RE*search* UPDATES

FOR THE LATEST IN WORLDWIDE INTEGRATED CANCER CARE

IN*side*

IN THIS ISSUE: The prevalent themes of this issue are colorectal cancer and vitamin D because the majority of this month's studies deal with these issues in one way or another. For instance, Mezawa et al. found that patients with colorectal cancer had a better survival rate if they had a higher vitamin D level at surgery. Pendyala and associates found that weight loss in obese individuals can lower the risk of colorectal cancer, and Lagunova and colleagues found that low vitamin D status can explain at least 20% of the cancer risk attributable to obesity in general, and 75% of the risk of colorectal cancer more specifically. Murata and colleagues found a significant association between higher salted food intake and stomach and rectal cancer in men, and in our study of the month, Thompson et al. discovered that short duration of sleep significantly increases the risk of colorectal cancer.

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PROSTATE CANCER

Williams, CD, B. M. Whitley, C. Hoyo, et al.

A High Ratio of Dietary n-6/n-3 Polyunsaturated Fatty Acids is Associated with Increased Risk of Prostate Cancer.

Nutr Res. 2011 January 2011; 311: 1-8.

BACKGROUND: Experimental studies suggest omega-3 (n-3) polyunsaturated fatty acids (PUFA) suppress and n-6 PUFA promote prostate tumor carcinogenesis. Epidemiologic evidence remains inconclusive. **METHODS:** The objectives of this study were to examine the association between n-3 and n-6 PUFA and prostate cancer risk and determine if these associations differ by race or disease aggressiveness. We hypothesize that high intakes of n-3 and n-6 PUFA will be associated with lower and higher prostate cancer risk, respectively. A case-control study comprising 79 prostate cancer cases and 187 controls was conducted at the Durham VA Medical Center. Diet was assessed using a food frequency questionnaire. Logistic regression analyses were used to obtain odds ratios (ORs) and 95% confidence intervals (95% CI) for the associations between n-3 and n-6 PUFA intakes, the dietary ratio of n-6/n-3 fatty acids, and prostate cancer risk.

RESULTS: Our results showed no significant associations between specific n-3 or n-6 PUFA intakes and prostate cancer risk. The highest dietary ratio of n-6/n-3 was significantly associated with elevated risk of high-grade (OR, 3.55; 95% CI, 1.18-10.69; P_{trend} = 0.03), but not low-grade prostate cancer (OR, 0.95; 95% CI, 0.43-2.17). In race-specific analyses, an increasing dietary ratio of n-6/n-3 fatty acids correlated with higher prostate cancer risk among white men (P_{trend} = 0.05), but not black men.

CONCLUSION: In conclusion, our findings suggest that a high dietary ratio of n-6/n-3 fatty acids may increase the risk of overall prostate cancer among white men and possibly increase the risk of high-grade prostate cancer among all men.

BREAST CANCER

Murff, HJ, X. -O Shu, H. Li, et al.

Dietary Polyunsaturated Fatty Acids and Breast Cancer Risk in Chinese Women: A Prospective Cohort Study.

International Journal of Cancer. 2011 15 Mar 2011; 1286: 1434-1441.

BACKGROUND: Breast cancer is the most common cancer in women. Controversy exists regarding the role of dietary fat in breast cancer etiology. **METHODS:** We investigated the association of dietary polyunsaturated fatty acids (PUFAs) and the ratio of n-6 PUFAs to marine-derived n-3 PUFAs with breast cancer risk in the Shanghai Women's Health Study, a prospective cohort study including 72,571 cancer-free participants at baseline. Dietary fatty acid intake was determined using food frequency questionnaires. We used Cox proportional hazards analysis to estimate the relative risks (RRs) and 95% confidence intervals (CIs) for the association of breast cancer risk with dietary fatty acids consumption.

RESULTS: In 583,998 person-years of follow-up, we identified 712 breast cancer cases. We found no association of breast cancer risk to dietary intake of linoleic acid, arachidonic acid, alpha-linolenic acid or marine-derived n-3 PUFA. We found a statistically significant interaction between n-6 PUFA intake, marine-derived n-3 PUFA intake and breast cancer risk (p = 0.008). Women with lower intake (the lowest tertile) of marine-derived n-3 PUFA and higher intake (the highest tertile) of n-6 PUFA had an increase risk for breast cancer (RR = 2.06; 95% CI = 1.27-3.34) compared to women with higher intake (the highest tertile) of marine-derived n-3 PUFAs and lower intake (the lowest tertile) of n-6 PUFAs after adjusting for potential confounders.

CONCLUSION: The relative amounts of n-6 PUFA to marine-derived n-3 PUFAs may be more important for breast cancer risk than individual dietary amounts of these fatty acids.

Prieto-Alhambra, D, M. K. Javaid, S. Servitja, et al.

Vitamin D Threshold to Prevent Aromatase Inhibitor-Induced Arthralgia: A Prospective Cohort Study.

Breast Cancer Res Treat. 2011 February 2011; 1253: 869-878.

BACKGROUND AND AIMS: Aromatase inhibitor (AI)-associated arthralgia limits adherence to therapy in breast cancer. The pathophysiology may involve vitamin D status. We wished to establish the optimal concentration of 25(OH)D that prevents or minimizes arthralgia. **METHODS:** We used a prospective cohort of 290 women starting AI in whom baseline vitamin D was measured. All received daily vitamin D(3) (800 IU) with calcium. Women with baseline 25(OH)D concentration <30 ng/ml also received 16,000 IU of D(3) orally every 2 weeks. The primary outcome was incident or worsening joint pain derived from baseline and 3-month visual analogic scale (VAS) for joint pain. Regression models were used to analyse the association between vitamin D concentrations at 3 months and pain adjusting for age, BMI, season when the sample was drawn, aromatase inhibitor (exemestane vs. letrozole/anastrozole), prior tamoxifen therapy, baseline NTX, and previous fracture.

RESULTS: 90% of women had a 25(OH)D <30 ng/ml at baseline. After supplementation (daily 800 IU and additional 16,000 IU every 2 weeks), 50% of them still failed to reach adequate concentrations at 3 months. In the whole cohort, there was an increase in joint pain (mean 1.16 points SD 2.66; P < 0.001) and the increase was significantly (P = 0.02) attenuated in those that reached concentrations of 25(OH)D of ≥40 ng/ml, with a lower risk of incident arthralgia (OR 0.12 ** [0.03 to 0.40]).

CONCLUSION: A target concentration of 40 ng/ml 25OHD may prevent development of AI arthralgia but higher loading doses are required to attain this level in women with deficiency at baseline.

COLORECTAL CANCER

Mezawa, H, T. Sugiura, M. Watanabe, et al.

Serum Vitamin D Levels and Survival of Patients with Colorectal Cancer: Post-Hoc Analysis of a Prospective Cohort Study.

BACKGROUND: Recently, serum 25-hydroxyvitamin D (25OHD) levels were shown to be associated with the survival of patients with colorectal cancer. However, 25OHD levels were measured a median of 6 years before diagnosis or were predicted levels. In this study, we directly measured serum 25OHD levels at surgery and examined the association with survival among patients with colorectal cancer. **METHODS:** We started a prospective cohort study to find prognostic factors in patients with colorectal cancer from 2003 to 2008 and stored serum samples and clinical data. As part of a post-hoc analysis, serum 25OHD levels were measured by radioimmunoassay. Association between overall survival and serum 25OHD levels were computed using the Cox proportional hazard model adjusted for month of serum sampling as well as age at diagnosis, gender, cancer stage, residual tumor after surgery, time period of surgery, location of tumor, adjuvant chemotherapy and number of lymph nodes with metastasis at surgery. Unadjusted and adjusted hazard ratios (HR) and 95% confidence intervals (95% CI) were determined.

RESULTS: Serum 25OHD levels were measured in 257 patients. Only 3% had sufficient levels (30 ng/ml and greater). Based on month of blood sampling, an annual oscillation of 25OHD levels was seen, with levels being lower in spring and higher in late summer. Higher 25OHD levels were associated with better overall survival under multi-variate analysis (HR, 0.91: 95% CI, 0.84 to 0.99, P = 0.027).

CONCLUSIONS: These results suggest that higher 25OHD levels at surgery may be associated with a better survival rate of patients with colorectal cancer.

Pendyala, S, L. M. Neff, M. Suarez-Farinas and P. R. Holt.

Diet-Induced Weight Loss Reduces Colorectal Inflammation: Implications for Colorectal Carcinogenesis.

BACKGROUND: Epidemiologic data have shown that obesity independently increases colorectal cancer (CRC) risk, but the mechanisms are poorly understood. Obesity is an inflammatory state, and chronic colonic inflammation induces CRC. **OBJECTIVE:** We conducted this proof-of-principle study to seek evidence of obesity-associated colorectal inflammation and to evaluate effects of diet-induced weight loss. **DESIGN:** We measured inflammatory cytokines, gene arrays, and macrophage infiltration in rectosigmoid mucosal biopsies of 10 obese premenopausal women [mean +/- SD body mass index (in kg/m2): 35 +/- 3.5] before and after weight loss induced by a very-low-calorie diet.

RESULTS: Subjects lost a mean (+/-SD) of 10.1 +/- 1% of their initial weight. Weight loss significantly reduced fasting blood glucose, total cholesterol, triglycerides, LDL, tumor necrosis factor-alpha (TNF-alpha), and interleukin (IL)-8 concentrations (P< 0.05). After weight loss, rectosigmoid biopsies showed a 25-57% reduction in TNF-alpha, IL-1beta, IL-8, and monocyte chemotactic protein 1 concentrations (P< 0.05). T cell and macrophage counts decreased by 28% and 42%, respectively (P< 0.05). Gene arrays showed dramatic down-regulation of proinflammatory cytokine and chemokine pathways, prostaglandin metabolism, and the transcription factors STAT3 (signal transducer and activator of transcription 3) and nuclear transcription factor B. Weight loss reduced expression of FOS and JUN genes and down-regulated oxidative stress pathways and the transcription factors ATF (activating transcription factor) and CREB (cyclic AMP response element-binding).

CONCLUSIONS: Our data show that diet-induced weight loss in obese individuals reduces colorectal inflammation and greatly modulates inflammatory and cancer-related gene pathways. These data imply that obesity is accompanied by inflammation in the colorectal mucosa and that diet-induced weight loss reduces this inflammatory state and may thereby lower CRC risk.

HEPATOCELLULAR CARCINOMA

Bang, MH, T. Van Riep, N. T. Thinh, et al.

Arabinoxylan Rice Bran (MGN-3) Enhances the Effects of Interventional Therapies for the Treatment of Hepatocellular Carcinoma: A Three-Year Randomized Clinical Trial.

BACKGROUND AND AIMS: This study examined the efficacy of arabinoxylan rice bran (MGN-3) in conjunction with an interventional therapy (IT) for the treatment of hepatocellular carcinoma patients. **PATIENTS AND METHODS:** A total of sixty-eight patients with hepatocellular carcinoma (stages I and II) participated in the study. Patients were randomized to receive IT (30 patients, control group) or IT+MGN-3 (38 patients), and randomly divided into two groups using a computer-generated randomization list. Patients and investigators were blinded. IT included transarterial oily chemoembolization (TOCE) or a combination of TOCE and percutaneous ethanol injection treatment (PEIT).

RESULTS: Patients in the IT+MGN-3 group showed: (i) lower recurrence of the disease, 31.6% (12/38), as compared to 46.7% (14/30) for the control; (ii) higher survival after the second year, 35%, as compared to 6.7% for the control; (iii) significantly lower alpha-fetoprotein level, a 38% decrease (p = 0.0001), as compared to baseline value, while the control showed no significant change; and (iv) a significant decrease in tumor volume, in contrast to the control, which showed no significant change. When the results were analyzed according to each IT modality, MGN-3+IT sub-groups displayed a greater response to treatment, in every aspect examined, than the IT sub-groups alone. However, the patients in the MGN-3+TOCE+PEIT sub-group demonstrated greater reduction in AFP levels and longer survival time than the MGN-3+TOCE sub-group.

CONCLUSION: MGN-3 in conjunction with IT may be useful for the treatment of hepatocellular carcinoma and warrants further investigation in multiple clinical trials.

OBESITY

Lagunova, Z, A. C. Porojnicu, W. B. Grant, et al.

Obesity and Increased Risk of Cancer: Does Decrease of Serum 25-Hydroxyvitamin D Level with Increasing Body Mass Index Explain some of the Association?

BACKGROUND: Low levels of vitamin D and excess body weight are both factors associated with increased risk of cancer. The increased risk seems to be proportional to the increase in BMI, and to decrease in serum 25-hydroxyvitamin D (25(OH)D) level. Our earlier investigations suggest that serum 25(OH)D levels decrease with increasing BMI. Although the connection between cancer risk, BMI and vitamin D status might be arbitrary, it has not been discussed in the literature so far. **METHODS**: In this study, we analyze data published in current meta-analysis, prospective studies, and systematic reviews on cancer-specific risk attributed to high BMI and low vitamin D status. The contribution of low 25(OH)D levels associated with high BMI to increased cancer risk was calculated for 13 vitamin-D-sensitive cancers with a focus on colorectal and breast cancer as the most frequently studied vitamin-D-sensitive cancer types.

RESULTS: Our study suggests that a low vitamin D status may explain at least 20% of the cancer risk attributable to high BMI. The contribution of low 25(OH)D to the increased cancer risk with increasing BMI may be different for different cancer types.

CONCLUSION: Thus, we find 40% for breast cancer, and 26 and 75% for colorectal cancer in men and women, respectively.

FOLATE

Aune, D, H. Deneo-Pellegrini, A. L. Ronco, et al.

Dietary Folate Intake and the Risk of 11 Types of Cancer: A Case-Control Study in Uruguay.

Annals of Oncology. 2011 2011; 222: 444-451.

BACKGROUND: There is limited, but inconclusive, epidemiological evidence that high folate intake decreases the risk of colorectal and esophageal cancers. For other cancer sites, the evidence is even less consistent or extensive. **MATERIALS AND METHODS:** We conducted a case-control study of dietary folate intake and risk of 11 cancer sites in Uruguay between 1996 and 2004, including 3539 cancer cases and 2032 hospital controls. Unconditional logistic regression was used to estimate odds ratios (ORs) and 95% confidence intervals (CIs) of cancer associated with folate intake.

RESULTS: In the multivariable model, there was a significant decrease in the risk of cancers of the oral cavity and pharynx (OR = 0.49, 95% CI 0.24-0.98), esophagus (OR = 0.29, 95% CI 0.14-0.60), upper aerodigestive tract (OR = 0.41, 95% CI 0.26-0.65), colorectum (OR = 0.42, 95% CI 0.23-0.76) and kidney (OR = 0.35, 95% CI 0.13-0.93) for the highest versus the lowest quartile of dietary folate intake.

CONCLUSIONS: Our results not only confirm earlier findings of decreased risk of colorectal and esophageal cancers with a high dietary folate intake but also suggest decreased risk of several other cancers. However, we cannot exclude the possibility that residual confounding, multiple comparisons or other forms of bias could explain these results.
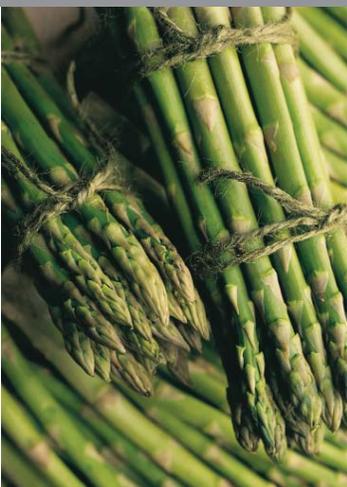
GASTROINTESTINAL TRACT CANCER

Murata, A, Y. Fujino, T. M. Pham, et al.

Prospective Cohort Study Evaluating the Relationship between Salted Food Intake and Gastrointestinal Tract Cancer Mortality in Japan.

Asia Pac J Clin Nutr. 2010 194: 564-571.

PURPOSE: To investigate whether a high salted food intake increases the risk of gastrointestinal tract cancer mortality. **METHODS:** We conducted a prospective study of 6830 Japanese inhabitants to evaluate the association between salted food consumption and the risk of gastrointestinal tract cancer mortality. Data were obtained from a prospective cohort study in Japan. Salted food consumption, determined from a baseline questionnaire, was classified into the two categories of 'low intake' and 'high intake'. The Cox proportional hazards model was used to estimate hazard ratios (HRs) and 95% confidence intervals (CI).

FINDINGS: Total of 174 gastrointestinal tract cancer deaths (47 esophagus cancer, 87 stomach cancer, 23 colon cancer and 17 rectal cancer) were observed during 94996 person-years of follow-up, with a mean follow-up period of 8.9 years. After adjustment for age, body mass index, physical activity, smoking, alcohol, history of diabetes mellitus and dietary items, including vegetables, fruit, tea, red meat and processed meat, the HR for stomach cancer in males with high salt intake was 2.05 (95% CI:1.25 - 3.38) whereas that of rectal cancer was 3.58 (95% CI: 1.08 - 11.89). In contrast, no association was seen in females. Further, no association was seen between higher salted food consumption and esophagus and colon cancer in either sex.

CONCLUSIONS: A significant association was seen between higher salted food consumption and stomach and rectal cancer mortality in men, but not in women. No association was seen between higher consumption and esophagus and colon cancer mortality in either men or women.

STUDY OF THE MONTH

Thompson, CL, E. K. Larkin, S. Patel, et al.

Short Duration of Sleep Increases Risk of Colorectal Adenoma.

Cancer. 2011 15 Feb 2011; 1174: 841-847.

BACKGROUND: Short duration and poor quality of sleep have been associated with increased risks of obesity, cardiovascular disease, diabetes mellitus, and total mortality. However, few studies have investigated their associations with risk of colorectal neoplasia. **METHODS:** In a screening colonoscopy-based case-control study, the Pittsburg Sleep Quality Index (PSQI) was administered to 1240 study

participants before colonoscopy.

RESULTS: Three hundred thirty-eight (27.3%) of the participants were diagnosed with incident colorectal adenomas. Although there was no appreciable difference in the overall PSQI score between cases and adenoma-free controls (5.32 vs 5.11; P =.37), the authors found a statistically significant association of colorectal adenoma with the PSQI component 3, which corresponds to sleep duration (P =.02). Cases were more likely to average less than 6 hours of sleep per night (28.9% vs 22.1% in controls, P =.01). In multivariate regression analysis adjusted for age, gender, race, smoking, family history of colorectal cancer, and waist-to-hip ratio, individuals averaging less than 6 hours per night had an almost 50% increase in risk of colorectal adenomas (OR = 1.47; CI = 1.05-2.06, P for trend =.02) as compared with individuals sleeping at least 7 hours per night. Cases were also more likely to report being diagnosed with sleep apnea (9.8% vs 6.5%, P =.05) and more likely to have worked alternate shifts (54.0% vs 46.1%, P =.01), although these differences were not significant in multivariate models.

CONCLUSIONS: Shorter duration of sleep significantly increases risk of colorectal adenomas. The authors' results suggest sleep duration as a novel risk factor for colorectal neoplasia.

ELECTRONIC RESEARCH UPDATES - BONUS ABSTRACTS

PROSTATE CANCER

Steinbrecher, A, C. Meplan, J. Hesketh, et al.

Effects of Selenium Status and Polymorphisms in Selenoprotein Genes on Prostate Cancer Risk in a Prospective Study of European Men.

Cancer Epidemiology, Biomarkers & Prevention. 2010 Nov; 1911: 2958-2968.

BACKGROUND: Evidence for an association between selenium status and prostate cancer risk is still inconclusive. Anticarcinogenic effects of selenium are supposedly mediated through cellular protective and redox properties of selenoenzymes in vivo. We evaluated the association between serum selenium status and prostate cancer risk in a population with relative low selenium concentrations considering effect modification by genetic variants in selenoprotein genes. **MATERIALS AND METHODS:** A case-control study of 248 incident prostate cancer cases and 492 matched controls was nested within the EPIC-Heidelberg cohort. Baseline blood samples were analyzed for serum selenium and selenoprotein P concentrations and glutathione peroxidase activity. Genotyping was carried out for SEP15 (rs5859, rs540049), SEPP1 (rs3877899, rs7579), GPX1 (rs1050450), and GPX4 (rs713041). Conditional logistic regression was used to calculate adjusted odds ratios (OR) and 95% confidence intervals (95% CI).

RESULTS: The OR for prostate cancer was 0.89 (95% CI, 0.79-1.01) per 10 g/L increase of serum selenium concentration. This association was modified by rs1050450 (C>T) in GPX1 (P(interaction) = 0.03), with carriers of one or two T alleles having a significantly reduced OR of 0.87 (95% CI, 0.76-0.99). Furthermore, there was an association between rs7579 genotype in SEPP1 and prostate cancer risk (OR, 1.72; 95% CI, 0.99-2.98).

CONCLUSIONS: Our results support a role of selenium and polymorphisms in selenoenzymes in prostate cancer etiology, which warrants confirmation in future studies. **IMPACT:** These findings might help to explain biological effects of selenium in prostate cancer development in order to overcome inconsistencies arising from former studies.

SERUM TRIGLYCERIDES

Borena, W, T. Stocks, H. Jonsson, et al.

Serum Triglycerides and Cancer Risk in the Metabolic Syndrome and Cancer (Me-can) Collaborative Study.

Cancer Causes and Control. 2011 February 2011; 222: 291-299.

OBJECTIVE: To assess the association between serum triglyceride levels and cancer risk. **METHODS:** The metabolic syndrome and cancer project (Me-Can) includes cohorts from Norway, Austria, and Sweden; the current study included data on 257,585 men and 256,512 women. The mean age at study entry was 43.8

years for men and 44.2 years for women. The mean follow-up time was 13.4 years (SD = 8.5) for men and 11.9 years (SD = 7.2) for women. Excluding the first year of follow-up, 23,060 men and 15,686 women were diagnosed with cancer. Cox regression models were used to calculate relative risk (RR) of cancer for triglyceride levels in quintiles and as a continuous variable. RRs were corrected for random error by use of regression dilution ratio.

RESULTS: Relative risk for top quintile versus bottom quintile of triglycerides of overall cancer was 1.16 (95% confidence interval 1.06-1.26) in men and 1.15 (1.05-1.27) in women. For specific cancers, significant increases for top quintile versus bottom quintile of triglycerides among men were found for cancers of the colon, respiratory tract, the kidney, melanoma and thyroid and among women, for respiratory, cervical, and non-melanoma skin cancers.

CONCLUSION: Data from our study provided evidence for a possible role of serum triglycerides in cancer development.

PHYSICIANS' EMPATHY

Hojat, M, D. Z. Louis, F. W. Markham, et al.

Physicians' Empathy and Clinical Outcomes for Diabetic Patients.

Acad Med. 2011 Mar; 863: 359-364.

PURPOSE: To test the hypothesis that physicians' empathy is associated with positive clinical outcomes for diabetic patients. **METHOD:** A correlational study design was used in a university-affiliated outpatient setting. Participants were 891 diabetic patients, treated between July 2006 and June 2009, by 29 family physicians. Results of the most recent hemoglobin A1c and LDL-C tests were extracted from the patients' electronic records. The results of hemoglobin A1c tests were categorized into good control (<7.0%) and poor control (>9.0%). Similarly, the results of the LDL-C tests were grouped into good control (<100) and poor control (>130). The physicians, who completed the Jefferson Scale of Empathy in 2009, were grouped into high, moderate, and low empathy scorers. Associations between physicians' level of empathy scores and patient outcomes were examined.

RESULTS: Patients of physicians with high empathy scores were significantly more likely to have good control of hemoglobin A1c (56%) than were patients of physicians with low empathy scores (40%, P < .001). Similarly, the proportion of patients with good LDL-C control was significantly higher for physicians with high empathy scores (59%) than physicians with low scores (44%, P < .001). Logistic regression analyses indicated that physicians' empathy had a unique contribution to the prediction of optimal clinical outcomes after controlling for physicians' and patients' gender and age, and patients' health insurance.

CONCLUSIONS: The hypothesis of a positive relationship between physicians' empathy and patients' clinical outcomes was confirmed, suggesting that physicians' empathy is an important factor associated with clinical competence and patient outcomes. Physicians with high empathy scores had better clinical outcomes than physicians with lower empathy scores.