REsearch UPDATES

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INTEGRATED CANCER CARE

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Breast

Pierce JP, Stefanick ML, Flatt SW, et al. **Greater survival after breast cancer in physically active women with high vegetable-fruit intake regardless of obesity.** *J Clin Oncol* 2007:2345–51.
Purpose: Single-variable analyses have associated physical activity, diet, and obesity with survival after breast cancer. This report investigates interactions among these variables. Patients and Methods: A prospective study was performed of 1,490 women diagnosed and treated for early-stage breast cancer between 1991 and 2000. Enrollment was an average of 2 years postdiagnosis. Only seven women were lost to follow-up through December 2005. Results: In univariate analysis, reduced mortality was weakly associated with higher vegetable-fruit consumption, increased physical activity, and a body mass index that was neither low weight nor obese. In a multivariate Cox model, only the combination of consuming five or more daily servings of vegetables-fruits, and accumulating 540+ metabolic equivalent tasks-min/wk (equivalent to walking 30 minutes 6 d/wk), was associated with a significant survival advantage (hazard ratio, 0.56; 95% CI, 0.31 to 0.98). The approximate 50% reduction in risk associated with these healthy lifestyle behaviors was observed in both obese and nonobese women, although fewer obese women were physically active with a healthy dietary pattern (16% *v* 30%). Among those who adhered to this healthy lifestyle, there was no apparent effect of obesity on survival. The effect was stronger in women who had hormone receptor–positive cancers. Conclusion: A minority of breast cancer survivors follow a healthy lifestyle that includes both recommended intakes of vegetables-fruits and moderate levels of physical activity. The strong protective effect observed suggests a need for additional investigation of the effect of the combined influence of diet and physical activity on breast cancer survival.

Slattery ML, Edwards S, Murtaugh MA, et al. **Physical activity and breast cancer risk among women in the southwestern United States.** *Ann Epidemiol* 2007;17(5): 342-53.
Physical activity may influence breast cancer risk through multiple mechanisms and at different periods in life. In this study, we evaluate breast cancer risk associated with total and vigorous physical activity at ages 15, 30, and 50 years and the referent year prior to diagnosis/selection. Participants were non-Hispanic white (NHW) (1527 cases and 1601 control subjects) and Hispanic/American Indian (HAI) (798 cases and 924 controls) women. Both total and vigorous activity reduced risk of breast cancer in a dose-response manner. Among premenopausal women, only high total metabolic equivalent of the task (MET) hours of activity during the referent year was associated with reduced breast cancer risk in NHW women (odds ratio [OR] 0.62; 95% confidence interval [CI] 0.43, 0.91). Among postmenopausal women, physical activity had the greatest influence among women not recently exposed to hormones. Among these women, high total lifetime activity reduced risk of breast cancer for both NHW (OR 0.60; 95% CI 0.36, 1.02; p trend 0.01) and HAI women (OR 0.52; 95% CI 0.23, 1.16; p trend 0.07). Additionally, high total MET hours of activity at age 30 years (OR 0.56; 95% CI 0.37, 0.85) and at age 15 years (OR 0.57; 95% CI 0.38, 0.88) reduced breast cancer risk among postmenopausal NHW women not recently exposed to hormones. Among HAI women, more recent activity performed during the referent year and at age 50 appeared to have the greatest influence on breast cancer risk. Among postmenopausal NHW women. there was a significant interaction between physical activity and hormone replacement therapy (p value, 0.01), while among postmenopausal HAI women, physical activity interacted with body mass index (p value, 0.04). These data suggest that physical activity is important in reducing risk of breast cancer in both NHW and HAI women.

Tjonneland A, Christensen J, Olsen A, et al. **Alcohol intake and breast cancer risk: the European Prospective Investigation into Cancer and Nutrition (EPIC).** *Cancer Causes Control* 2007;18(4):361-73.
OBJECTIVE: Most epidemiologic studies have suggested an increased risk of breast cancer with increasing alcohol intake. Using data from 274,688 women participating in the European Prospective Investigation into Cancer and Nutrition study (EPIC), we investigated the relation between alcohol intake and the risk of breast cancer. METHODS: Incidence rate ratios (IRRs) based on Cox proportional hazard models were calculated using reported intake of alcohol,

recent (at baseline) and lifetime exposure. We adjusted for known risk factors and stratified according to study center as well as potentially modifying host factors. RESULTS: During 6.4 years of follow up, 4,285 invasive cases of breast cancer within the age group 35-75 years were identified. For all countries together the IRR per 10 g/day higher recent alcohol intake (continuous) was 1.03 (95% confidence interval (CI): 1.01-1.05). When adjusted, no association was seen between lifetime alcohol intake and risk of breast cancer. No difference in risk was shown between users and non-users of HRT, and there was no significant interaction between alcohol intake and BMI, HRT or dietary folate. CONCLUSION: This large European study supports previous findings that recent alcohol intake increases the risk of breast cancer.

Lin J, Manson JE, Lee I-M, et al. **Intakes of calcium and vitamin D and breast cancer risk in women.** *Arch Intern Med* 2007;167:1050-9.
Background: Animal data suggest the potential anticarcinogenic effects of calcium and vitamin D on breast cancer development. However, epidemiologic data relating calcium and vitamin D levels to breast cancer have been inconclusive. Methods: We prospectively evaluated total calcium and vitamin D intake in relation to breast cancer incidence among 10 578 premenopausal and 20 909 postmenopausal women 45 years or older who were free of cancer and cardiovascular disease at baseline in the Women's Health Study. Baseline dietary intake was assessed by a food frequency questionnaire. We used Cox proportional hazards regression to estimate hazard ratios and 95% confidence intervals. Results: During an average of 10 years of follow-up, 276 premenopausal and 743 postmenopausal women had a confirmed diagnosis of incident invasive breast cancer. Higher intakes of total calcium and vitamin D were moderately associated with a lower risk of premenopausal breast cancer; the hazard ratios in the group with the highest relative to the lowest quintile of intake were 0.61 (95% confidence interval, 0.40-0.92) for calcium (*P*=.04 for trend) and 0.65 (95% confidence interval, 0.42-1.00) for vitamin D intake (*P*=.07 for trend). The inverse association with both nutrients was also present for large or poorly differentiated breast tumors among premenopausal women (*P_*.04 for trend). By contrast, intakes of both nutrients were not inversely associated with the risk of breast cancer among postmenopausal women. Conclusions: Findings from this study suggest that higher intakes of calcium and vitamin D may be associated with a lower risk of developing premenopausal breast cancer. The likely apparent protection in premenopausal women may be more pronounced for more aggressive breast tumors.

Irdesel J, Kahraman Celiktas S. **Effectiveness of exercise and compression garments in the treatment of breast cancer related lymphedema.** *Ftr - Turkiye Fiziksel Tip Ve Rehabilitasyon Dergisi* 2007;53(1): 16-21.
Objective: Lymphedema (LE) is a long term and important complication observed in patients with breast cancer that causes functional impairment and affects the quality of life. Total recovery could not be reached by current treatments. Therapeutic efforts remain focused on minimizing the edema and on reversing and restoring the functional and cosmetic nature of the limb. There are a limited number of randomized, controlled studies looking for the effectiveness of treatments, either seperately or combined. This study was designed to investigate the effectiveness of exercise and compression garment in the treatment of breast cancer related LE. Materials and Methods: Nineteen patients with breast cancer related LE

were randomly assigned to receive exercises (n=9) or exercises and compression garment (n=10). The efficacy of treatment was evaluated by reduction in lymphedema volume which was determined by measurement of arm circumference and by improvement in shoulder range of motion and in symptoms potentially related to lymphedema such as pain and tender points. Results: The patients were followed-up for a total of six months. Almost all parameters improved in the second group whereas no significant improvement was seen in the first group. Conclusion: As a conclusion, it can be suggested that the combination of compression garments and exercise therapy is an effective and simple way of treating LE. Since none of the treatment methods offer full recovery, educating the patients about the formation and characteristics of LE and preventive measures are very important.

Almquist M, Manjer J, Bondeson L, et al. **Serum calcium and breast cancer risk: Results from a prospective cohort study of 7,847 women.** *Cancer Causes Control* 2007;18(6): 595-602.
Experimental and epidemiological studies suggest that calcium-regulating hormones-parathyroid hormone (PTH) and vitamin D-may be associated with breast cancer risk. No prospective cohort study has investigated the association between pre-diagnostic calcium levels and subsequent risk of breast cancer. We have examined this in a cohort of 7,847 women where serum calcium levels and established risk factors for breast cancer had been assessed at baseline. During a mean follow-up of 17.8 years, 437 incident breast cancer cases were diagnosed. Incidence of breast cancer was calculated in different quartiles of serum calcium levels and a Cox's proportional hazards analysis was used to obtain corresponding relative risks (RR), with a 95% confidence interval (CI), adjusted for potential confounders. In premenopausal women, serum calcium levels were inversely associated with breast cancer risk in a dose-response manner. The adjusted RR (95% CI) of breast cancer was in the 2nd calcium quartile 0.91 (0.65-1.30), in the 3rd quartile 0.89 (0.60-1.31), and in the 4th quartile 0.56 (0.32-0.98), as compared to the 1st calcium quartile. In postmenopausal overweight women (BMI > 25), breast cancer risk was higher in calcium quartiles 2-4 as compared to the 1st quartile. Our findings may have implications for primary prevention of breast cancer and for the management of asymptomatic primary hyperparathyroidism.

Prostate

George SL, Polascik TJ, Albala DM, et al. **Impact of flaxseed supplementation and dietary fat restriction on prostate cancer proliferation and other biomarkers: Results of a Phase II randomized controlled trial (RCT) using a presurgical model.** *J Clin Oncol* ASCO Annual Meeting Proceedings 2007; 25(18s):1510.
Background: Diet may play a key role in the etiology of prostate cancer (PC). Dietary fat restriction (DFR) and flaxseed supplementation (FS) may reduce risk, though results are mixed. We undertook an RCT to test the comparative effects of these dietary regimens on the biology of the prostate and other biomarkers. Methods: PC patients (N=161) scheduled $\geq$ 21 days prior to prostatectomy were block randomized on race (black vs non-black) and biopsy Gleason sum (<7 vs 7+) to these diets: 1) control; 2) FS (30 g/day); 2) DFR (<20% total energy); or 4) FS+DFR. Blood was drawn upon accrual and prior to surgery and analyzed for prostate specific antigen (PSA), sex hormone binding globulin (SHBG), total

testosterone (T), insulin-like growth factor 1 (IGF1), IGF binding protein 3 (IGFBP3), c- reactive protein (CRP), and total and low density lipoprotein cholesterol (TC & LDL-C). Proliferation (MIB-1) and apoptosis (TUNEL) was assessed in the malignant and benign prostate. Results: Complete data were collected on 93% of the sample; mean length on protocol was 30 days. Median MIB-1 positive (+) cells/total nuclei ratios were: 1=2.38;2=1.71;3=2.93;4=1.58. Primary analyses suggest a significant protective effect (p=0.016) of FS. Secondary analyses of MIB-1 + nuclei (controlling for total cell counts) show increased proliferation with DFR (p=.017), and a significant interaction with FS and DFR (p<.0001). No differences were observed between groups with regard to PC apoptosis, and histology of benign tissue. No differences were observed between arms for PSA, SHBG, T, IGF1, IGFBP3 or CRP. Significant differences were observed between arms for changes in serum lipids and body weight [ΔTC = +9/-26/-46/-37 mg/dL; ΔLDLC = -14/-17/-29/-21 mg/dL and Δ weight = +0.3/-1.3/-1.7/-1.1 kg (p's<.05)]; effects were attributed to DFR and not FS. Side effects did not differ between arms Conclusions: Preliminary findings suggest that FS is safe and exerts a protective effect (main effect or via interaction with DFR) on PC. Data also provide further support of DFR for cardiovascular disease, though its role in PC is less clear. Further controlled analyses and additional studies are needed to confirm findings.

BC Foundation for *strength unity courage* **Prostate Disease**

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Colorectal

Wakai K, Date C, Fukui M, et al. **Dietary fiber and risk of colorectal cancer in the Japan collaborative cohort study.** *Cancer Epidemiol Biomarkers Prev* 2007; 16(4):668-75.
To examine the association of dietary fiber with the risk of colorectal cancer in a population with a high incidence of cancer and a low fiber intake, we analyzed the data from the Japan Collaborative Cohort Study. From 1988 to 1990, 43,115 men and women aged 40 to 79 years completed a questionnaire on dietary and other factors. Intake of dietary fiber was estimated using a food frequency questionnaire. Rate ratios (RR) were computed by fitting proportional hazards models. During the mean follow-up of 7.6 years, 443 colorectal cancer cases were recorded. In all participants, we found a decreasing trend in risk of colorectal cancer with increasing intake of total dietary fiber; the multivariate-adjusted RRs across quartiles were 1.00, 0.96 [95% confidence interval (95% CI), 0.72-1.27], 0.72 (0.53-0.99), and 0.73 (0.51-1.03; P(trend) = 0.028). This trend was exclusively detected for colon cancer: the corresponding RRs were 1.00, 0.90 (95% CI, 0.64-1.26), 0.56 (0.38-0.83), and 0.58 (0.38-0.88; P(trend) = 0.002). The decrease in RRs with increasing intake of dietary fiber was larger in men than in women. No material differences appeared in the strength of associations with the risk between water-soluble and insoluble dietary fiber. For food sources of fiber, bean fiber intake was somewhat inversely correlated with colorectal cancer risk. This prospective study supported potential protective effects of dietary fiber against colorectal cancer, mainly against colon cancer. The role of dietary fiber in the prevention of colorectal cancer seems to remain inconsistent, and further investigations in various populations are warranted.

Supplements

Lappe JM, Travers-Gustafson D, Davies KM, et al. **Vitamin D and calcium supplementation reduces cancer risk: Results of a randomized trial.** *Am J Clin Nutr* 2007;85(6):1586-91.
Background: Numerous observational studies have found supplemental calcium and vitamin D to be associated with reduced risk of common cancers. However, interventional studies to test this effect are lacking. Objective: The purpose of this analysis was to determine the efficacy of calcium alone and calcium plus vitamin D in reducing incident cancer risk of all types. Design: This was a 4-y, population-based, double-blind, randomized placebo-controlled trial. The primary outcome was fracture incidence, and the principal secondary outcome was cancer incidence. The subjects were 1179 community-dwelling women randomly selected from the population of healthy postmenopausal women aged >55 y in a 9-county rural area of Nebraska centered at latitude 41.4 degrees N. Subjects were randomly assigned to receive 1400-1500 mg supplemental calcium/d alone (Ca-only), supplemental calcium plus 1100 IU vitamin D3/d (Ca + D), or placebo. Results: When analyzed by intention to treat, cancer incidence was lower in the Ca + D women than in the placebo control subjects (P < 0.03). With the use of logistic regression, the unadjusted relative risks (RR) of incident cancer in the Ca + D and Ca-only groups were 0.402 (P = 0.01) and 0.532 (P = 0.06), respectively. When analysis was confined to cancers diagnosed after the first 12 mo, RR for the Ca + D group fell to 0.232 (CI: 0.09, 0.60; P < 0.005) but did not change significantly for the Ca-only group. In multiple logistic regression models, both treatment and serum 25-hydroxyvitamin D concentrations were significant, independent predictors of cancer risk. Conclusions: Improving calcium and vitamin D nutritional status substantially reduces all-cancer risk in postmenopausal women.

Barton DL, Soori GS, Bauer B, et al. **A pilot, multi-dose, placebo-controlled evaluation of american ginseng (panax quinquefolius) to improve cancer-related fatigue: NCCTG trial N03CA.** *J Clin Oncol* ASCO Annual Meeting Proceedings 2007;25(18s):9001.
Background: Fatigue is one of the most common symptoms in people diagnosed with cancer. Ginseng is a popular herb for treatment of this. It has been termed an "adaptogen", felt to be able to restore balance to the body; its potential anti-fatigue efficacy is supported by animal data. The purpose of this pilot trial was to evaluate three doses of American Ginseng versus placebo for cancer-related fatigue. Methods: Patients with a life expectancy = 6 months and a history of cancer-related fatigue who had been experiencing fatigue = 1 month were eligible. Exclusion criteria included prior use of ginseng, chronic systemic steroids and brain malignancies. Other etiologies for fatigue, such as pain, were also excluded. Participants were randomized to receive, in a double blind manner, placebo, 750 mg/d, 1,000 mg/d or 2,000 mg/d of American Ginseng in BID dosing for 8 weeks. Endpoints included The Brief Fatigue Inventory (BFI), the Vitality Subscale of the SF-36 and several numeric analogue questions of perceived benefit; endpoints were measured at baseline, 4 weeks and 8 weeks. Area under the curve (AUC) and change from baseline were calculated. Results: Two hundred eighty two patients (69-72 per arm) were enrolled from 10/21/2005 to 07/05/2006. Available 8-week data are provided in the table below; higher numbers are better.

There were no statistically significant differences in any grade of toxicity between active and placebo arms, and an equivalent number of patients discontinued the study due to adverse events in each arm. Conclusion: This randomized pilot trial provided data to suggest that American Ginseng doses of 1000-2000 mg/d may be effective for alleviating cancer related fatigue. Therefore, further study of American Ginseng in cancer survivors appears warranted.

Exercise

Kruk J, Aboul-Enein HY. **Physical activity and cancer prevention: updating the evidence. The role of oxidative stress in carcinogenesis.** *Curr Cancer Ther Rev* 2007;3(2):81-95.
Objective: Cancer has been hypothesized being influenced by oxidative stress. Physical activity may offer one means for the influence on possible mechanisms operating on malignancy development. Hypothesis holds that physical activity influences on cell homeostasis. Design: Update the evidence on a link between physical activity and cancer of the colon, rectal and colorectal, breast, prostate, lung, endometrial and ovarian, using research studies published between 2004-2006. Review of the accumulated evidence for possible role of oxidative stress in cancer development. Methods: Studies were identified through a systematic review of literature available on the NLM PubMed, Medline, Current Contents, Elsevier-Science Direct databases. Results: The reduction in cancer risk associated with exercise and physical activity was more likely to be found in case-control studies than in cohort studies. The maximal magnitudes of the risk reduction reported were: 63% for colon, 38% for breast cancer, 80% for prostate, 32% for lung, 40% for endometrial, and 33% for ovarian cancer. The available data show that physical activity could modify the tissue redox balance. Conclusion: Recent evidence on the physical activity and cancer risk relation confirms previous findings that moderate in intensity exercise and physical activity prevents against some types of cancer; the best evidence remains for colon and breast cancer. Regular exercise at moderate levels seems to increase level of antioxidant enzymes; this might partially explain the lower cancer risk among physically active people.

Nutrition

Larsson SC, Wolk A. **Coffee consumption and risk of liver cancer: a meta-analysis.** *Gastroenterol* 2007;132(5): 1740-5.
Background & Aims: Mounting evidence indicates that coffee drinking may protect against liver injury and lower the risk of liver cancer. We quantitatively assessed the relation between coffee consumption and the risk of liver cancer in a meta-analysis of epidemiologic studies. *Methods:* Relevant studies were identified by searching MEDLINE (from 1966 to February 2007) and the reference lists of retrieved articles. We included cohort and case–control studies that reported relative risk (RR) estimates with 95% confidence intervals (CIs) of primary liver cancer or hepatocellular carcinoma by quantitative categories of coffee consumption. Study-specific RRs were pooled using a random-effects model. *Results:* Four cohort and 5 case–control studies, involving 2260 cases and 239,146 noncases, met the inclusion criteria. All studies observed an inverse relation between coffee consumption and risk of liver cancer, and in 6 studies the association was statistically significant. Overall, an increase in consumption of 2 cups of coffee per day was associated with a 43% reduced risk of liver cancer (RR,

0.57; 95% CI, 0.49–0.67). There was no statistically significant heterogeneity among studies ($P = .17$). In stratified analysis, the summary RRs of liver cancer for an increase in consumption of 2 cups of coffee per day were 0.69 (95% CI, 0.55–0.87) for persons without a history of liver disease and 0.56 (95% CI, 0.35–0.91) for those with a history of liver disease. *Conclusions:* Findings from this meta-analysis suggest that an increased consumption of coffee may reduce the risk of liver cancer.

CAM of the Month

Kissane DW, Grabsch B, Clarke DM, et al. **Supportive-expressive group therapy for women with metastatic breast cancer: survival and psychosocial outcome from a randomized controlled trial.** *Psychooncol* 2007;16(4):277-86.
Background: Mixed reports exist about the impact of supportive-expressive group therapy (SEGT) on survival. Methods: From 485 women with advanced breast cancer recruited between 1996-2002, 227 (47%) consented and were randomized within an average 10 months of cancer recurrence in a 2:1 ratio to intervention with 1 year or more of weekly SEGT plus three classes of relaxation therapy (147 women) or to control receiving three classes of relaxation therapy (80 women). The primary outcome was survival; psychosocial well-being was appraised secondarily. Analysis was by intention-to-treat. Results: SEGT did not prolong survival (median survival 24.0 months in SEGT and 18.3 in controls; univariate hazard ratio for death 0.92 [95% CI, 0.69-1.26]; multivariate hazard ratio, 1.06 [95% CI, 0.74-1.51]). Significant predictors of survival were treatment with chemotherapy and hormone therapy ($p < 0.001$), visceral metastases ($p < 0.001$) and advanced disease at first diagnosis ($p < 0.05$). SEGT ameliorated and prevented new DSM-IV depressive disorders ($p = 0.002$), reduced hopeless-helplessness ($p = 0.004$), trauma symptoms ($p = 0.04$) and improved social functioning ($p = 0.03$). Conclusions: SEGT did not prolong survival. It improved quality of life, including treatment of and protection against depression.

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

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