REsearch UPDATES

For the latest in world-wide integrated cancer care research

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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

Brisson J, Berube S, Diorio C, et al. **Synchronized seasonal variations of mammographic breast density and plasma 25-hydroxyvitamin D.** *Cancer Epidemiol Biomarkers Prev* 2007;16(5):929-33.
Background: Dietary vitamin D has been associated with lower mammographic breast density, a strong biomarker for breast cancer risk. Blood 25-hydroxyvitamin D [25(OH)D] is an integrated measure of vitamin D status (from food, supplements, and sun exposure) and varies with season. Our objective was to assess seasonal variations of breast density and compare such variations, if any, with that of 25(OH)D. Methods: This cross-sectional study includes 741 premenopausal women recruited at screening mammography. Plasma 25(OH)D at recruitment was measured by RIA. Breast density was evaluated using a computer-assisted method. Seasonal variations were modeled using multivariate linear regression and semi-parametric cubic smoothing splines. Results: Season was strongly associated with 25(OH)D (P < 0.0001). The highest smoothed mean 25(OH)D levels were seen at the end of July (81.5 nmol/L) and the lowest in mid-April (52.4 nmol/L). Breast density showed modest seasonal variations (P = 0.028). The lowest smoothed mean breast density was observed in early December (38.5%) and the highest at the beginning of April (44.3%). When a 4-month lag time was presumed, seasonal variations of breast density appeared to be a mirror image of those of 25(OH)D, and the correlation of daily smoothed estimates of mean breast density and 25(OH)D was negative and strong (r = -0.90). Conclusion: In premenopausal women, changes in blood vitamin D seem to be inversely related to changes in breast density with a lag time of about 4 months. This finding encourages further investigation of the possibility that vitamin D could reduce breast density and breast cancer risk.

Kesse-Guyot E, Bertrais S, Duperray B, et al. **Dairy products, calcium and the risk of breast cancer: results of the French SU.VI.MAX prospective study.** *Ann Nutr Metab* 2007;51(2): 139-45.

The aim was to estimate the association between dairy products (total and their subgroups), calcium intake and the risk of breast cancer. As few studies have considered menopausal status, we also investigated stratified analyses. This analysis included 3,627 women from the French SU.VI.MAX study, among whom 92 developed breast cancer during the follow-up period. Food consumption was assessed based on five 24-hour records completed during the previous 18 months to follow-up. Calcium intake was calculated using an ad-hoc food composition database. Cox proportional hazards models were used to estimate relative risk (RR), comparing 4th quartile vs. 1st quartile, and 95% confidence intervals (95% CI). A lower risk of breast cancer was observed with high total dairy product consumption in the whole population (RR = 0.55, 95% CI = 0.29-1.03, p trend = 0.03) and among premenopausal women with a RR of 0.35 (95% CI = 0.12-0.95, p trend = 0.01). None of these associations remained after control for calcium intake. Increasing calcium intake was inversely associated with breast cancer risk considering the whole population (RR = 0.50, 95% CI = 0.27-0.91, p trend = 0.04) and among the subgroup of premenopausal women (RR = 0.26, 95% CI = 0.10-0.71, p trend= 0.01) respectively. Our data support the hypothesis that dairy products, through calcium content or a correlated component, might have a negative association with the risk of breast cancer, particularly among premenopausal women.

Monroe KR, Murphy SP, Kolonel LN, Pike MC. **Prospective study of grapefruit intake and risk of breast cancer in postmenopausal women: the Multiethnic Cohort Study**. *Br J Cancer* 2007;97(3):440-5.
In vitro and in vivo studies have shown that cytochrome *P*450 3A4 (CYP3A4) is involved in the metabolism of oestrogens. There is evidence that grapefruit, an inhibitor of CYP3A4, increases plasma oestrogen concentrations. Since it is well established that oestrogen is associated with breast cancer risk, it is plausible that regular intake of grapefruit would increase a woman's risk of breast cancer. We investigated the association of grapefruit intake with breast cancer risk in the Hawaii-Los Angeles Multiethnic Cohort Study, a prospective cohort that includes over 50 000 postmenopausal women from five racial/ethnic groups. A total of 1657 incident breast cancer cases were available for analysis. Grapefruit intake was significantly associated with an

increased risk of breast cancer (relative risk=1.30, 95% confidence interval 1.06-1.58) for subjects in the highest category of intake, that is, one-quarter grapefruit or more per day, compared to non-consumers (P_{trend}=0.015). An increased risk of similar magnitude was seen in users of oestrogen therapy, users of oestrogen+progestin therapy, and among never users of hormone therapy. Grapefruit intake may increase the risk of breast cancer among postmenopausal women.

Prostate

Mitrou PN, Albanes D, Weinstein SJ, et al. **A prospective study of dietary calcium, dairy products and prostate cancer risk (Finland).** *Int J Cancer* 2007;120 (11):2466-73.
High dietary intakes of calcium and dairy products have been hypothesized to enhance prostate cancer risk, but available prospective data regarding these associations are inconsistent. We examined dietary intakes of calcium and dairy products in relation to risk of prostate cancer in the Alpha-Tocopherol, Beta-Carotene (ATBC) Cancer Prevention Study, a cohort of 29,133 male smokers aged 50-69 years at study entry. Dietary intake was assessed at baseline using a validated 276-item food use questionnaire. Cox proportional hazards regression was used to adjust for known or suspected risk factors for prostate cancer. During 17 years of follow-up, we ascertained 1,267 incident cases of prostate cancer. High *versus* low intake of dietary calcium was associated with a marked increase in prostate cancer risk. The multivariate relative risk (RR) of prostate cancer for ≥2,000 mg/day compared to <1,000 mg/day of calcium intake was 1.63 (95% confidence interval (CI), 1.27-2.10; *p* trend < 0.0001). Total dairy intake was also positively associated with risk of prostate cancer. The multivariate RR of prostate cancer comparing extreme quintiles of intake was 1.26 (95% CI, 1.04-1.51; *p* trend = 0.03). However, no association with total dairy intake remained after we adjusted for calcium (*p* trend = 0.17). Findings were similar by stage and grade of prostate cancer. The results from this large prospective study suggest that intake of calcium or some related component contained in dairy foods is associated with increased prostate cancer risk.

John EM, Koo J, Schwartz GG. **Sun exposure and prostate cancer risk: Evidence for a protective effect of early-life exposure.** *Cancer Epidemiol Biomarkers Prev* 2007;16(6):1283-6.
Mounting experimental and epidemiologic evidence supports the hypothesis that vitamin D reduces the risk of prostate cancer. Some evidence suggests that prostate cancer risk may be influenced by sun exposure early in life. We analyzed data from the National Health and Nutrition Examination Survey I Epidemiologic Follow-up Study to examine associations of prostate cancer risk with early-life and adult residential sun exposure and adult sun exposures that were assessed through self-report, physician report, and dermatologic examination. We used solar radiation in the state of birth as a measure of sun exposure in early life. Follow-up from 1971 to 1975 (baseline) to 1992 identified 161 prostate cancer cases (102 nonfatal and 59 fatal) among non-Hispanic white men for whom sun exposure data were available. Significant inverse associations were found for men born in a region of high solar radiation (relative risk, 0.49, 95% confidence interval, 0.27-0.90 for high versus low solar radiation), with a slightly greater reduction for fatal than for nonfatal prostate cancer. Frequent recreational sun exposure in adulthood was associated with a

significantly reduced risk of fatal prostate cancer only (relative risk, 0.47; 95% confidence interval, 0.23-0.99). These findings suggest that, in addition to sun exposure in adulthood, sun exposure in early life protects against prostate cancer.

De Vries E, Soerjomataram I, Houterman S, Louwman MW. **Decreased risk of prostate cancer after skin cancer diagnosis: a protective role of ultraviolet radiation?** *Am J Epidemiol* 2007;165(8):966-72.
Ultraviolet radiation causes skin cancer but may protect against prostate cancer. The authors hypothesized that skin cancer patients had a lower prostate cancer incidence than the general population. In the southeastern part of the Netherlands, a population-based cohort of male skin cancer patients diagnosed since 1970 (2,620 squamous cell carcinomas, 9,501 basal cell carcinomas, and 1,420 cutaneous malignant melanomas) was followed up for incidence of invasive prostate cancer until January 1, 2005, within the framework of the Eindhoven Cancer Registry. The incidence rates of prostate cancer among skin cancer patients were compared with those in the reference population, resulting in standardized incidence ratios. Skin cancer patients were at decreased risk of developing prostate cancer compared with the general population (standardized incidence ratio (SIR) = 0.89, 95% confidence interval (CI): 0.78, 0.99), especially shortly after diagnosis. The risk of advanced prostate cancer was significantly decreased (SIR = 0.73, 95% CI: 0.56, 0.94), indicating a possible antiprogression effect of ultraviolet radiation. Patients with a skin cancer in the chronically ultraviolet radiation-exposed head and neck area (SIR = 0.84, 95% CI: 0.73, 0.97) and those diagnosed after the age of 60 years (SIR = 0.86, 95% CI: 0.75, 0.97) had decreased prostate cancer incidence rates. These results support the hypothesis that ultraviolet radiation protects against prostate cancer.

Colorectal

Theodoratou E, McNeill G, Catnarskyj R, et al. **Dietary fatty acids and colorectal cancer: a case-control study**. *Am J Epidemiol* 2007;166(2):181-95.
Fatty acid effects on colorectal cancer risk were examined in a national prospective case-control study in Scotland (1999–2006), including 1,455 incident cases and 1,455 matched controls. Three conditional logistic regression models adjusted for energy (residual method) and for other risk factors were applied in the whole sample and were stratified by sex, cancer site, age, and tumor staging. Total and *trans*-monounsaturated fatty acids and palmitic, stearic, and oleic acids were dose-dependently associated with colorectal cancer risk, but these effects did not persist after further energy adjustment. Significant dose-dependent reductions in risk were associated with increased consumption of omega-3 polyunsaturated fatty acids (highest vs. lowest quartile of intake: odds ratio = 0.63, 95% confidence interval: 0.50, 0.80; *p* < 0.0005 for trend) and of eicosapentaenoic (odds ratio = 0.59, 95% confidence interval: 0.47, 0.75; *p* < 0.0005 for trend) and docosahexaenoic (odds ratio = 0.63, 95% confidence interval: 0.50, 0.80; *p* < 0.0005 for trend) acids. These associations persisted after including energy with the nutrient-energy-adjusted term or total fatty acid intake (energy adjusted). The observed different

effects of different types of fatty acids underline the importance of type of fat in the etiology and prevention of colorectal cancer.

Skin

Tuohimaa P, Pukkala E, Scelo G. et al. **Does solar exposure, as indicated by the non-melanoma skin cancers, protect from solid cancers: vitamin D as a possible explanation.** *Eur J Cancer* 2007;43(11):1701-12.

Background: Skin cancers are known to be associated with sun exposure, whereas sunlight through the production of vitamin D may protect against some cancers. The aim of this study was to assess whether patients with skin cancer have an altered risk of developing other cancers. Methods: The study cohort consisted of 416,134 cases of skin cancer and 3,776,501 cases of non-skin cancer as a first cancer extracted from 13 cancer registries. 10,886 melanoma and 35,620 non-melanoma skin cancer cases had second cancers. The observed numbers (O) of 46 types of second primary cancer after skin melanoma, basal cell carcinoma or non-basal cell carcinoma, and of skin cancers following non-skin cancers were compared to the expected numbers (E) derived from the age, sex and calendar period specific cancer incidence rates in each of the cancer registries (O/E = SIR, standardised incidence ratios). Rates from cancer registries classified to sunny countries (Australia, Singapore and Spain) and less sunny countries (Canada, Denmark, Finland, Iceland, Norway, Scotland, Slovenia and Sweden) were compared to each other. Results: SIR of all second solid primary cancers (except skin and lip) after skin melanoma were significantly lower for the sunny countries (SIR(S) = 1.03; 95% CI 0.99-1.08) than in the less sunny countries (SIR(L) = 1.14; 95%CI 1.11-1.17). The difference was more obvious after non-melanoma skin cancers: after basal cell carcinoma SIR(S)/SIR(L) = 0.65 (95%CI = 0.58-0.72); after non-basal cell carcinoma SIR(S)/SIR(L) = 0.58 (95%CI = 0.50-0.67). In sunny countries, the risk of second primary cancer after non-melanoma skin cancers was lower for most of the cancers except for lip, mouth and non-Hodgkin lymphoma. Conclusions: Vitamin D production in the skin seems to decrease the risk of several solid cancers (especially stomach, colorectal, liver and gallbladder, pancreas, lung, female breast, prostate, bladder and kidney cancers). The apparently protective effect of sun exposure against second primary cancer is more pronounced after non-melanoma skin cancers than melanoma, which is consistent with earlier reports that non-melanoma skin cancers reflect cumulative sun exposure, whereas melanoma is more related to sunburn.

Supplements

Walji R, Boon H, Guns E, et al. **Black cohosh (Cimicifuga racemosa [L.] Nutt.): safety and efficacy for cancer patients.** *Support Care Cancer* 2007;15(8):913-21.

GOALS OF WORK: Black cohosh is commonly used to treat hot flashes and other symptoms associated with menopause. It is thought to have multiple mechanisms of action, including potential phytoestrogenic properties. This has caused some concern about its use by patients with hormone-sensitive cancer. This paper will present the results of a systematic review of the safety and efficacy of black cohosh (Cimicifuga racemosa [L.] Nutt.) in patients with cancer. MATERIALS AND METHODS: A critical assessment of clinical (n = 5) and preclinical (n = 21) studies of black cohosh and cancer (breast and prostate) to treat hot flashes and other related symptoms is presented. In addition, clinical studies, case reports, animal studies, and in vitro assessments of the safety of black cohosh

for patients with hormonally sensitive cancers is summarized and interpreted. MAIN RESULTS: In general, the research assessing efficacy of black cohosh for the treatment of hot flashes in women with breast cancer is inconclusive. There is laboratory evidence of antiproliferative properties but no confirmation from clinical studies for a protective role in cancer prevention. Black cohosh seems to have a relatively good safety profile. Concerns about liver toxicity are inconclusive. With relevance to cancer patients, black cohosh also seems not to exhibit phytoestrogenic activity and is in fact possibly an inhibitor of tumor growth. CONCLUSIONS: The use of black cohosh appears to be safe in breast cancer patients without risk for liver disease, although further research is needed in this and other populations.

Schernhammer E, Wolpin B, Rifai N, et al. **Plasma folate, vitamin B6, Vitamin B12, and homocysteine and pancreatic cancer risk in four large cohorts.** *Cancer Res* 2007;67(11):5553-60.

Folate deficiency induces DNA breaks and may alter cellular capacity for mutation and epigenetic methylation. Few studies have examined the influence of one-carbon nutrients on pancreatic cancer risk, although recent studies suggest a potential protective effect for one-carbon nutrients from food sources, but not from supplements. We conducted a prospective nested case-control study to examine plasma concentrations of folate, vitamin B6 [whose main circulating form is pyridoxal-5'-phosphate (PLP)], vitamin B12, and homocysteine in relationship to pancreatic cancer, using four large prospective cohorts. Multivariable adjusted odds ratios (OR) and 95% confidence intervals (95% CI) were calculated using conditional logistic regression. All statistical tests were two sided. Among 208 cases and 623 controls, we observed no association between folate, PLP, vitamin B12 or homocysteine and pancreatic cancer risk. Comparing the highest to lowest quartiles of plasma concentration, the ORs were 1.20 (95% CI, 0.76-1.91) for folate, 0.80 (95% CI, 0.51-1.25) for B6 0.91 (95% CI, 0.57-1.46) for B12 and 1.43 (95% CI, 0.90-2.28) for homocysteine. In analyses restricted to nonusers of multivitamins, we observe a modest inverse trend between folate, PLP, and B12 and pancreatic cancer risk. In contrast, no such inverse associations were observed among study subjects who reported multivitamin supplement use. Among all participants, plasma levels of folate, B6, B12 and homocysteine were not associated with a significant reduction in the risk of pancreatic cancer. Among participants who obtain these factors exclusively through dietary sources, there may be an inverse relation between circulating folate, B6 and B12 and risk.

Exercise

Karvinen KH, Courneya KS, North S, Venner P. **Associations between exercise and quality of life in bladder cancer survivors: A population-based study.** *Cancer Epidemiol Biomarkers Prev* 2007;16(5):984-90.

Background: Exercise has been shown to improve quality of life (QoL) in some cancer survivor groups, but it is unknown if the unique QoL issues faced by bladder cancer survivors are also amenable to an exercise intervention. This study provides the first data examining the association between exercise and QoL in bladder cancer survivors. Methods: Bladder cancer survivors identified through a provincial cancer registry were mailed a survey that included the Godin Leisure Time Exercise Questionnaire, the Functional Assessment of Cancer Therapy-Bladder (FACT-B1) scale, and the Fatigue Symptom Inventory.

Results: Of the 525 bladder cancer survivors (51% response rate) that completed the survey, 22.3% were meeting public health exercise guidelines in the past month, 16.0% were insufficiently active (i.e., some exercise but less than the guidelines), and 61.7% were completely sedentary. ANOVA indicated a general linear association between meeting guidelines and QoL, with those meeting guidelines reporting more favorable scores than completely sedentary survivors on the FACT-B1 (mean difference, 7.6; 95% confidence interval, 3.6-11.7; $P < 0.001$), the FACT ($P = 0.001$), the trial outcome index ($P < 0.001$), functional well-being ($P < 0.001$), additional concerns ($P = 0.001$), sexual functioning ($P < 0.001$), erectile function ($P < 0.001$), body image ($P < 0.001$), and various fatigue indicators ($P < 0.05$). Adjusting for key medical and demographic factors slightly attenuated the magnitude of the associations but did not alter the substantive conclusions. Conclusions: Exercise is positively associated with QoL in bladder cancer survivors, although few are meeting public health exercise guidelines. Studies testing the causal effects of exercise on QoL issues unique to this population are warranted.

Nutrition

Nomura AM, Hankin JH, Henderson BE, et al. **Dietary fiber and colorectal cancer risk: the multiethnic cohort study.** *Cancer Causes Control* 2007;18(7):753-64.
OBJECTIVE: To investigate the association of dietary fiber with colorectal cancer METHODS: A total of 85,903 men and 105,108 women completed a quantitative food frequency questionnaire in 1993-1996. A total of 1,138 men and 972 women were subsequently diagnosed with adenocarcinoma of the large bowel. Cox proportional hazards models were used to calculate multivariate adjusted relative risks (RR) and 95% confidence intervals (95% CI) for colorectal cancer. RESULTS: High consumers of dietary fiber were more active, less overweight, and less likely to be cigarette smokers than low consumers in both sexes. Fiber was inversely associated with colorectal cancer risk after adjustment for age and ethnicity in men (RR = 0.49; 95% CI, 0.41-0.60, highest vs. lowest quintile) and women (RR = 0.75; 95% CI, 0.61-0.92). After further adjustment for lifestyle and dietary factors, the inverse association remained significant in men (RR = 0.62; 95% CI, 0.48-0.79), but not in women (RR = 0.88; 95% CI, 0.67-1.14). Adjustment for the combination of replacement hormone use with either cigarette smoking or body mass index accounted for the lack of association with fiber in women. CONCLUSION: Dietary fiber was inversely associated with colorectal cancer risk in men, but its relation to replacement hormone use and other factors affected its inverse association in women.

Kudlich T, Gostner A, Holub I, et al. Stubs D. **The role of the diet in the prevention of gastrointestinal tumors.** *MMW Fortschr Med* 2007;149(17):36-8.
Second only to cardiovascular diseases, malignant tumors are the most common fatal disease, with malignant neoplasms in the gastrointestinal tract playing an important role. Underlying the most numerous of these malignancies is a complex interaction between genetic and environmental factors. The data relating to the role of environmental factors (for the most part dietary factors) in the development of gastrointestinal tumors derive mainly from, epidemiological research. The current evidence is 'convincing' with regard to complex lifestyle patterns, but at most 'plausible' when the chemically defined individual substances are considered. Summarizing the potential protective value of dietary factors reveals that the risk

of contracting the majority of the gastrointestinal tumors can be reduced by increasing the intake of fruit and vegetables. An additional protective effect is associated with a balanced diet, physical activity, preservation of normal weight, avoidance of smoking, and moderation in the amount of alcohol consumed.

CAM of the Month

Bergs JWJ, Franken NAP, Haveman J, et al. **Hyperthermia, cisplatin and radiation trimodality treatment: A promising cancer treatment? A review from preclinical studies to clinical application.** *Int J Hyperthermia* 2007;23(4):329-41.
This review discusses available clinical and experimental data and the underlying mechanisms involved in trimodality treatment consisting of hyperthermia, cisplatin and radiotherapy. The results of phase I/II clinical trials show that trimodality treatment is effective and feasible in various cancer types and sites with tolerable toxicity. Based on these results, phase III trials have been launched to investigate whether significant differences in treatment outcome exist between trimodality and standard treatment. In view of the clinical interest, it is surprising to find so few preclinical studies on trimodality treatment. Although little information is available on the doses of the modalities and the treatment sequence resulting in the largest degree of synergistic interaction, the results from in vivo and in vitro preclinical studies support the use of trimodality treatment for cancer patients. Animal studies show an improvement in treatment outcome after trimodality treatment compared with mono- and bimodality treatment. Studies in different human tumour cell lines show that a synergistic interaction can be obtained between hyperthermia, cisplatin and radiation and that this interaction is more likely to occur in cell lines which are more sensitive to cisplatin.