



# RESEARCH UPDATES

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**Research Updates** is InspireHealth's monthly publication that informs those interested about authoritative articles in integrated cancer care. Articles are selected based on their evidence and relevance to integrated cancer care.

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## Vitamin D & Cancer

Garland, CF, E. D. Gorham, S. B. Mohr and F. C. Garland. **Vitamin D for Cancer Prevention: Global Perspective** *Ann Epidemiol.* 2009 Jul; 197: 468-483.

**PURPOSE:** Higher serum levels of the main circulating form of vitamin D, 25-hydroxyvitamin D (25(OH)D), are associated with substantially lower incidence rates of colon, breast, ovarian, renal, pancreatic, aggressive prostate and other cancers. **METHODS:** Epidemiological findings combined with newly discovered mechanisms suggest a new model of cancer etiology that accounts for these actions of 25(OH)D and calcium. Its seven phases are disjunction, initiation, natural selection, overgrowth, metastasis, involution, and transition (abbreviated DINOMIT). Vitamin D metabolites prevent disjunction of cells and are beneficial in other phases. **RESULTS/CONCLUSIONS:** It is projected that raising the minimum year-around serum 25(OH)D level to 40 to 60 ng/mL (100-150 nmol/L) would prevent approximately 58,000 new cases of breast cancer and 49,000 new cases of colorectal cancer each year, and three fourths of deaths from these diseases in the United States and Canada, based on observational studies combined with a randomized trial. Such intakes also are expected to reduce case-fatality rates of patients who have breast, colorectal, or prostate cancer by half. There are no unreasonable risks from intake of 2000 IU per day of vitamin D(3), or from a population serum 25(OH)D level of 40 to 60 ng/mL. The time has arrived for nationally coordinated action to substantially increase intake of vitamin D and calcium.

Grant, WB and S. B. Mohr. **Ecological Studies of Ultraviolet B, Vitamin D and Cancer since 2000** *Ann Epidemiol.* 2009 Jul; 197: 446-454.

**PURPOSE:** The purpose of this review is to summarize ecological studies of solar ultraviolet B (UVB), vitamin D and cancer since 2000. **METHODS:** The journal literature is surveyed and summarized.

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**RESULTS:** The ecological approach has been the primary tool used during the past two decades to extend the applicability of the UVB-vitamin D-cancer theory to include at least 18 types of cancer. Many of these studies were conducted in the United States, which has the advantages of availability of reliable age-standardized cancer incidence and mortality rate data for geographic areas at various spatial resolutions, and an asymmetric solar UVB dose pattern, with higher UVB irradiance in the west and lower in the east, at any particular latitude. In addition, indices for other cancer risk-modifying factors are readily available including those for smoking, alcohol consumption, ethnic background, urban/rural residence, socioeconomic status, air pollution, and in limited fashion, diet. The ecological approach has also been used to identify latitudinal variations in cancer mortality rates in Australia, China, Japan, and Spain, and in multi country studies. It has been used to investigate the relative roles of solar UVB and dietary factors on a global scale. The ecological approach has also been applied to cancer survival. Studies in Norway and England found that individuals diagnosed with cancer in summer or fall, when serum 25-hydroxyvitamin D levels are highest, had a milder clinical course and longer survival than those diagnosed in winter or spring. **CONCLUSION:** These findings provide strong evidence that vitamin D status plays an important role in controlling the outcome of cancer. Support for the UVB-vitamin D-cancer theory is now scientifically strong enough to warrant use of vitamin D in cancer prevention, and as a component of treatment. More research studies would help to explore whether there are benefits beyond the substantial effects that have been observed.

Ng, K, B. M. Wolpin, J. A. Meyerhardt, et al. **Prospective Study of Predictors of Vitamin D Status and Survival in Patients with Colorectal Cancer.** *Br J Cancer.* 2009 Sep 15; 1016: 916-923.

**BACKGROUND:** In an earlier study, a 25-hydroxyvitamin D(3) (25(OH)D) score calculated from known predictors of vitamin D status significantly predicted plasma levels of 25(OH)D and the risk of colorectal cancer, but the influence of the 25(OH)D score on survival after diagnosis is unknown. **MATERIALS AND METHODS:** We prospectively examined the influence of post-diagnosis predicted 25(OH)D levels on mortality among 1017 participants in the Nurses' Health Study and Health Professionals Follow-Up Study who were diagnosed with colorectal cancer from 1986 to 2004. Colorectal cancer-specific and overall mortality according to quintiles of predicted 25(OH)D levels were assessed. Cox proportional hazards models were used to calculate hazard ratios (HRs) adjusted for other risk factors of survival. **RESULTS:** Higher predicted 25(OH)D levels were associated with a significant reduction in colorectal cancer-specific (P trend=0.02) and overall mortality (P trend=0.002). Compared with levels in the lowest quintile, participants with predicted 25(OH)D levels in the highest quintile had an adjusted HR of 0.50 (95% CI, 0.26-0.95) for cancer-specific mortality and 0.62 (95% CI, 0.42-0.93) for overall mortality. **CONCLUSION:** Higher predicted 25(OH)D levels after a diagnosis of colorectal cancer may be associated with improved survival. Further study of the vitamin D pathway in colorectal cancer is warranted.

## Nutrition

Bandera, EV, D. M. Gifkins, D. F. Moore, M. L. McCullough and L. H. Kushi. **Antioxidant Vitamins and the Risk of Endometrial Cancer: A Dose-Response Meta-Analysis.** *Cancer Causes & Control.* 2009 Jul; 205: 699-711.

Antioxidant vitamins may reduce cancer risk by limiting oxidative DNA damage. To summarize and quantify the current epidemiologic evidence of an association between antioxidant vitamin intake and endometrial cancer, we conducted a systematic literature review and meta-analysis. One cohort and 12 case-control studies presenting relevant risk estimates were identified by conducting bibliographical searches through June 2008. Dose-response meta-analyses were conducted for beta-carotene, vitamin C, and vitamin E from food sources. Intake from supplements was not considered in the meta-analyses because of the few studies that reported relevant information. Based on case-control data, the random-effects summary odds ratios (OR) were, for beta-carotene: 0.88 (95% CI: 0.79-0.98) per 1,000 mcg/1,000 kcal (I2: 77.7%; p < 0.01); for vitamin C: 0.85 (95% CI: 0.73-0.98) per 50 mg/1,000 kcal (I2: 66.1%; p < 0.01); and, for vitamin E: 0.91 (95% CI: 0.84-0.99) per 5 mg/1,000 kcal (I2: 0.0%; p: 0.45). In contrast, the only prospective study identified provided little indication of an association. Although the current case-control data suggest an inverse relationship of endometrial cancer risk with dietary intakes of beta-carotene, vitamin C, and vitamin E from food sources, additional studies are needed, particularly cohort studies, to confirm an association.

Deng, G, H. Lin, A. Seidman, et al. **A Phase I/II Trial of a Polysaccharide Extract from Grifola Frondosa (Maitake Mushroom) in Breast Cancer Patients: Immunological Effects.** *J Cancer Res Clin Oncol.* 2009 September; 1359: 1215-1221.

Cancer patients commonly use dietary supplements to "boost immune function". A polysaccharide extract from *Grifola frondosa* (Maitake extract) showed immunomodulatory effects in preclinical studies and therefore the potential for clinical use. Whether oral administration in human produces measurable immunologic effects, however, is unknown. In a phase I/II dose escalation trial, 34 postmenopausal breast cancer patients, free of disease after initial treatment, were enrolled sequentially in five cohorts. Maitake liquid extract was taken orally at 0.1, 0.5, 1.5, 3, or 5 mg/kg twice daily for 3 weeks. Peripheral blood was collected at days -7, 0 (prior to the first dosing), 7, 14, and 21 for ex vivo analyses. The primary endpoints were safety and tolerability. No dose-limiting toxicity was encountered. Two patients withdrew prior to completion of the study due to grade I possibly related side effects: nausea and joint swelling in one patient; rash and pruritus in the second. There was a statistically significant association between Maitake and immunologic function (p < 0.0005). Increasing doses of Maitake increased some immunologic parameters and depressed others; the dose-response curves for many endpoints were non-monotonic with intermediate doses having either immune enhancing or immune suppressant effects compared with both high and low doses. Oral administration of a polysaccharide extract from Maitake mushroom is associated with both immunologically stimulatory and inhibitory measurable effects in peripheral blood. Cancer patients should be made aware of the fact that botanical agents produce more complex effects than assumed, and may depress as well as enhance immune function.

## Exercise

Carnide, N, N. Kreiger and M. Cotterchio. **Association between Frequency and Intensity of Recreational Physical Activity and Epithelial Ovarian Cancer Risk by Age Period.** *European Journal of Cancer Prevention.* 2009 August; 184: 322-330.

The objective of this study was to examine the association between recreational physical activity across the life span and epithelial ovarian cancer. This relationship was investigated using data from the Ontario arm of the National Enhanced Cancer Surveillance Study, a Canadian population-based case-control study. Data were collected from 240 epithelial ovarian cases and 891 female controls using a self-administered questionnaire. The frequency and intensity of recreational activity in four age periods (mid-teens, early 30s, early 50s, 2 years ago) were examined. Odds ratios (OR) and 95% confidence intervals (CI) were estimated using multivariate logistic regression. Participation up to two times/week, but not more than two times/week, in strenuous recreational activity in mid-teens (OR = 1.69, 95% CI=1.15-2.49) and early 30s (OR = 1.45, 95% CI=1.03-2.05) was associated with increased risk of ovarian cancer. For activity 2 years ago, participation in both strenuous activity (OR = 0.69, 95% CI=0.47-1.01) and moderate activity (OR = 0.55, 95% CI=0.34-0.88) up to two times/week was associated with reduced ovarian cancer risk. Participating more than two times/week was not associated with ovarian cancer risk. Strenuous activity performed in early 50s and moderate activity performed in mid-teens, early 30s, and early 50s were unrelated to risk. In conclusion, strenuous

recreational activity early in life may increase the risk of ovarian cancer, whereas more recent recreational activity may reduce the risk.

## Colorectal Cancer

Sansbury, LB, K. Wanke, P. S. Albert, et al. **The Effect of Strict Adherence to a High-Fiber, High-Fruit and -Vegetable, and Low-Fat Eating Pattern on Adenoma Recurrence.** *Am J Epidemiol.* 2009 Sep 1; 1705: 576-584.

Individual differences in dietary intake are thought to account for substantial variation in cancer incidence. However, there has been a consistent lack of effect for low-fat, high-fiber dietary interventions and risk of colorectal cancer. These inconsistencies may reflect the multistage process of cancer as well as the range and timing of dietary change. Another potential reason for the lack of effect is poor dietary adherence among participants in these trials. The authors examined the effect of strict adherence to a low-fat, high-fiber, high-fruit and -vegetable intervention over 4 years among participants (n = 1,905) in the US Polyp Prevention Trial (1991-1998) on colorectal adenoma recurrence. There was a wide range of individual variation in the level of compliance among intervention participants. The most adherent participants, defined as "super compliers" (n = 210), consistently reported that they met or exceeded each of the 3 dietary goals at all 4 annual visits. Multivariate logistic regression models were used to estimate the association between dietary adherence and adenoma recurrence. The authors observed a 35% reduced odds of adenoma recurrence among super compliers compared with controls (odds ratio = 0.65, 95% confidence interval: 0.47, 0.92). Findings suggest that high compliance with a low-fat, high-fiber diet is associated with reduced risk of adenoma recurrence.

## Cervical Cancer

Piyathilake, CJ, M. Macaluso, R. D. Alvarez, W. C. Bell, D. C. Heimburger and E. E. Partridge. **Lower Risk of Cervical Intraepithelial Neoplasia in Women with High Plasma Folate and Sufficient Vitamin B12 in the Post-Folic Acid Fortification Era.** *Cancer Prevention Research.* 2009 July; 27: 658-664.

The purpose of this study was to determine the influence of plasma folate and vitamin B12 concentrations on cervical cancer risk in the U.S. after the folic acid fortification era. The study included 376 premenopausal women of childbearing age who tested positive for infections with high-risk (HR) human papillomaviruses (HPVs) and were diagnosed with cervical intraepithelial neoplasia (CIN) grade 2 or higher (CIN 2+, cases) or [less-than or equal to]CIN 1 (noncases). CIN 2+ (yes/no) was the dependent variable in logistic regression models that specified plasma folate concentrations combined with plasma B12 concentrations as the independent predictors of primary interest, adjusting for age, race, education, smoking, parity, number of lifetime male sexual partners, use of contraceptives, waist circumference, physical activity, healthy eating index, and circulating concentrations of vitamins A, C, tocopherol, and total carotene. Women with supraphysiologic concentrations of plasma folate (>19.8 ng/mL) who also had sufficient

plasma vitamin B12 ([greater-than or equal to]200.6 pg/mL) had 70% lower odds of being diagnosed with CIN 2+ (P = 0.04) when compared with women with plasma folate of [less-than or equal to]19.8 ng/mL and plasma vitamin B12 of <200.6 pg/mL. Our results do not corroborate the concern that supraphysiologic plasma folate concentrations seen in the post-U.S. folic acid fortification era increase the risk of CIN in premenopausal women of childbearing age. In fact, higher folate is associated with significantly lower risk of CIN, especially when vitamin B12 is sufficient, demonstrating the importance of vitamin B12 in the high-folate environment created by the folic acid fortification program.

## Prostate Cancer

Neuhouser, ML, M. J. Barnett, A. R. Kristal, et al. **Dietary Supplement use and Prostate Cancer Risk in the Carotene and Retinol Efficacy Trial.** *Cancer Epidemiology Biomarkers and Prevention.* 2009 August; 188: 2202-2206.

We investigated dietary supplement use and prostate cancer risk in the Carotene and Retinol Efficacy Trial (CARET). CARET was a randomized, double-blinded, placebo-controlled trial testing a daily dose of 30 mg beta-carotene + 25,000 IU retinyl palmitate for lung cancer prevention (1985-1996; active follow-up occurred through 2005). Secondary outcomes, including prostate cancer, were also assessed. Participants were queried about dietary supplements, health history, family history of cancer, smoking, and lifestyle habits. Cox proportional hazards regression estimated multivariate-adjusted relative risk [and 95% confidence intervals (95% CI)] of prostate cancer for dietary supplement users and nonusers with or without the high-dose CARET vitamins during the intervention and post-intervention phases. After an average of 11 years of follow-up, 890 prostate cancer cases were reported. Neither the CARET nor other supplements were associated with total prostate cancer risk. For aggressive prostate cancer, men in the CARET intervention arm who used additional supplements had a relative risk for aggressive prostate cancer (Gleason [greater-than or equal to]7 or stage III/IV) of 1.52 (95% CI, 1.03-2.24; P < 0.05), relative to all others. These associations disappeared in the post-intervention period (0.75; 95% CI, 0.51-1.09). Conversely, there was no association of CARET + other supplements with nonaggressive disease, relative to all others. There was no effect modification by smoking or time on CARET intervention in any analyses. CARET only included smokers, so findings reported here may not apply to nonsmokers. Our results are consistent with other studies suggesting that dietary supplements may influence prostate cancer risk.

We are grateful to the **Prostate Cancer Foundation BC** for their generous support.



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## Renal Cell Cancer

Wilson, RT, J. Wang, V. Chinchilli, et al. **Fish, Vitamin D, and Flavonoids in Relation to Renal Cell Cancer among Smokers.** *Am J Epidemiol.* 2009 Sep 15; 1706: 717-729.

Fish, vitamin D, flavonoids, and flavonoid-containing foods may have cardiovascular benefits and therefore may also reduce the risk of renal cell cancer. Risk was prospectively assessed in the Alpha-Tocopherol Beta-Carotene Cancer Prevention Study (1985-2002) cohort (N = 27,111; 15.2 mean person-years of follow-up). At enrollment, demographic, health, and dietary history information was recorded. Individuals who smoked less than 5 cigarettes/day, with chronic renal insufficiency or prior cancer, were excluded. Hazard ratios and 95% confidence intervals from Cox regression were used to compare upper quartiles (quartiles 2-4) with the lowest quartile (quartile 1) of dietary intake. Among 228 cases, risk (quartile 4 vs. quartile 1) was associated with consumption of the flavonoid quercetin (hazard ratio = 0.6, 95% confidence interval: 0.4, 0.9; P(trend) = 0.015) and Baltic herring (hazard ratio = 2.0, 95% confidence interval: 1.4, 3.0; P(trend) < 0.001), with adjustment for age, body mass index, smoking, blood pressure, alcohol use, physical activity, urban residence, and education. In geographically stratified models, the risks associated with herring and total fish intake appeared to be highest in the urban coast region, although the interaction was not statistically significant. These results suggest that the flavonoid quercetin may prevent renal cell cancer among male smokers. The possible risk associated with fish intake warrants further investigation before conclusions may be drawn.

Lee, JE, S. Mannisto, D. Spiegelman, et al. **Intakes of Fruit, Vegetables, and Carotenoids and Renal Cell Cancer Risk: A Pooled Analysis of 13 Prospective Studies.** *Cancer Epidemiology, Biomarkers & Prevention.* 2009 Jun; 186: 1730-1739.

Fruit and vegetable consumption has been hypothesized to reduce the risk of renal cell cancer. We conducted a pooled analysis of 13 prospective studies, including 1,478 incident cases of renal cell cancer (709 women and 769 men) among 530,469 women and 244,483 men followed for up to 7 to 20 years. Participants completed a validated food-frequency questionnaire at baseline. Using the primary data from each study, the study-specific relative risks (RR) were calculated using the Cox proportional hazards model and then pooled using a random effects model. We found that fruit and vegetable consumption was associated with a reduced risk of renal cell cancer. Compared with or=600 g/d was 0.68 [95% confidence interval (95% CI) = 0.54-0.87; P for between-studies heterogeneity = 0.86; P for trend = 0.001]. Compared with or=400 g/d were 0.79 (0.63-0.99; P for trend = 0.03) for total fruit and 0.72 (0.48-1.08; P for trend = 0.07) for total vegetables. For specific carotenoids, the pooled multivariate RRs (95% CIs) comparing the highest and lowest quintiles were 0.87 (0.73-1.03) for alpha-carotene, 0.82 (0.69-0.98) for beta-carotene, 0.86 (0.73-1.01) for beta-cryptoxanthin, 0.82 (0.64-1.06) for lutein/zeaxanthin, and 1.13 (0.95-1.34) for lycopene. In conclusion, increasing fruit and vegetable

consumption is associated with decreasing risk of renal cell cancer; carotenoids present in fruit and vegetables may partly contribute to this protection.

## Study of the Month

Ford, ES, M. M. Bergmann, J. Kroger, A. Schienkiewitz, C. Weikert and H. Boeing. **Healthy Living is the Best Revenge: Findings from the European Prospective Investigation into Cancer and Nutrition-Potsdam Study.** *Arch Intern Med.* 2009 10 Aug; 16915: 1355-1362.

Background: Our objective was to describe the reduction in relative risk of developing major chronic diseases such as cardiovascular disease, diabetes, and cancer associated with 4 healthy lifestyle factors among German adults. Methods: We used data from 23 153 German participants aged 35 to 65 years from the European Prospective Investigation into Cancer and Nutrition-Potsdam study. End points included confirmed incident type 2 diabetes mellitus, myocardial infarction, stroke, and cancer. The 4 factors were never smoking, having a body mass index lower than 30 (calculated as weight in kilograms divided by height in meters squared), performing 3.5 h/wk or more of physical activity, and adhering to healthy dietary principles (high intake of fruits, vegetables, and whole-grain bread and low meat consumption). The 4 factors (healthy, 1 point; unhealthy, 0 points) were summed to form an index that ranged from 0 to 4. Results: During a mean follow-up of 7.8 years, 2006 participants developed new-onset diabetes (3.7%), myocardial infarction (0.9%), stroke (0.8%), or cancer (3.8%). Fewer than 4% of participants had zero healthy factors, most had 1 to 3 healthy factors, and approximately 9% had 4 factors. After adjusting for age, sex, educational status, and occupational status, the hazard ratio for developing a chronic disease decreased progressively as the number of healthy factors increased. Participants with all 4 factors at baseline had a 78% (95% confidence interval [CI], 72% to 83%) lower risk of developing a chronic disease (diabetes, 93% [95% CI, 88% to 95%]; myocardial infarction, 81% [95% CI, 47% to 93%]; stroke, 50% [95% CI, -18% to 79%]; and cancer, 36% [95% CI, 5% to 57%]) than participants without a healthy factor. Conclusion: Adhering to 4 simple healthy lifestyle factors can have a strong impact on the prevention of chronic diseases.

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