



# REsearch UPDATES

FOR THE LATEST IN WORLDWIDE INTEGRATIVE CANCER CARE

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**IN THIS ISSUE:** Joshi et al. found additional supporting evidence that soy can benefit men with prostate cancer. Vollbracht and colleagues found that intravenous vitamin C helped to reduce treatment-related side effects for women with breast cancer. Ruder and associates reported that adolescent and midlife diet may play a role in the development of colorectal cancer. Tasevska and colleagues investigated the link between sugar and cancer development. Borch and associates found that low levels of physical activity are associated with an increased risk of mortality, and Pronk et al. found that increased physical activity is associated with lower breast cancer risk. Kastelein and associates reported that use of statins and nonsteroidal anti-inflammatory medicines helped to slow the progression of Barrett's esophagus. Naing and colleagues reported that utilization of complementary and alternative medicine is

common in patients in phase 1 clinical trials. Lim and associates found that patients with incurable cancer benefited from acupuncture and nurse-led care also was beneficial in the longer term. Pardanani and colleagues found that low levels of vitamin D are common in cancer patients and that its relevance to prognosis is limited. In our study of the month, Parkin et al. drew a link between lifestyle and environmental risk factors for cancer such as smoking, alcohol consumption, diet, exercise, etc. and provided a fractional analysis of the incidence of 18 different types of cancer in the UK in 2010.

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## PROSTATE CANCER

Joshi, M, N. M. Agostino, R. Gingrich et al.

### Effects of Commercially Available Soy Products on PSA in Androgen-Deprivation-Naive and Castration-Resistant Prostate Cancer.

*South Med J.* 2011 November 2011; 104(11): 736-740.

**OBJECTIVE:** No standard therapeutic option exists for men with prostate cancer who have failed local therapy, have no gross metastatic disease, and whose only manifestation of disease is a rising prostate-specific antigen (PSA) level. Soy products are able to affect PSA kinetics in some men with prostate cancer, and this effect has been attributed to the decreased expression of the androgen receptor and other mechanisms. **METHODS:** We treated 10 men with rising PSA levels after radical prostatectomy and salvage radiotherapy with commercially available soy products. Scans revealed no gross metastatic disease. Three men also had been receiving androgen-deprivation therapy (ADT) and had rising PSA levels that were consistent with castration-resistant (CR) disease. We reported the results of this modality on PSA levels, PSA kinetics, and the duration of PSA response.

**RESULTS:** Responses occurred in 4 of 7 (57%) patients with ADT-naive disease and 1 of 3 (33%) patients with CR disease. The median duration of treatment response was 24 months. The overall clinical benefit, therefore, was noted in 5 of 10 (50%) patients. Therapy was well tolerated.

**CONCLUSIONS:** Our findings are fairly congruent with what has been described in the literature on the use of this modality in prostate cancer. We used commercially available soy products. We also show that soy can provide benefit in CR prostate cancer. Our clinical experience suggests that soy supplementation using commercially available soy products can have durable beneficial effects on PSA levels and PSA kinetics in some men with prostate cancer.



## BREAST CANCER

Vollbracht, C, B. Schneider, V. Leendert, et al.

### Intravenous Vitamin C Administration Improves Quality of Life in Breast Cancer Patients during Chemo-/radiotherapy and Aftercare: Results of a Retrospective, Multicentre, Epidemiological Cohort Study in Germany.

*In Vivo*. 2011 November-December 2011; 256: 983-990.

**AIM:** The aim of the study was to evaluate under praxis conditions the safety and efficacy of intravenous (i.v.) vitamin C administration in the first postoperative year of women with breast cancer. **PATIENTS AND**

**METHODS:** Epidemiological multicentre cohort study, including 15 gynaecologists and general practitioners representatively distributed in Germany. Data from 125 breast cancer patients in UICC stages IIa to IIIb were selected for the study. A total of 53 of these patients were treated with i.v. vitamin C (supplied as Pascorbin 75 g) additional to standard tumour therapy for at least 4 weeks (study group) and 72 without this additional therapy (control group). Main outcome measures were efficacy in regard to outcome and severity of disease- or therapy-induced complaints during adjuvant chemo- and radiotherapy and aftercare.

**RESULTS:** Comparison of control and study groups revealed that i.v. vitamin C administration resulted in a significant reduction of complaints induced by the disease and chemo-/radiotherapy, in particular of nausea, loss of appetite, fatigue, depression, sleep disorders, dizziness and haemorrhagic diathesis. After adjustment for age and baseline conditions (intensity score before adjuvant therapy, chemotherapy, radio-therapy), the overall intensity score of symptoms during adjuvant therapy and after-care was nearly twice as high in the control group compared to the study group. No side-effects of the i.v. vitamin C administration were documented.

**DISCUSSION:** Oxidative stress and vitamin C deficiency play an important role in the etiology of adverse effects of guideline-based adjuvant chemo-/radiotherapy. Restoring antioxidative capacity by complementary i.v. vitamin C administration helps to prevent or reduce disease-, or therapy-induced complaints in breast cancer patients.

**CONCLUSION:** Complementary treatment of breast cancer patients with i.v. vitamin C was shown to be a well tolerated optimization of standard tumour-destructive therapies, reducing quality of life-related side-effects.

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## COLORECTAL CANCER

Ruder, EH, A. C. M. Thiebaut, F. E. Thompson, et al.

### Adolescent and Mid-Life Diet: Risk of Colorectal Cancer in the NIH-AARP Diet and Health Study.

*Am J Clin Nutr*. 2011 01 Dec 2011; 946: 1607-1619.

**BACKGROUND:** Colorectal cancer has a natural history of several decades; therefore, the diet consumed decades before diagnosis may aid in understanding this malignancy. **OBJECTIVE:** The objective was to investigate diet during adolescence and 10 y before baseline (ages 40-61 y) in relation to colorectal cancer.

**DESIGN:** Participants in the NIH-AARP Diet and Health Study (n = 292,797) completed a 124-item food-frequency questionnaire (FFQ) about diet in the past 12 mo and two 37-item FFQs about diet at ages 12-13 y and 10 y previously. Cox regression was used to estimate multivariate HRs and 95% CIs for colon (n = 2794) and rectal (n = 979) cancers within quintiles of exposures.

**RESULTS:** Colon cancer risk was lower in the highest than in the lowest quintile of vitamin A (HR: 0.82; 95% CI: 0.72, 0.92) and vegetable (HR: 0.81, 0.70, 0.92) intakes during adolescence. Those in the highest intake category 10 y previously for calcium (HR: 0.83; 95% CI: 0.73, 0.94), vitamin A (HR: 0.81; 95% CI: 0.71, 0.92), vitamin C (HR: 0.83; 95% CI: 0.72, 0.95), fruit (HR: 0.84; 95% CI: 0.73, 0.97), and milk (HR: 0.78; 95% CI: 0.67, 0.90) had a lower risk of colon cancer, but a higher risk was observed for total fat (HR: 1.15; 95% CI: 1.01, 1.30), red meat (HR: 1.31; 95% CI: 1.12, 1.53), and processed meat (HR: 1.24; 95% CI: 1.06, 1.45). For rectal cancer, milk was inversely associated (HR: 0.75; 95% CI: 0.58, 0.96) with risk.

**CONCLUSION:** Adolescent and midlife diet may play a role in colorectal carcinogenesis.



## EXERCISE

Borch, KB, T. Braaten, E. Lund et al.

### Physical Activity and Mortality among Norwegian Women - the Norwegian Women and Cancer Study.

*Clinical Epidemiology.* 2011 29 Jul 2011; 31: 229-235.

**BACKGROUND:** Physical activity (PA) and its relationship with all-cause mortality suggest a strong and consistent inverse association. This study prospectively investigated the association between PA level and mortality among participants of the Norwegian Women and Cancer (NOWAC) Study. **METHODS:** A total of 66,136 NOWAC participants were followed-up until December 31st 2008. PA level and possible confounding factors were obtained through a self-administered questionnaire at enrolment. Cox proportional hazards regression was used to calculate adjusted relative risks (RRs) and 95% confidence intervals (CIs) for all-cause, cardiovascular disease (CVD) and cancer mortality and PA levels defined from 1 to 10 on a global scale.

**RESULTS:** PA levels 1-4 were associated with a significantly increased risk of all-cause mortality (level 1 RR = 2.35; 95% CI: 1.94-2.84, level 2 RR = 1.71; 95% CI: 1.45-2.00, level 3 RR = 1.30; 95% CI: 1.14-1.49, level 4 RR = 1.07; 95% CI: 0.95-1.22), compared with PA level 5. CVD mortality risk increased in PA levels 1-3 (level 1 RR = 3.50; 95% CI: 2.41-5.10, level 2 RR = 1.50; 95% CI: 0.99-2.25, level 3 RR = 1.12; 95% CI: 0.79-1.60) as did cancer mortality risk (RR = 1.32; 95% CI: 0.96-1.81, RR = 1.48; 95% CI: 1.19-1.84, RR = 1.26; 95% CI: 1.06-1.50, respectively). The magnitude of the associations was consistent across strata of age, smoking, and body mass index. The population attributable fractions for PA levels 1-4 were: all-cause mortality, 11.5%; CVD mortality, 11.3%; cancer mortality, 7.8%.

**CONCLUSION:** There is a significant trend of increased risk of all-cause, CVD and cancer mortality in relation to low PA levels among Norwegian women.



Pronk, A, B. -T Ji, X. -O Shu, et al.

### Physical Activity and Breast Cancer Risk in Chinese Women.

*Br J Cancer.* 2011 25 Oct 2011; 1059: 1443-1450.

**BACKGROUND:** The influence of different types and intensities of physical activity on risk for breast cancer is unclear. **METHODS:** In a prospective cohort of 73 049 Chinese women (40-70 years), who had worked outside the home, we studied breast cancer risk in relation to specific types of self-reported and work history-related physical activity, including adolescent and adult exercise and household activity and walking and cycling for transportation. Occupational sitting time and physical activity energy expenditure were assigned based on lifetime occupational histories.

**RESULTS:** In all, 717 incident breast cancer cases were diagnosed. Breast cancer risk was lower for women in the lowest quartile of average occupational sitting time and in the highest quartile of average occupational energy expenditure (adjusted hazard ratio (HR): 0.81 and 0.73, respectively,  $P \leq 0.05$ ). Adult exercise at or above the recommended level (8 metabolic equivalent (MET) h per week per year) was associated with lower risk (adjusted HR: 0.73,  $P < 0.05$ ) in post-menopausal women. Analysis of joint effects showed that having both an active job and exercise participation did not confer an additional benefit. Other common daily activities were not associated with lower risk.

**INTERPRETATION:** These findings suggest that both exercise and occupational activity are associated with lower breast cancer risk, which supports current health promotion campaigns promoting exercise.

## BARRETT'S ESOPHAGUS

Kastelein, F, M. C. W. Spaander, K. Biermann, et al.

### Nonsteroidal Anti-Inflammatory Drugs and Statins have Chemopreventative Effects in Patients with Barrett's Esophagus.

*Gastroenterology.* 2011 December 2011; 1416: 2000-2008.

**BACKGROUND & AIMS:** The incidence of Barrett's esophagus and esophageal adenocarcinoma has increased despite surveillance of patients with Barrett's esophagus. Limited data indicate that nonsteroidal anti-inflammatory drug (NSAID) and statin use reduce the risk for esophageal adenocarcinoma. We



investigated whether NSAID or statin use reduces the risk of neoplastic progression from Barrett's esophagus. **METHODS:** We performed a prospective study of 570 patients with Barrett's esophagus at 3 academic and 12 regional Dutch hospitals. Information on medication use was collected in patient interviews at each surveillance visit and cross-checked with pharmacy records. Patients completed a questionnaire about use of over-the-counter medication. Incident cases of high-grade dysplasia and adenocarcinoma were identified during the follow-up period.

**RESULTS:** During a median follow-up period of 4.5 years, 38 patients (7%) developed high-grade dysplasia or adenocarcinoma. After Barrett's esophagus had been diagnosed, 318 patients (56%) used NSAIDs for a median duration of 2 months, 161 (28%) used aspirin for a median duration of 5 years, 209 (37%) used statins for a median duration of 5 years, and 107 (19%) used NSAIDs and statins. NSAID and statin use were each associated with a reduced risk of neoplastic progression (hazard ratio [HR], 0.47;  $P = .030$  and HR, 0.46;  $P = .048$ , respectively). Use of a combination of NSAIDs and statins increased the protective effect (HR, 0.22;  $P = .028$ ).

**CONCLUSIONS:** NSAID and statin use reduce the risk of neoplastic progression in patients with Barrett's esophagus. Use of a combination of NSAIDs and statins appears to have an additive protective effect.

## COMPLEMENTARY AND ALTERNATIVE MEDICINE (CAM)

Naing, A, S. K. Stephen, M. Frenkel, et al.

### Prevalence of Complementary Medicine use in a Phase 1 Clinical Trials Program: The MD Anderson Cancer Center Experience.

*Cancer.* 2011 15 Nov 2011; 11722: 5142-5150.

**BACKGROUND:** A key end point of early cancer clinical trials is the assessment of toxicities and their possible association with new experimental drugs. Therefore, the concurrent use of complementary and alternative medicine (CAM) in patients with advanced malignancies seen in a dedicated phase 1 clinic was evaluated. **METHODS:** An investigator-designed survey was anonymously completed by patients seen in the phase 1 clinic. Pharmacologic CAM included any oral, topical, or intravenous agent, including vitamins, dietary supplements, and herbal products. Nonpharmacologic CAM included prayer, meditation, hypnosis, massage, and acupuncture.

**RESULTS:** Of the 404 patients approached about completing the CAM survey, 394 (98%) agreed to respond, and 309 (78%) surveys were returned. Of those 309 patients, 162 (52%) used 1 or more CAM. Of the 162 CAM users, 77% utilized pharmacologic CAM, 71% used nonpharmacologic CAM, and 48% used both modalities. The most frequent CAM used were vitamins (70%), prayer (57%), and herbal products (26%). CAM utilization was not significantly associated with race, age, level of education, employment, or income level but was used more by women than men ( $P = .05$ ). Only 5% reported having side effects from using CAM, whereas 23% did not fully disclose their CAM use to their physicians.

**CONCLUSIONS:** CAM usage is common in patients with advanced malignancies seen in a phase 1 clinic.

## ACUPUNCTURE

Lim, JT, E. T. Wong and S. K. Aung.

### Is there a Role for Acupuncture in the Symptom Management of Patients Receiving Palliative Care for Cancer? A Pilot Study of 20 Patients Comparing Acupuncture with Nurse-Led Supportive Care.

*Acupuncture in Medicine.* 2011 Sep; 293: 173-179.

**PURPOSE:** A pilot study to document changes in symptoms after acupuncture or nurse-led supportive care in patients with incurable cancer. **METHODS:** Patients receiving palliative care with estimated survival of at least 3 months were screened with the Edmonton Symptom Assessment System (ESAS). Patients ( $n=20$ ) with significant symptoms were randomised to receive weekly acupuncture or nurse-led supportive care for 4 weeks. ESAS scores were obtained before and after each treatment, and weekly for 6 weeks after treatment by telephone.

**RESULTS:** 42 of 170 patients screened were eligible. 20 gave consent for recruitment. The compliance rate was 90% for acupuncture and 80% for nurse-led supportive care. Total symptom scores were reduced by an average of 22% after each acupuncture visit and by 14% after each supportive care visit. Compared with



baseline, ESAS scores at the end of the follow-up period were reduced by 19% for the acupuncture arm and 26% for nurse-led supportive care.

**CONCLUSION:** Patients appear to benefit from incorporating acupuncture in the treatment of advanced incurable cancer. Acupuncture was well tolerated with no significant or unexpected side effects. Acupuncture had an immediate effect on all symptoms, whereas nurse-led supportive care had a larger impact 6 weeks after the final session. Both interventions appear helpful to this population and warrant further study.

## VITAMIN D

Pardanani, A, M.T. Drake, C. Finke, et al.

### Vitamin D Insufficiency in Myeloproliferative Neoplasms and Myelodysplastic Syndromes: Clinical Correlates and Prognostic Studies.

*Am J Hematol.* 2011 December 2011; 8612: 1013-1016.

**BACKGROUND:** Vitamin D insufficiency is commonly observed in the general population; observational studies have suggested an association with increased risk of cancer development. **METHODS:** We examined the clinical and prognostic relevance of low plasma levels of 25-hydroxyvitamin D (25[OH]D) in myeloproliferative neoplasms (MPN) and myelodysplastic syndromes (MDS). A total of 409 patients were studied: 247 (60%) with primary myelofibrosis (PMF), 74 (18%) with de novo MDS, 63 (15%) with polycythemia vera (PV), and 25 (6%) with essential thrombocythemia (ET). Plasma 25(OH)D levels were measured by liquid chromatography-tandem mass spectrometry; a level lower than 25 ng/mL indicated vitamin D insufficiency and a level lower than 10 ng/mL indicated severe deficiency.

**RESULTS:** The proportion of patients with 25(OH)D insufficiency was significantly greater in PMF (48%) and PV (43%) when compared with ET (28%) and MDS (28%) ( $P = 0.01$ ). Severe 25(OH)D deficiency was significantly more frequent in ET (12%) and PMF (9%), compared with PV (3%) and MDS (1%) ( $P = 0.05$ ). There were no significant correlations between 25(OH)D insufficiency, or severe deficiency, and a variety of clinical or laboratory variables in PMF, MDS, or PV. Furthermore, Vitamin D insufficiency did not influence either overall or leukemia-free survival in PMF, MDS, or PV ( $P > 0.05$ ).

**CONCLUSION:** We conclude that while hypovitaminosis D is relatively common in MPN and MDS, its clinical relevance for prognosis is limited.

## STUDY OF THE MONTH

Parkin, DM, L. Boyd and L. C. Walker.

### The Fraction of Cancer Attributable to Lifestyle and Environmental Factors in the UK in 2010.

*Br J Cancer.* 2011 Dec 6; 105S2: S77-S81.

**BACKGROUND:** This chapter summarises the results of the preceding sections, which estimate the fraction of cancers occurring in the UK in 2010 that can be attributed to sub-optimal, past exposures of 14 lifestyle and environmental risk factors. **METHODS:** For each of 18 cancer types, we present the percentage of cases attributable to one or all of the risk factors considered (tobacco, alcohol, four elements of diet (consumption of meat, fruit and vegetables, fibre, and salt), overweight, lack of physical exercise, occupation, infections, radiation (ionising and solar), use of hormones, and reproductive history (breast feeding)).

**RESULTS:** Exposure to less than optimum levels of the 14 factors was responsible for 42.7% of cancers in the UK in 2010 (45.3% in men, 40.1% in women) - a total of about 134,000 cases. Tobacco smoking is by far the most important risk factor for cancer in the UK, responsible for 60,000 cases (19.4% of all new cancer cases) in 2010. The relative importance of other exposures differs by sex. In men, deficient intake of fruits and vegetables (6.1%), occupational exposures (4.9%) and alcohol consumption (4.6%) are next in importance, while in women, it is overweight and obesity (because of the effect on breast cancer) - responsible for 6.9% of cancers, followed by infectious agents (3.7%).

**CONCLUSION:** Population-attributable fractions provide a valuable quantitative appraisal of the impact of different factors in cancer causation, and are thus helpful in prioritising cancer control strategies. However, quantifying the likely impact of preventive interventions requires rather complex scenario modelling, including specification of realistically achievable population distributions of risk factors, and the timescale of change, as well as the latent periods between exposure and outcome, and the rate of change following modification in exposure level.



## FOR FURTHER READING ON THE WEB:

## SUGAR

Tasevska, N, L. Jiao, A. J. Cross, et al.

**Sugars in Diet and Risk of Cancer in the NIH-AARP Diet and Health Study.***International Journal of Cancer.* 2012 11 Jan 2012; 1301: 159-169.

**BACKGROUND:** Prospective epidemiologic data on the effects of different types of dietary sugars on cancer incidence have been limited. In this report, we investigated the association of total sugars, sucrose, fructose, added sugars, added sucrose and added fructose in the diet with risk of 24 malignancies.

**METHODS:** Participants (n = 435,674) aged 50-71 years from the NIH-AARP Diet and Health Study were followed for 7.2 years. The intake of individual sugars was assessed using a 124-item food frequency questionnaire (FFQ). Cox proportional hazards regression was used to estimate hazard ratios (HR) and 95% confidence intervals (CI) in multivariable models adjusted for confounding factors pertinent to individual cancers.

**RESULTS:** We identified 29,099 cancer cases in men and 13,355 cases in women. In gender-combined analyses, added sugars were positively associated with risk of esophageal adenocarcinoma (HRQ5 vs. Q1: 1.62, 95% CI: 1.07-2.45; ptrend = 0.01), added fructose was associated with risk of small intestine cancer (HRQ5 vs. Q1: 2.20, 95% CI: 1.16-4.16; p trend = 0.009) and all investigated sugars were associated with increased risk of pleural cancer. In women, all investigated sugars were inversely associated with ovarian cancer. We found no association between dietary sugars and risk of colorectal or any other major cancer. Measurement error in FFQ-reported dietary sugars may have limited our ability to obtain more conclusive findings.

**CONCLUSION:** Statistically significant associations observed for the rare cancers are of interest and warrant further investigation.



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