



Research Updates

For the latest in integrated cancer care research

The Centre
for Integrated
Healing
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Research Updates is produced once a month by the Centre for Integrated Healing 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

Larsson SC, Giovannucci E, Wolk A. **Folate and risk of breast cancer: a meta-analysis.** *J Nat Cancer Inst* 2007;99(1):64-76.

BACKGROUND: Epidemiologic findings are inconsistent concerning risk for breast cancer associated with low folate intake or blood folate levels. We performed a meta-analysis of prospective and case-control studies to examine folate intake and levels in relation to risk of breast cancer. **METHODS:** We searched MEDLINE for studies of this association that were published in any language from January 1, 1966, through November 1, 2006. Study-specific risk estimates were pooled by use of a random-effects model. All statistical tests were two-sided. **RESULTS:** Folate intake in increments of 200 microg/day was not associated with the risk of breast cancer in prospective studies (estimated summary relative risk [RR] = 0.97, 95% confidence interval [CI] = 0.88 to 1.07, for dietary folate [eight studies; 302,959 participants and 8367 patients with breast cancer], and RR = 1.01, 95% CI = 0.97 to 1.05, for total folate [six studies; 306,209 participants and 8165 patients with breast cancer]) but was statistically significantly inversely associated with risk in case-control studies (estimated summary odds ratio [OR] = 0.80, 95% CI = 0.72 to 0.89, for dietary folate [13 studies; 8558 case patients and 10,812 control subjects], and OR = 0.93, 95% CI = 0.81 to 1.07, for total folate [three studies; 2184 case patients and 3233 control subjects]). High blood folate levels versus low levels were not statistically significantly associated with the risk of breast cancer in prospective studies (OR = 0.81, 95% CI = 0.59 to 1.10 [three studies]) or in case-control studies (OR = 0.41, 95% CI = 0.15 to 1.10 [two studies]). Among the two prospective studies and two case-control studies that stratified by alcohol consumption, high folate intake (comparing the highest with the lowest category) was associated with a statistically significant decreased risk of breast cancer among women with moderate or high alcohol consumption (summary estimate = 0.51, 95% CI = 0.41 to 0.63) but not among women with low or no alcohol consumption (summary

estimate = 0.95, 95% CI = 0.78 to 1.15). Few studies examined whether the relation between folate intake and breast cancer was modified by intakes of methionine or vitamins B6 and B12, and the findings were inconsistent. **CONCLUSION:** No clear support for an overall relationship between folate intake or blood folate levels and breast cancer risk was found. Adequate folate intake may reduce the increased risk of breast cancer that has been associated with moderate or high alcohol consumption.

Touillaud MS, Thiébaud ACM, Fournier A, et al. **Dietary lignan intake and postmenopausal breast cancer risk by estrogen and progesterone receptor status.** *J Nat Cancer Inst* 2007;99(6):475-86.

Background: Studies conducted in Asian populations have suggested that high consumption of soy-based foods that are rich in isoflavone phytoestrogens is associated with a reduced risk of breast cancer. However, the potential associations of other dietary phytoestrogens—i.e., the lignans or their bioactive metabolites, the enterolignans—with the risk of breast cancer are unclear. **Methods:** We prospectively examined associations between the risk of postmenopausal invasive breast cancer and dietary intakes of four plant lignans (pinoresinol, lariciresinol, secoisolariciresinol, and matairesinol) and estimated exposure to two enterolignans (enterodiols and enterolactone), as measured with a self-administered diet history questionnaire, among 58 049 postmenopausal French women who were not taking soy isoflavone supplements. Relative risks (RRs) and 95% confidence intervals (CIs) were estimated using multivariable Cox proportional hazards regression models. Analyses were further stratified by the combined estrogen and progesterone receptor (ER/PR) status of the tumors. Statistical tests were two-sided. **Results:** During 383 425 person-years of follow-up (median follow-up, 7.7 years), 1469 cases of breast cancer were diagnosed. Compared with women in the lowest intake quartiles, those in the highest quartile of total lignan intake (>1395 µg/day) had a reduced risk of breast cancer (RR = 0.83, 95% CI = 0.71 to 0.95, $P_{trend} = .02$, 376 versus 411 cases per 100 000 person-years), as did those in the highest quartile of lariciresinol intake (RR = 0.82, 95% CI = 0.71 to 0.95, $P_{trend} = .01$). The inverse associations between phytoestrogen intakes and

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postmenopausal breast cancer risk were limited to ER- and PR-positive disease (e.g., RR for highest versus lowest quartiles of total plant lignan intake = 0.72, 95% CI = 0.58 to 0.88, $P_{\text{trend}} = .01$, 174 versus 214 cases per 100 000 person-years, and RR for highest versus lowest quartiles of total enterolignan level = 0.77, 95% CI = 0.62 to 0.95, $P_{\text{trend}} = .01$, 164 versus 204 cases per 100 000 person-years). Conclusions: High dietary intakes of plant lignans and high exposure to enterolignans were associated with reduced risks of ER- and PR-positive postmenopausal breast cancer in a Western population that does not consume a diet rich in soy.

Dallal CM, Sullivan-Halley J, Ross RK, et al. **Long-term recreational physical activity and risk of invasive and in situ breast cancer: the California Teachers Study.** *Arch Intern Med* 2007;167:408-15.

Background: Long-term physical activity may affect breast cancer risk. Few prospective studies have evaluated in situ or invasive breast cancer risk, or breast cancer receptor subtypes, in relation to long-term activity. Methods: We examined the association between recreational physical activity and risk of invasive and in situ breast cancer in the California Teachers Study, a cohort of women established in 1995-1996. Of 110 599 women aged 20 to 79 years with no history of breast cancer followed up through December 31, 2002, 2649 were diagnosed as having incident invasive breast cancer and 593 were diagnosed as having in situ breast cancer. Information was collected at cohort entry on participation in strenuous and moderate recreational activities during successive periods from high school through the current age or age 54 years (if older at enrollment) and in the past 3 years. A summary measure of long-term activity up to the current age, or age 54 years if older, was constructed for each woman. Results: Invasive breast cancer risk was inversely associated with long-term strenuous activity (>5 vs ≤0.5 h/wk per year: relative risk, 0.80; 95% confidence interval, 0.69-0.94; $P_{\text{trend}} = .02$), as was in situ breast cancer risk (>5 vs ≤0.5 h/wk per year: relative risk, 0.69; 95% confidence interval, 0.48-0.98; $P_{\text{trend}} = .04$). Strenuous and moderate long-term activities were associated with reduced risk of ER-negative (strenuous: $P_{\text{trend}} = .003$; moderate: $P_{\text{trend}} = .003$) but not ER-positive (strenuous: $P_{\text{trend}} = .23$; moderate: $P_{\text{trend}} = .53$) invasive breast cancer. Conclusion: These results support a protective role of strenuous long-term exercise activity against invasive and in situ breast cancer and suggest differing effects by hormone receptor status.

Prostate

Hedelin M, Chang ET, Wiklund F, et al. **Association of frequent consumption of fatty fish with prostate cancer risk is modified by COX-2 polymorphism.** *Int J Cancer* 2007;120(2):398-405.


Dietary intake of marine fatty acids from fish may protect against prostate cancer development. We studied this association and whether it is modified by genetic variation in cyclooxygenase (COX)-2, a key enzyme in fatty acid metabolism and inflammation. We assessed dietary intake of fish among 1,499 incident prostate cancer cases and 1,130 population controls in Sweden. Five single nucleotide polymorphisms (SNPs) were identified and genotyped in available blood samples for 1,378 cases and 782 controls. Odds ratios (OR) and 95% confidence intervals (CI) were estimated by multivariate logistic regression. Multiplicative and additive interactions between fish intake and COX-2 SNPs on prostate cancer risk were evaluated. Eating fatty fish (e.g. salmon-type fish) once or more per week, compared to never, was associated with reduced risk of prostate

cancer (OR: 0.57. 95% CI: 0.43-0.76). The OR comparing the highest to the lowest quartile of marine fatty acids intake was 0.70 (95% CI: 0.51-0.97). We found a significant interaction ($p < 0.001$) between salmon-type fish intake and a SNP in the COX-2 gene (rs5275: +6365 T/C), but not with the 4 other SNPs examined. We found strong inverse associations with increasing intake of salmon-type fish among carriers of the variant allele (OR for once per week or more vs. never = 0.28, 95% CI: 0.18-0.45; $p_{\text{trend}} < 0.01$), but no association among carriers of the more common allele. Frequent consumption of fatty fish and marine fatty acids appears to reduce the risk of prostate cancer, and this association is modified by genetic variation in the COX-2 gene.

Rodriguez C, Freedland SJ, Deka A, et al. **Body mass index, weight change, and risk of prostate cancer in the Cancer Prevention Study II Nutrition Cohort.** *Cancer Epidemiol Biomarkers Prev* 2007;16(1):63-9.

Background: Obesity has been associated with aggressive prostate cancer. The extent of this association, which varies by stage and grade, remains unclear. The role of recent weight change had not been previously examined. Methods: We examined body mass index (BMI) and weight change in relation to incident prostate cancer by disease stage and grade at diagnosis among 69,991 men in the Cancer Prevention Study II Nutrition Cohort. Participants provided information on height and weight in 1982, and again at enrollment in 1992. During follow-up through June 30, 2003 (excluding the first 2 years of follow-up), we documented 5,252 incident prostate cancers. Cox proportional hazards models were used to estimate rate ratios (RR) and 95% confidence intervals (95% CI). Results: The association between BMI in 1992 and risk of prostate cancer differed by stage and grade at diagnosis. BMI was inversely associated with risk of nonmetastatic low-grade prostate cancer (RR, 0.84; 95% CI, 0.66-1.06), but BMI was positively associated with risk of nonmetastatic high-grade prostate cancer (RR, 1.22; 95% CI, 0.96-1.55) and risk of metastatic or fatal prostate cancer (RR, 1.54; 95% CI, 1.06-2.23). Compared with weight maintenance, men who lost >11 pounds between 1982 and 1992 were at a decreased risk of nonmetastatic high-grade prostate cancer (RR, 0.58; 95% CI, 0.42-0.79). Conclusion: Obesity increases the risk of more aggressive prostate cancer and may decrease either the occurrence or the likelihood of diagnosis of less-aggressive tumors. Men who lose weight may reduce their risk of prostate cancer.

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Thank you for your generous support!

Lung

Mahabir S, Spitz MR, Barrera SL, et al. **Dietary zinc, copper and selenium, and risk of lung cancer.** *Int J Cancer* 2007;120(5):1108-15.

Zinc, copper and selenium are important cofactors for several enzymes that play a role in maintaining DNA integrity. However, limited epidemiologic research on these dietary trace metals and lung cancer risk is available. In an ongoing study of 1,676 incident lung cancer cases and 1,676 matched healthy controls, we studied the associations between dietary zinc, copper and selenium and lung cancer risk. Using multiple logistic regression

analysis, the odds ratios (OR) and 95% confidence intervals (CI) of lung cancer for all subjects by increasing quartiles of dietary zinc intake were 1.0, 0.80 (0.65-0.99), 0.64 (0.51-0.81), 0.57 (0.42-0.75), respectively (p trend = 0.0004); similar results were found for men. For dietary copper, the ORs and 95% CI for all subjects were 1.0, 0.59 (0.49-0.73), 0.51 (0.41-0.64), 0.34 (0.26-0.45), respectively (p trend < 0.0001); similar reductions in risk and trend were observed by gender. Dietary selenium intake was not associated with risk, except for a significant inverse trend (p = 0.04) in men. Protective trends (p < 0.05) against lung cancer with increased dietary zinc intake were also found for all ages, BMI > 25, current smokers, pack-years ≤30, light drinkers and participants without emphysema. Increased dietary copper intake was associated with protective trends (p < 0.05) across all ages, BMI, smoking and vitamin/ mineral supplement categories, pack-years ≤30 and 30.1-51.75 and participants without emphysema. Our results suggest that dietary zinc and copper intakes are associated with reduced risk of lung cancer. Given the known limitations of case-control studies, these findings must be interpreted with caution and warrant further investigation.

Nutrition

Gill CIR, Haldar S, Boyd LA, et al. **Watercress supplementation in diet reduces lymphocyte DNA damage and alters blood antioxidant status in healthy adults.** *Am J Clin Nutr* 2007;85(2):504-10.

Background: Cruciferous vegetable (CV) consumption is associated with a reduced risk of several cancers in epidemiologic studies. Objective: The aim of this study was to determine the effects of watercress (a CV) supplementation on biomarkers related to cancer risk in healthy adults. Design: A single-blind, randomized, crossover study was conducted in 30 men and 30 women (30 smokers and 30 nonsmokers) with a mean age of 33 y (range: 19-55 y). The subjects were fed 85 g raw watercress daily for 8 wk in addition to their habitual diet. The effect of supplementation was measured on a range of endpoints, including DNA damage in lymphocytes (with the comet assay), activity of detoxifying enzymes (glutathione peroxidase and superoxide dismutase) in erythrocytes, plasma antioxidants (retinol, ascorbic acid, α-tocopherol, lutein, and beta-carotene), plasma total antioxidant status with the use of the ferric reducing ability of plasma assay, and plasma lipid profile. Results: Watercress supplementation (active compared with control phase) was associated with reductions in basal DNA damage (by 17%; P = 0.03), in basal plus oxidative purine DNA damage (by 23.9%; P = 0.002), and in basal DNA damage in response to ex vivo hydrogen peroxide challenge (by 9.4%; P = 0.07). Beneficial changes seen after watercress intervention were greater and more significant in smokers than in nonsmokers. Plasma lutein and beta-carotene increased significantly by 100% and 33% (P < 0.001), respectively, after watercress supplementation. Conclusion: The results support the theory that consumption of watercress can be linked to a reduced risk of cancer via decreased damage to DNA and possible modulation of antioxidant status by increasing carotenoid concentrations.

Bravi F, Bosetti C, Scotti L, et al. **Food groups and renal cell carcinoma: A case-control study from Italy.** *Int J Cancer* 2007;120(3):681-5.

Although nutrition and diet have been related to renal cell carcinoma (RCC), the role of specific foods or nutrients on this cancer is still controversial. We evaluated the relation between a wide range of foods and the risk of RCC in an Italian case-control study including 767 patients (494 men and 273 women) younger than 79 years with incident, histologically confirmed

RCC, and 1,534 controls (988 men and 546 women) admitted to the same hospitals as cases for a wide spectrum of acute, non-neoplastic conditions, not related to long term diet modifications. A validated and reproducible food frequency questionnaire, including 78 foods and beverages, plus a separate section on alcohol drinking, was used to assess patients' dietary habits 2 years before diagnosis or hospital admission. Multivariate odds ratios (OR) were obtained after allowance for energy intake and other major confounding factors. A significant direct trend in risk was found for bread (OR = 1.94 for the highest versus the lowest intake quintile), and a modest excess of risk was observed for pasta and rice (OR = 1.29), and milk and yoghurt (OR = 1.27). Poultry (OR = 0.74), processed meat (OR = 0.64) and vegetables (OR = 0.65) were inversely associated with RCC risk. No relation was found for coffee and tea, soups, eggs, red meat, fish, cheese, pulses, potatoes, fruits, desserts and sugars. The results of this study provide further indications on dietary correlates of RCC, and in particular indicate that a diet rich in refined cereals and poor in vegetables may have an unfavorable role on RCC.

Massage

Mehling WE. **Symptom management with massage and acupuncture in postoperative cancer patients: a randomized controlled trial.** *J Pain Symptom Manage* 2007;33(3):258-66.

The level of evidence for the use of acupuncture and massage for the management of perioperative symptoms in cancer patients is encouraging but inconclusive. We conducted a randomized, controlled trial assessing the effect of massage and acupuncture added to usual care vs. usual care alone in postoperative cancer patients. Cancer patients undergoing surgery were randomly assigned to receive either massage and acupuncture on postoperative Days 1 and 2 in addition to usual care, or usual care alone, and were followed over three days. Patients' pain, nausea, vomiting, and mood were assessed at four time points. Data on health care utilization were collected. Analyses were done by mixed-effects regression analyses for repeated measures. One hundred fifty of 180 consecutively approached cancer patients were eligible and consented before surgery. Twelve patients rescheduled or declined after surgery, and 138 patients were randomly assigned in a 2:1 scheme to receive massage and acupuncture (n=93) or to receive usual care only (n=45). Participants in the intervention group experienced a decrease of 1.4 points on a 0-10 pain scale, compared to 0.6 in the control group (P=0.038), and a decrease in depressive mood of 0.4 (on a scale of 1-5) compared to +/-0 in the control group (P=0.003). Providing massage and acupuncture in addition to usual care resulted in decreased pain and depressive mood among postoperative cancer patients when compared with usual care alone. These findings merit independent confirmation using larger sample sizes and attention control.

Supplements

Goh YI, Bollano E, Einarson TR, Koren G. **Prenatal multivitamin supplementation and rates of pediatric cancers: a meta-analysis.** *Clin Pharmacol Ther* 2007; 81(5):685-91.

Prenatal supplementation of folic acid has been shown to decrease the risk of several congenital malformations. Several studies have recently suggested a potential protective effect of folic acid on certain pediatric cancers. The protective role of prenatal multivitamins has not been elucidated. We conducted a systematic review and meta-analysis to assess the potential protective effect of prenatal multivitamins on several pediatric

cancers. Medline, PubMed, EMBASE, Toxline, Healthstar, and Cochrane databases were searched for studies published in all languages from 1960 to July 2005 on multivitamin supplementation and pediatric cancers. References from all articles collected were reviewed for additional articles. Two blinded independent reviewers assessed the articles for inclusion and exclusion. Rates of cancers in women supplemented with multivitamins were compared with unsupplemented women using a random effects model. Sixty-one articles were identified in the initial search, of which, seven articles met the inclusion criteria. There was an apparent protective effect for leukemia (odds ratio (OR)=0.61, 95% confidence interval (CI)=0.50–0.74), pediatric brain tumors (OR=0.73, 95% CI=0.60–0.88) and neuroblastoma (OR=0.53, 95% CI=0.42–0.68). In conclusion, maternal ingestion of prenatal multivitamins is associated with a decreased risk for pediatric brain tumors, neuroblastoma, and leukemia. Presently, it is not known which constituent(s) among the multivitamins confer this protective effect.

Peters U, Foster CB, Chatterjee N, et al. Serum selenium and risk of prostate cancer: a nested case-control study. *Am J Clin Nutr* 2007;85(1):209-17.

Background: Selenium is a potential chemopreventive agent against prostate cancer, whose chemoprotective effects are possibly mediated through the antioxidative properties of selenoenzymes. Interrelations with other antioxidative agents and oxidative stressors, such as smoking, are poorly understood. Objectives: The aims were to investigate the association between serum selenium and prostate cancer risk and to examine interactions with other antioxidants and tobacco use. Design: A nested case-control study was performed within the screening arm of the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial. Serum selenium in prospectively collected samples was compared between 724 incident prostate cancer case subjects and 879 control subjects, frequency-matched for age, time since initial screen, and year of blood draw. The men were followed for up to 8 y. Results: Overall, serum selenium was not associated with prostate cancer risk (P for trend = 0.70); however, higher serum selenium was associated with lower risks in men reporting a high (more than the median: 28.0 IU/d) vitamin E intake [odds ratio (OR) for the highest compared with the lowest quartile of selenium: 0.58; 95% CI: 0.37, 0.91; P for trend = 0.05; P for interaction = 0.01] and in multivitamin users (OR for highest compared with the lowest quartile of selenium: 0.61; 95% CI: 0.36, 1.04; P for trend = 0.06; P for interaction = 0.05). Furthermore, among smokers, high serum selenium concentrations were related to reduced prostate cancer risk (OR for the highest compared with the lowest quartile of selenium: 0.65; 95% CI: 0.44, 0.97; P for trend = 0.09; P for interaction = 0.007). Conclusion: Greater prediagnostic serum selenium concentrations were not associated with prostate cancer risk in this large cohort, although greater concentrations were associated with reduced prostate cancer risks in men who reported a high intake of vitamin E, in multivitamin users, and in smokers.

individuals diagnosed with cancer. All residents in Nord-Trøndelag County, Norway, aged 20 and older, were invited to take part in a public health survey during 1995-97, and 66,140 individuals (71.2%) participated. Sense of humor was estimated by responses to a cognitive (n= 53,546), social (n= 52,198) and affective (n= 53,132) item, respectively, taken from the Sense of Humor Questionnaire (SHQ: Svebak, 1997). Scores were related to mortality statistics up to 2003 using Cox survival regression analyses. Unadjusted statistics stated that hazard risk (HR) was significantly linearly reduced in those with higher scores on the cognitive (p<.001), social (p<.001) as well as affective (p<.001) facets of sense of humor. Adjustment for age, gender, demographics, life style and subjective as well as somatic health status caused reduced linear HR for all three facets and was still significant for scores on the cognitive item. A sub-population diagnosed with cancer at screening (n= 2,015) also presented a significant linear reduction of seven-year unadjusted HR for scores on all three SHQ items. Adjustment as above (except for cancer) yielded curvilinear trends due to significant reductions in HR among individuals who scored medium as well as high on the cognitive facet of sense of humor (HR at or below .36, p=.04 - .002), whereas non-significant results emerged for the social and affective facets. These findings suggest that the cognitive facet of sense of humor can significantly reduce mortality risk among adults over a seven-year period and that the cognitive facet can reduce HR also among adults who are faced with the life-threatening diagnosis of cancer.

The Centre for Integrated Healing provides an integrated whole person approach to health for individuals living with cancer. Our medical doctors coach patients to explore and learn about a variety of wellness approaches to health and healing in addition to conventional cancer treatment. Our integrated cancer care model engages people in their own care and improves quality of life. The editorial board includes: Dr. Hal Gunn, CEO and Co-founder of the Centre, Dr. Janice Wright, and Dr. Teresa Clarke.

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CAM of the Month

Svebak S. **Sense of humor and mortality: a seven-year prospective study of an unselected adult county population and a sub-population diagnosed with cancer. The Hunt Study.** American Psychosomatic Society 65th Annual Meeting. March 7-10, 2007.

This study prospectively explored the significance of sense of humor for survival (mortality) over a seven-year period in a large, unselected adult county population and in a sub-population of