



# RESEARCH UPDATES

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August 2009

## Breast

Mignone, LI, E. Giovannucci, P. A. Newcomb, et al. **Dietary Carotenoids and the Risk of Invasive Breast Cancer.** *International Journal of Cancer.* 2009 Jun 15; 12412: 2929-2937. Certain classes of vitamins and nutrients found in fruits and vegetables have been of particular interest in relation to cancer prevention, owing to their potential anticarcinogenic properties. We examined the association between certain fruits, vegetables, carotenoids, and vitamin A and breast cancer risk in a large population-based case-control study of women residing in the states of Massachusetts, New Hampshire and Wisconsin. The study was comprised of 5,707 women with incident invasive breast cancer (2,363 premenopausal women and 3,516 postmenopausal women) and 6,389 population controls (2,594 premenopausal women and 3,516 postmenopausal women). In an interview, women were asked about their intake of carotenoid rich fruits and vegetables 5 years prior to a referent date. An inverse association observed among premenopausal women was for high levels of vitamin A (OR: 0.82, 95% CI: 0.68-0.98, p for trend = 0.01), beta-carotene (OR: 0.81, 95% CI 0.68-0.98, p for trend = 0.009), alpha-carotene (OR: 0.82, 95% CI: 0.68-0.98, p for trend = 0.07) and lutein/zeaxanthin (OR: 0.83, 95% CI 0.68-0.99, p for trend = 0.02). An inverse association was not observed among postmenopausal women. Among premenopausal women who reported ever smoking, these results were stronger than among never smokers, although tests for interaction were not statistically significant. Results from this study are comparable to previous prospective studies, and suggest that a high consumption of carotenoids may reduce the risk of premenopausal but not postmenopausal breast cancer, particularly among smokers. Copyright 2008 UICC.

Velentzis, LS, M. M. Cantwell, C. Cardwell, M. R. Keshtgar, A. J. Leatham and J. V. Woodside. **Lignans and Breast Cancer Risk in Pre- and Post-Menopausal Women: Meta-Analyses of Observational Studies.** *Br J Cancer.* 2009 May 5; 1009: 1492-1498. Phyto-oestrogens are plant compounds structurally similar to oestradiol, which have been proposed to have protective effects against breast cancer. The main class of phyto-oestrogens in the Western diet is lignans. Literature reports on the effect of lignans in breast cancer risk have been conflicting. We

performed three separate meta-analyses to examine the relationships between (i) plant lignan intake, (ii) enterolignan exposure and (iii) blood enterolactone levels and breast cancer risk. Medline, BIOSIS and EMBASE databases were searched for publications up to 30 September 2008, and 23 studies were included in the random effects meta-analyses. Overall, there was little association between high plant lignan intake and breast cancer risk (11 studies, combined odds ratio (OR): 0.93, 95% confidence interval (95% CI): 0.83-1.03, P=0.15), but this association was subjected to marked heterogeneity (I(2)=44%). Restricting the analysis to post-menopausal women, high levels of plant lignan intake were associated with reduced breast cancer risk (7 studies, combined OR: 0.85, 95% CI: 0.78, 0.93, P<0.001) and heterogeneity was markedly reduced (I(2)=0%). High enterolignan exposure was also associated with breast cancer (5 studies, combined OR: 0.73, 95% CI: 0.57, 0.92, P=0.009) but, again, there was marked heterogeneity (I(2)=63%). No association was found with blood enterolactone levels (combined OR: 0.82, 95% CI: 0.59-1.14, P=0.24). In conclusion, plant lignans may be associated with a small reduction in post-menopausal breast cancer risk, but further studies are required to confirm these results.

## Prostate

Watters, JL, M. H. Gail, S. J. Weinstein, J. Virtamo and D. Albanes. **Associations between Alpha-Tocopherol, Beta-Carotene, and Retinol and Prostate Cancer Survival.** *Cancer Res.* 2009 01 May; 69: 3833-3841. Previous studies suggest that carotenoids and tocopherols (vitamin E compounds) may be inversely associated with prostate cancer risk, yet little is known about how they affect prostate cancer progression and survival. We investigated whether serum alpha-tocopherol, beta-carotene, and retinol concentrations, or the alpha-tocopherol and beta-carotene trial supplementation, affected survival of men diagnosed with prostate cancer during the alpha-Tocopherol, beta-Carotene Cancer Prevention Study, a randomized, double-blind, placebocontrolled primary prevention trial testing the effects of beta-carotene and alpha-tocopherol supplements on cancer incidence in adult male smokers in southwestern Finland (n = 29,133). Prostate cancer



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survival was examined using the Kaplan-Meier method with deaths from other causes treated as censoring, and using Cox proportional hazards regression models with hazard ratios (HR) and 95% confidence intervals (CI) adjusted for family history of prostate cancer, age at randomization, benign prostatic hyperplasia, age and stage at diagnosis, height, body mass index, and serum cholesterol. As of April 2005, 1,891 men were diagnosed with prostate cancer and 395 died of their disease. Higher serum A-tocopherol at baseline was associated with improved prostate cancer survival (HR, 0.67; 95% CI, 0.45-1.00), especially among cases who had received the alpha-tocopherol intervention of the trial and who were in the highest quintile of alpha-tocopherol at baseline (HR, 0.51; 95% CI, 0.20-0.90) or at the 3-year follow-up measurement (HR, 0.26; 95% CI, 0.09-0.71). Serum beta-carotene, serum retinol, and supplemental beta-carotene had no apparent effects on survival. These findings suggest that higher alpha-tocopherol (and not beta-carotene or retinol) status increases overall prostate cancer survival. Further investigations, possibly including randomized studies, are needed to confirm this observation. copyright 2009 American Association for Cancer Research.

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## Colorectal

Huxley, RR, A. Ansary-Moghaddam, P. Clifton, S. Czernichow, C. L. Parr and M. Woodward. **The Impact of Dietary and Lifestyle Risk Factors on Risk of Colorectal Cancer: A Quantitative Overview of the Epidemiological Evidence.** *International Journal of Cancer.* 2009 Jul 1; 1251: 171-180. Colorectal cancer is a major cause of cancer mortality and is considered to be largely attributable to inappropriate lifestyle and behavior patterns. The purpose of this review was to undertake a comparison of the strength of the associations between known and putative risk factors for colorectal cancer by conducting 10 independent meta-analyses of prospective cohort studies. Studies published between 1966 and January 2008 were identified through EMBASE and MEDLINE, using a combined text word and MESH heading search strategy. Studies were eligible if they reported estimates of the relative risk for colorectal cancer with any of the following: alcohol, smoking, diabetes, physical activity, meat, fish, poultry, fruits and vegetables. Studies were excluded if the estimates were not adjusted at least for age. Overall, data from 103 cohort studies were included. The risk of colorectal cancer was significantly associated with alcohol: individuals consuming the most alcohol had 60% greater risk of colorectal cancer compared with non- or light drinkers (relative risk 1.56, 95% CI 1.42-1.70). Smoking, diabetes, obesity and high meat intakes were each associated with a significant 20% increased risk of colorectal cancer (compared with individuals in the lowest categories for each) with little evidence of between-study heterogeneity or publication bias. Physical activity was protective against colorectal cancer. Public-health strategies that promote modest alcohol consumption, smoking cessation, weight loss, increased physical activity and moderate consumption of red and processed meat are likely to have significant benefits at the population level for reducing the incidence of colorectal cancer.

Rohrmann, S, S. Hermann and J. Linseisen. **Heterocyclic Aromatic Amine Intake Increases Colorectal Adenoma Risk: Findings from a Prospective European Cohort Study.** *Am J Clin Nutr.* 2009 May; 895: 1418-1424.

**BACKGROUND:** Heterocyclic aromatic amines (HCAs), which arise from cooking meat and fish at high temperatures, may increase the risk of colorectal adenomas. Conversely, flavonoids might counteract the negative effects of HCAs. **OBJECTIVE:** The association between dietary HCA intake and colorectal adenoma incidence was investigated in a prospective cohort study. **DESIGN:** At recruitment (1994-1998), detailed information on diet, anthropometric measures, lifestyle, and medication use was assessed in 25,540 participants of the European Prospective Investigation into Cancer and Nutrition-Heidelberg cohort study. Dietary HCA intake was estimated by using information from food-frequency questionnaires on meat consumption, applied cooking methods, and preferred degree of browning. Until June 2007, 516 verified incident colorectal adenomas were identified. Participants with negative colonoscopy (n = 3966) were also included in the analytic cohort. Multivariate Cox proportional hazards regression was used to examine the association between colorectal adenoma risk and intake of 2-amino-1-methyl-6-phenylimidazo[4,5-b]pyridine (PhIP), 2-amino-3,8-dimethylimidazo[4,5-f]quinoxaline (MeIQx), and 2-amino-3,4,8-dimethylimidazo[4,5-f]quinoxaline (DiMeIQx). **RESULTS:** In multivariate analyses, the intake of PhIP as the most abundant dietary HCA was associated with an increased risk of colorectal adenoma (relative risk: 1.47; 95% CI: 1.13, 1.93; quartile 4 compared with quartile 1; P for trend = 0.002), but no statistically significant associations were observed for MeIQx and DiMeIQx intakes. In addition, adenoma risk also increased with the consumption of strongly or extremely browned meat (P for trend = 0.04). The association of PhIP intake with adenoma risk was most pronounced for small adenomas (P for trend = 0.01) and adenomas localized in the distal colon (P for trend = 0.002). **CONCLUSION:** The results of this first European cohort study support data from case-control studies of a positive association between HCA intake and colorectal adenoma risk.

## Pancreatic

Jiao, L, P. N. Mitrou, J. Reedy, et al. **A Combined Healthy Lifestyle Score and Risk of Pancreatic Cancer in a Large Cohort Study.** *Arch Intern Med.* 2009 Apr 27; 1698: 764-770. **BACKGROUND:** Smoking, alcohol use, diet, body mass index (calculated as weight in kilograms divided by height in meters squared), and physical activity have been studied independently in relation to pancreatic cancer. We generated a healthy lifestyle score to investigate their joint effect on risk of pancreatic cancer. **METHODS:** In the prospective National Institutes of Health-AARP Diet and Health Study, a total of 450 416 participants aged 50 to 71 years completed the baseline food frequency questionnaire (1995-1996) eliciting diet and lifestyle information and were followed up through December 31, 2003. We identified 1057 eligible incident pancreatic cancer cases. Participants were scored on 5 modifiable lifestyle factors as unhealthy (0 points) or healthy (1 point) on the basis of current epidemiologic evidence. Participants received 1 point for each respective lifestyle factor: nonsmoking, limited alcohol use, adherence to the Mediterranean dietary pattern, body mass index (> or =18 and <25), or regular physical activity. A combined score (0-5 points) was calculated by summing the scores of the 5 factors. Cox proportional hazards regression models were used to estimate relative risk (95% confidence interval) for pancreatic cancer. **RESULTS:** Compared with the lowest combined score (0 points), the highest score (5 points) was associated with a 58% reduction in risk of developing pancreatic cancer in all participants (relative risk, 0.42; 95%

confidence interval, 0.26-0.66; P(trend) <.001). Scores of less than 5 points were associated with 27% of pancreatic cancer cases in our population. **CONCLUSION:** Findings from this large study suggest that having a high score, as opposed to a low score, on an index combining 5 modifiable lifestyle factors substantially reduces the risk of developing pancreatic cancer.

Jiao, L, D. T. Silverman, C. Schairer, et al. **Alcohol use and Risk of Pancreatic Cancer.** *Am J Epidemiol.* 2009 May; 1699: 1043-1051.

The epidemiologic evidence for the role of alcohol use in pancreatic cancer development is equivocal. The authors prospectively examined the relation between alcohol use and risk of pancreatic cancer among 470,681 participants who were aged 50-71 years in 1995-1996 in the US National Institutes of Health-AARP Diet and Health Study. The authors identified 1,149 eligible exocrine pancreatic cancer cases through December 2003. Multivariate Cox proportional hazards regression models were used to calculate relative risks and 95% confidence intervals with the referent group being light drinkers (<1 drink/day). The relative risks of developing pancreatic cancer were 1.45 (95% confidence interval (CI): 1.17, 1.80; P<sub>trend</sub>=0.002) for heavy total alcohol use ([greater than or equal to]3 drinks/day, [similar to]40 g of alcohol/day) and 1.62 (95% CI: 1.24, 2.10; P<sub>trend</sub>=0.001) for heavy liquor use, compared with the respective referent group. The increased risk with heavy total alcohol use was seen in never smokers (relative risk=1.35, 95% CI: 0.79, 2.30) and participants who quit smoking 10 or more years ago before baseline (relative risk=1.41, 95% CI: 1.01, 2.00). These findings suggest a moderately increased pancreatic cancer risk with heavy alcohol use, particularly liquor; however, residual confounding by cigarette smoking cannot be completely excluded.

## Esophageal & Gastric

Carman, S, F. Kamangar, N. D. Freedman, et al. **Vitamin E Intake and Risk of Esophageal and Gastric Cancers in the NIH-AARP Diet and Health Study.** *International Journal of Cancer.* 2009 Jul 1; 1251: 165-170.

We investigated the association of dietary alpha-tocopherol, gamma-tocopherol and supplemental vitamin E intake with the risk of esophageal squamous cell carcinoma (n = 158), esophageal adenocarcinoma (n = 382), gastric cardia adenocarcinoma (n = 320) and gastric noncardia adenocarcinoma (GNCA; n = 327) in the NIH-AARP Diet and Health Study, a cohort of approximately 500,000 people. Data on dietary and supplemental vitamin E intake were collected using a validated questionnaire at baseline and were analyzed using Cox regression models. Intakes were analyzed as continuous variables and as quartiles. For dietary alpha-tocopherol, we found some evidence of association with decreased esophageal squamous cell carcinoma and increased esophageal adenocarcinoma risk in the continuous analyses, with adjusted hazard ratios and 95% confidence intervals of 0.90 (0.81-0.99) and 1.05 (1.00-1.11), respectively, per 1.17 mg (half the interquartile range) increased intake. However, in quartile analyses, the p value for trend was nonsignificant for both these cancers. There was no association between dietary alpha-tocopherol and gastric cardia adenocarcinoma or GNCA. We observed no statistically significant associations with gamma-tocopherol. For supplemental vitamin E, the results were mainly null, except for a significantly lower risk of GNCA with higher doses of supplemental vitamin E. An increase of 71 mg/day (half the interquartile range) in supplemental vitamin E had an hazard ratio (95% confidence interval) of 0.92 (0.85-1.00) and the p

value for trend in the quartile analysis was 0.015.

## Leukemia

Kuo, Y-, C. -L Yu, C. -Y Liu, et al. **A Population-Based, Case-Control Study of Green Tea Consumption and Leukemia Risk in Southwestern Taiwan.** *Cancer Causes and Control.* 2009 February; 201: 57-65.

Objective: This study investigated the association between green tea consumption and leukemia. Methods: A total of 252 cases (90.3% response) and 637 controls (53.4% response) were enrolled. Controls were matched for cases on age and gender. Information was collected on participants' living habits, including tea consumption. Green tea was used as a standard to estimate the total amount of individual catechin consumption. We stratified individual consumption of catechins into four levels. Conditional logistic regression models were fit to subjects aged 0-15 and 16-29 years to evaluate separate associations between leukemia and catechin consumption. Results: A significant inverse association between green tea consumption and leukemia risk was found in individuals aged 16-29 years, whereas no significant association was found in the younger age groups. For the older group with higher amounts of tea consumption (>550 units of catechins), the adjusted odds ratio (OR) compared with the group without tea consumption was 0.47 [95% confidence interval (CI) = 0.23-0.97]. After we adjusted for smoking status and medical irradiation exposure, the overall OR for all participants was 0.49 (95% CI = 0.27-0.91), indicating an inverse relation between large amounts of catechins and leukemia. Conclusion: Drinking sufficient amounts of tea, especially green tea, which contains more catechins than oolong tea and black tea, may reduce the risk of leukemia. copyright 2008 Springer Science+Business Media B.V.

## Isoflavones

Kurahashi, N, M. Inoue, M. Iwasaki, Y. Tanaka, M. Mizokami and S. Tsugane. **Isoflavone Consumption and Subsequent Risk of Hepatocellular Carcinoma in a Population-Based Prospective Cohort of Japanese Men and Women.** *International Journal of Cancer.* 2009 01 Apr; 1247: 1644-1649.

The incidence of hepatocellular carcinoma (HCC) is much higher in men than in women. Several experiment and epidemiological studies have suggested that estrogen might play an inhibitory role in the development of HCC. Because isoflavones have a similar structure as 17p-estradiol and appear to have an anti-estrogenic effect in women and estrogenic effect in men, we hypothesized that the effect of isoflavones on HCC differs by sex. We investigated the association between isoflavones (genistein and daidzein) and soy products and HCC in Japan in a population-based prospective study in 19,998 Japanese (7,215 men and 12,783 women) aged 40-69 years. During 11.8 years of follow-up, 101 subjects (69 men and 32 women) were newly diagnosed with HCC. Case patients were grouped according to consumption of isoflavones and soy products and stratified by hepatitis virus infection. Hazard ratios (HRs) and 95% confidence intervals (CIs) for HCC were calculated by Cox proportional-hazards modeling. In women, genistein and daidzein were dose-dependently associated with an increased risk of HCC, with multivariable HRs for the highest versus lowest tertile of 3.19 (95%CI = 1.13-9.00, p<sub>trend</sub> = 0.03) and 3.90 (95% CI = 1.30-11.69, p<sub>trend</sub> = 0.01), respectively. No association between

isoflavones and HCC was observed in men. These results persisted when analysis was restricted to subjects positive for either or both hepatitis C and B virus. In conclusion, isoflavone consumption may be associated with an increased risk of HCC in women. Women with hepatitis virus infection may be advised to abstain from isoflavone consumption. Further studies are warranted to confirm these findings. copyright 2008 Wiley-Liss, Inc.

## Exercise

Newton, RU and D. A. Galvao. **Exercise in Prevention and Management of Cancer** *Current Treatment Options in Oncology*. 2008 Jun; 92-3: 135-146. **OPINION STATEMENT:** Regular and vigorous physical exercise has been scientifically established as providing strong preventative medicine against cancer with the potential to reduce incidence by 40%. The effect is strongest for breast and colorectal cancer; however, evidence is accumulating for the protective influence on prostate cancer, although predominantly for more advanced disease and in older men. Following cancer diagnosis, exercise prescription can have very positive benefits for improving surgical outcomes, reducing symptom experience, managing side effects of radiation and chemotherapy, improving psychological health, maintaining physical function, and reducing fat gain and muscle and bone loss. There is now irrefutable evidence from large prospective studies that regular exercise postdiagnosis will actually increase survivorship by 50%-60% with the strongest evidence currently for breast and colorectal cancers. In our work with prostate cancer patients, we have found that exercise can limit or even reverse some of the androgen deprivation therapy (ADT) adverse effects by increasing muscle mass, functional performance, and cardiorespiratory fitness without elevating testosterone levels. Hormone therapies for breast and prostate cancer can result in alarmingly increased risk of cardiovascular disease, obesity, type 2 diabetes, osteoporosis, and sarcopenia. Increasingly, patients are questioning the benefit of some cancer treatments as the risk of morbidity and mortality from other chronic diseases begins to outweigh the initial cancer diagnosis. Over three decades of research in exercise science and many hundreds of RCTs demonstrate the efficacy of appropriate physical activity for preventing and managing these secondary diseases. Based on this evidence it is now clear to us that exercise is a critical adjuvant therapy in the management of many cancers and will greatly enhance the therapeutic effects of traditional radiation and pharmaceutical treatments by increasing tolerance, reducing side effects, and lowering risk of chronic diseases, even those not aggravated by cancer treatment. While patients and their clinicians deal with their cancer, other chronic disease mechanisms continue unabated. Anxiety, depression, poor nutritional choices, and a counterproductive rest strategy will accelerate these processes, while a well-designed exercise program adhered to by the patient and supported by the medical and exercise professionals will effectively control and even reverse these diseases and disabilities. In the wide range of cancer populations that we work with, both young and old and with curative and palliative intent, our overwhelming experience is that exercise is first well tolerated, and benefits the patient psychologically and

physically. While some of our patients are on individual, home-based programs, we find that small group exercise sessions with close supervision by Exercise Physiologists (EP) provides a more motivating setting and the social interaction is critical for adherence and retention as well as greater psychological benefits such as reduced anxiety and depression and enhanced social connectedness. While managing many hundreds of cancer patients over the last 6 years, our clinic has not experienced any instances of the exercise hindering patient recovery or treatment purpose, nor have any significant injuries occurred. However, it is critical that the exercise prescription and management be tailored to the individual patient and that they are monitored by appropriately trained and professionally accredited exercise specialists. For those patients at low exercise risk and without significant musculoskeletal issues, community-based physical activity is of excellent benefit where the emphasis should be on adherence, affordability, convenience, and enjoyment. [References: 45]

## CAM of the Month

Messina, M and A. H. Wu. **Perspectives on the Soy-Breast Cancer Relation.** *Am J Clin Nutr*. 2009 May; 89(5): 1673S-1679S. There has been considerable investigation of the potential for soy foods to reduce risk of breast cancer. Initial enthusiasm for this research was partially based on the historically low incidence rates of breast cancer and high soy food intake in Japan. There are several putative soybean chemopreventive agents, but most cancer research has focused on isoflavones. Isoflavones possess both hormonal and nonhormonal properties relevant to carcinogenesis. Recent epidemiologic analyses indicate that among Asians high soy intake is associated with an approximate one-third reduction in the risk of both pre- and postmenopausal breast cancer. However, several lines of evidence suggest that to derive maximum protection against breast cancer, soy must be consumed early in life. This evidence is consistent with the lack of significant effects noted in clinical studies that have evaluated the effects of isoflavone-containing products on breast cancer risk markers. Isoflavones may exert their putative protective effects by stimulating breast cell differentiation in a manner similar to that which is thought to occur during early pregnancy. Finally, the ability of the isoflavone genistein to stimulate the growth of mammary tumors in ovariectomized athymic nude mice implanted with estrogen-sensitive breast cancer cells has raised concern that soy foods, and especially isoflavone supplements, are contraindicated for patients with breast cancer and women at high risk of breast cancer. However, findings from clinical studies, in which breast biopsies have been taken or breast tissue density measured after isoflavone exposure, are reassuring and contrast with the proliferative effects of conventional combined hormone therapy, although understanding of the effect of soy and isoflavones on breast tissues remains imprecise.

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