a rich resource to examine behavioral and molecular factors and breast cancer prognosis. copyright 2008 Springer Science+Business Media B.V.

Sonestedt, E, S. Borgquist, U. Ericson, et al. **Plant Foods and Oestrogen Receptor Alpha- and Beta-Defined Breast Cancer: Observations from the Malmo Diet and Cancer Cohort.** *Carcinogenesis.* 2008 2911: 2203-2209. The associations between plant foods and breast cancer incidence are inconsistent. The objective of this study was to examine prospectively the association between dietary fibre, plant foods and breast cancer, especially the association between plant food intake and oestrogen receptor (ER) alpha- and beta-defined breast cancer. Among women without prevalent cancer from the population-based prospective Malmo Diet and Cancer cohort (n = 15 773, 46-75 years at baseline), 544 women were diagnosed with incident invasive breast cancer during a mean follow-up of 10.3 years. Information on dietary habits was collected by a modified diet history method. ER status of the tumours was determined by immunohistochemistry using tissue microarray. Cox proportional hazards regression estimated hazard ratios (HRs) and 95% confidence intervals (CIs) of breast cancer associated with fibre and 11 plant food groups. High-fibre bread was significantly associated with a decreased breast cancer incidence (HR, 0.75; 95% CI, 0.57-0.98, for highest compared with lowest quintile). The other plant food groups were not significantly associated with breast cancer incidence. There was a tendency for a negative association for high-fibre bread among ERalpha (+) breast cancer (P for trend = 0.06) and ERbeta (+) breast cancer (P for trend = 0.06). Fried potatoes were statistically significantly associated with increased risk of ERbeta (-) breast cancer (P = 0.01). This study suggests that different plant foods may be differently associated with breast cancer, with fibre-rich bread showing an inverse association. We did not observe strong evidence for differences in incidence according to the ERalpha and ERbeta status of breast cancer.

Prostate

Hamilton, RJ, K. C. Goldberg, E. A. Platz and S. J. Freedland. **The Influence of Statin Medications on Prostate-Specific Antigen Levels.** *Journal of the National Cancer Institute.Oxford University Press.* 2008 November; 10021: 1511-1518. Background: Recent data suggest that statin use may be associated with a reduced risk of advanced prostate cancer. However, the influence of statins on prostate-specific antigen (PSA) levels and what effect this could potentially have on prostate cancer diagnosis are unknown. Methods: We conducted a longitudinal study of 1214 men who were prescribed a statin between 1990 and 2006 at the Durham Veterans Affairs Medical Center who were free of prostate cancer, had not undergone prostate surgery or taken medications known to alter androgen levels and who had at least one PSA value within 2 years before and at least one PSA value within 1 year after starting a statin. The change in PSA from before to after statin treatment was analyzed as a continuous variable using the Wilcoxon signed rank test. The association between change in PSA and change in cholesterol parameters (low-density lipoprotein [LDL], high-density lipoprotein [HDL], and total cholesterol) was analyzed using multivariate linear regression. All statistical tests were two-sided. Results: Mean (SD) age when starting statins was 60.3 (8.3) years; median prestatin PSA concentration was 0.9 (1.9) ng/mL; and mean prestatin LDL cholesterol concentration was 144 (34) mg/dL. After starting a statin, the median LDL decline was 27.5%, and the median PSA decline was 4.1% (P 41% declines in LDL (highest quartile) after starting a statin experienced a 17.4% (95% CI = 10.0% to 24.9%) decline in serum PSA. Conclusions: PSA levels declined by a statistically significant extent after initiation of statin treatment. The reduction was most pronounced among men with the largest LDL declines and those with PSA levels that would make them candidates for prostate biopsy. By lowering PSA levels, statins may complicate cancer detection, although further studies are needed to quantify the clinical significance of this effect.

Singer, EA, G. S. Palapattu and E. Van Wijngaarden**. Prostate-Specific Antigen Levels in Relation to Consumption of Nonsteroidal Anti-Inflammatory Drugs and Acetaminophen: Results from the 2001-2002 National Health and Nutrition Examination Survey**. *Cancer.John Wiley and Sons Inc.* 2008 15 Oct; 1138: 2053-2057. BACKGROUND. Inflammation has been implicated in prostate carcinogenesis; therefore, the use of nonsteroidal anti-inflammatory drugs (NSAIDs) has the potential of decreasing the risk of prostate cancer. However, to the authors' knowledge the precise correlation between oral NSAID use, serum prostate-specific antigen (PSA), and prostate cancer risk is unknown. To further characterize this association, the authors evaluated serum PSA levels with regard to NSAID and acetaminophen consumption in a large cross-sectional study of men in the US. METHODS. PSA levels were determined in 1319 men aged >40 years in the 2001-2002 National Health and Nutrition Examination Survey (NHANES). Linear regressions were performed on log-transformed PSA levels, accounting for the complex survey design, to evaluate the relations between PSA and the use of NSAIDs and acetaminophen after adjusting for the effects of age, race, educational level, smoking status, body mass index, coexisting inflammatory conditions, and heart disease. RESULTS. NSAID and acetaminophen consumption displayed a negative association with PSA levels, namely, individuals who reported using NSAIDs (19.8%) or acetaminophen (1.3%) regularly had lower PSA levels than individuals who did not take these drugs, although the impact of acetaminophen was not statistically significant. PSA levels among NSAID users were 0.9 times the levels among non-drug takers (P = .038), whereas PSA levels among acetaminophen users were 0.76 times the levels in nondrug takers (P = .14). Individuals who stated they took both NSAIDs and acetaminophen (0.99%) on a regular basis had higher PSA levels (1.8 times greater), although not statistically significantly so (P = .24), than individuals who stated they did not take either of these drugs regularly. CONCLUSIONS. The findings of the current study suggest that regular NSAID consumption may reduce serum PSA levels. Whether this is indicative of a protective effect on prostate cancer risk or masks possible prostate injury resulting in reduced detection of prostate cancer is unclear. Given the widespread consumption of NSAIDs and the regular use of PSA for the assessment of prostate cancer risk, the potential implications of the current study's findings may be substantial and warrant further investigation.

Magura, L, R. Blanchard, B. Hope, J. R. Beal, G. G. Schwartz and A. E. Sahmoun. **Hypercholesterolemia and Prostate Cancer: A Hospital-Based Case-Control Study.** *Cancer Causes and Control.* 2008 December; 1910: 1259-1266. Objective: High levels of serum cholesterol have been proposed to increase the risk of prostate cancer but the epidemiologic evidence is limited. Methods: We conducted a hospital-based case-control study in Fargo, ND, USA, to examine the

association between hypercholesterolemia and prostate cancer. Cases were men with incident, histologically confirmed prostate cancer. Controls were men without clinical cancer who were seen at the same hospital for an annual physical exam. Demographic and clinical data were abstracted from patients' medical charts. Results: From a patient population aged 50 to 74 years old, we obtained data on 312 White cases and 319 White controls. Hypercholesterolemia was defined as total cholesterol greater than 5.17 (mmol/l). Univariate logistic regression showed a significant association between hypercholesterolemia and prostate cancer (odds ratio (OR) = 1.64, 95% confidence interval (CI): 1.19-2.27). This association changed only slightly after adjustment for age, family history of prostate cancer, body mass index, type 2 diabetes, smoking, and multivitamin use (OR = 1.58, 95% CI: 1.11-2.24). A significant association was found between low HDL and prostate cancer (OR = 1.57, 95% CI: 1.04-2.36). High LDL was associated with a 60% increased risk for prostate cancer (OR = 1.60, 95% CI: 1.09-2.34). Compared to never smokers, current smokers had an 84% increased risk for prostate cancer (OR = 1.84, 95% CI: 1.09-3.13). Conclusion: This study adds to recent evidence that hypercholesterolemia may increase the risk of prostate cancer in white men. copyright 2008 Springer Science+Business Media B.V.

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

Leung, EYL, J. E. M. Crozier, D. Talwar, et al. **Vitamin Antioxidants, Lipid Peroxidation, Tumour Stage, the Systemic Inflammatory Response and Survival in Patients with Colorectal Cancer**. *International Journal of Cancer.Wiley-Liss Inc.* 2008 15 Nov; 12310: 2460-2464. Both the tumour growth and progression and the systemic inflammatory response have the potential to increase oxidative stress. We therefore examined the relationship between lipid-soluble antioxidant vitamins, lipid peroxidation, the systemic inflammatory response and survival in patients with primary operable (n = 53) and advanced inoperable (n = 53) colorectal cancer. Compared with those patients with primary operable colorectal cancer, patients with unresectable liver disease had significantly lower median concentrations of alpha-tocopherol ($p < 0.001$), lutein ($p < 0.001$), lycopene ($p < 0.001$), alpha-carotene ($p < 0.01$) and beta-carotene ($p < 0.001$) and higher malondialdehyde concentrations. An elevated systemic inflammatory response (Glasgow prognostic score, mGPS) was associated with a greater proportion of females ($p < 0.05$) and more advanced tumour stage ($p < 0.05$), lower circulating levels of retinol ($p < 0.01$), lutein ($p < 0.01$), lycopene ($p < 0.01$) and alpha- ($p < 0.01$) and beta-carotene but not MDA ($p = 0.633$). In the liver metastases group 41 patients died of their cancer and a further 1 patient died of intercurrent disease on follow-up. On univariate survival analysis, mGPS ($p < 0.01$), retinol ($p < 0.001$), atocopherol ($p < 0.05$) and a-carotene ($p < 0.05$) were associated significantly with cancer-specific survival. On multivariate survival analysis of these significant variables, only mGPS ($p < 0.01$) and retinol ($p < 0.001$) were independently associated with cancer-specific survival. The results of the present study showed that the systemic inflammatory response was associated with a reduction of lipid-soluble antioxidant vitamins, whereas advanced tumour stage was associated with increased lipid peroxidation in patients with colorectal cancer. Of the antioxidant vitamins measured, only retinol was independently associated with cancer-specific survival. copyright 2008 Wiley-Liss, Inc.

Gastrointestinal

Hogervorst, JGF, L. J. Schouten, E. J. M. Konings, R. A. Goldbohm and P. A. Van Den Brandt. **Dietary Acrylamide Intake is Not Associated with Gastrointestinal Cancer Risk.** *J Nutr.* 2008 November; 13811: 2229-2236. Acrylamide is a probable human carcinogen that was detected in several heat-treated foods, such as French fries and crisps, in 2002. Prospective studies are needed on acrylamide and human cancer risk. We prospectively investigated the association between acrylamide and gastrointestinal cancer risk. In 1986, 120,852 men and women (aged 55-69 y) were included in the Netherlands Cohort Study on diet and cancer. At baseline, a random subcohort of 5000 participants was selected for a case-cohort approach. Acrylamide intake was assessed with a FFQ at baseline and was based on acrylamide analyses in relevant Dutch foods. After 13.3 y of follow-up, 2190, 563, 349, and 216 cases of colorectal, gastric, pancreatic, and esophageal cancer, respectively, were available for analysis. The daily acrylamide intake of the subcohort was (mean +/- SD) 21.7 +/- 12.1mug. A 10-mug/d increment of acrylamide intake was associated with multivariable-adjusted Cox proportional hazard rate ratios (HR) (95% CI) of 1.00 (0.96-1.06), 1.02 (0.94-1.10), 1.06 (0.96-1.17), and 0.96 (0.85-1.09) for colorectal, gastric, pancreatic, and esophageal cancer, respectively. For former or never-smokers, the corresponding HR were: 1.03 (0.94-1.12), 1.09 (0.98-1.22), 1.07 (0.93-1.24), and 0.92 (0.76-1.11). There were some significantly increased risks within subgroups stratified by obesity, nonoccupational physical activity, and age, factors that were a priori selected based on their capacity to modify cytochrome P4502E1 activity. Overall, acrylamide intake was not associated with colorectal, gastric, pancreatic, and esophageal cancer risk, but some subgroups deserve further attention. copyright 2008 American Society for Nutrition.

Nutrition

Hu, J, C. La Vecchia, M. DesMeules, et al. **Nutrient and Fiber Intake and Risk of Renal Cell Carcinoma.** *Nutr Cancer.* 2008 November; 606: 720-728. This study examines the association between nutrient and fiber intake and the risk of renal cell carcinoma (RCC). Between 1994 and 1997 in 8 Canadian provinces, mailed questionnaires were completed by 1,138 incident, histologically confirmed cases of RCC and 5,039 population controls. Measurement included information on socioeconomic status, lifestyle habits, and diet. A 69-item food frequency questionnaire provided data on eating habits 2 yr before data collection. Odds ratios (ORs) and 95% confidence intervals were derived through unconditional logistic regression. Intakes of total fat, saturated fat, monounsaturated fat, trans-fat, and cholesterol were associated with the risk of RCC; the ORs for the highest vs. the lowest quartile were 1.67, 1.53 and 1.46, 1.31, and 1.48, respectively. The positive association was apparently stronger in women, overweight or obese, and never smokers. Sucrose was related to the risk of RCC. High fiber intake was inversely associated with RCC risk. No association was found with intake of total protein and polyunsaturated fat, n-3 and n-6 polyunsaturated fatty acids, and total carbohydrates. The results were consistent across strata of sex, tobacco, and BMI. The findings suggest that a diet low in fats and cholesterol and

rich in fiber could favorably affect the risk of RCC. Copyright copyright 2008, Taylor & Francis Group, LLC.

De Stefani, E, P. Boffetta, A. L. Ronco, H. Deneo-Pellegrini, G. Acosta and M. Mendilaharsu. **Dietary Patterns and Risk of Bladder Cancer: A Factor Analysis in Uruguay**. *Cancer Causes and Control*. 2008 December; 1910: 1243-1249. Objective: To determine the major dietary patterns associated with bladder cancer risk, we conducted a principal components analysis (PCA) in a case-control study from Uruguay. Methods: A total of 255 newly diagnosed and microscopically confirmed cases of transitional cell carcinoma of the bladder and 501 hospitalized controls were included in the study. Both series were drawn from the four major public hospitals in Montevideo, Uruguay. Cases and controls were frequency matched on age and sex. Controls were submitted to factor (principal components) analysis. Results: We retained three factors that explained 25.1% of the total variance (including error variance). The first factor was labeled as the sweet beverages pattern. This factor was characterized by high loadings of coffee, tea, and added sugar and was strongly associated with risk of bladder cancer (OR 3.27, 95% CI 1.96-5.45). The second factor was labeled as the Western pattern and displayed high loadings of red meat, fried eggs, potatoes, and red wine. This pattern was directly associated with risk of bladder cancer (OR 2.35, 95% CI 1.42-3.89). Finally, the third factor was labeled as the prudent pattern and showed high loadings of fresh vegetables, cooked vegetables, and fruits. This pattern was not associated with risk of bladder cancer. Conclusions: According to our study, non-alcoholic beverages were the strongest risk factor for bladder cancer, whereas the Western pattern was also associated with a significant increase in risk of bladder cancer. copyright 2008 Springer Science+Business Media B.V

Lueth, NA, K. E. Anderson, L. J. Harnack, J. A. Fulkerson and K. Robien. **Coffee and Caffeine Intake and the Risk of Ovarian Cancer: The Iowa Women's Health Study.** *Cancer Causes and Control.* 2008 December; 1910: 1365-1372. Laboratory data suggest that caffeine or some components of coffee may cause DNA mutations and inhibit tumor suppressor mechanisms, leading to neoplastic growth. However, coffee consumption has not been clearly implicated in the etiology of human postmenopausal ovarian cancer. This study evaluated the relationship of coffee and caffeine intake with risk of epithelial ovarian cancer in a prospective cohort study of 29,060 postmenopausal women. The participants completed a mailed questionnaire that assessed diet and health history and were followed for ovarian cancer incidence from 1986 to 2004. Age-adjusted and multivariate-adjusted hazard ratios were calculated for four exposure variables: caffeinated coffee, decaffeinated coffee, total coffee, and total caffeine to assess whether or not coffee or caffeine influences the risk of ovarian cancer. An increased risk was observed in the multivariate model for women who reported drinking five or more cups/day of caffeinated coffee compared to women who reported drinking none (HR = 1.81, 95% CI: 1.10-2.95). Decaffeinated coffee, total coffee, and caffeine were not statistically significantly associated with ovarian cancer incidence. Our results suggest that a component of coffee other than caffeine, or in combination with caffeine, may be associated with increased risk of ovarian cancer in postmenopausal women who drink five or more cups of coffee a day. copyright 2008 Springer Science+Business Media B.V.

Malagoli, C, M. Vinceti, G. Pellacani, et al. **Diet and Melanoma Risk: Effects of Choice of Hospital Versus Population Controls.** *Tumori.* 2008 September/October; 945: 669-673. Aims and background. Hospital-referred subjects are widely used as controls in studies on the relation between diet and cancer risk. However, concern has been raised about the potential for bias of such type of referents, and few studies seem to have examined their reliability in estimating dietary habits of the underlying general population. Methods. In a northern Italian setting, the differences in dietary patterns between 41 individuals referred for non-neoplastic lesions to hospital surgical outpatient units and age- and sex-matched subjects drawn from the general population were examined. The effects of such differences when carrying out a case-control study on a neoplastic disease, cutaneous melanoma, were also analyzed. Dietary intake was assessed using the EPIC food frequency questionnaire. Results. Population controls showed higher intakes of energy, animal proteins and animal fats compared with sex- and age-matched hospital controls, whereas intake of carbohydrates and fiber was comparable. An excess melanoma risk associated with intake of animal proteins and fats emerged when hospital controls were used as the referent group, whereas no such relation was detected when cases were compared to population controls. Conclusions. The results suggest that hospital-referred subjects may not reflect dietary habits of the underlying general population and may be unsuitable for case-control studies concerning the relation between diet and cancer risk.

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CAM of the Month

Premkumar, VG, S. Yuvaraj, P. Shanthi and P. Sachdanandam. **Co-Enzyme Q10, Riboflavin and Niacin Supplementation on Alteration of DNA Repair Enzyme and DNA Methylation in Breast Cancer Patients Undergoing Tamoxifen Therapy**. *Br J Nutr.* 2008 1006: 1179-1182. In the present study, eighty-four breast cancer patients were randomized to receive a daily supplement of 100 mg co-enzyme Q10, 10 mg riboflavin and 50 mg niacin (CoRN), one dosage per d along with 10 mg tamoxifen twice per d. A significant increase in poly(ADP-ribose) polymerase levels and disappearance of RASSF1A DNA methylation patterns were found in patients treated with supplement therapy along with tamoxifen compared to untreated breast cancer patients and tamoxifen alone-treated patients. An increase in DNA repair enzymes and disappearance of DNA methylation patterns attributes to reduction in tumour burden and may suggest good prognosis and efficacy of the treatment. copyright The Authors 2008.

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