**Breast**


BACKGROUND: Few studies have evaluated carotenoids and vitamins C and E in association with the risk of breast cancers defined by estrogen receptor (ER) and progesterone receptor (PR) status. OBJECTIVE: We examined the associations between dietary and supplemental intakes of these nutrients and risk of breast cancers jointly defined by both ER and PR status among postmenopausal women. DESIGN: Our investigation was conducted in the Women's Health Initiative Observational Study. After following 84,805 women for an average of 7.6 y, 2,879 incident invasive breast cancer cases had been ascertained, of whom 2,509 had receptor data. We used Cox proportional hazards models to assess the associations of interest. RESULTS: Dietary alpha-carotene (highest versus lowest quintile: RR = 0.83; 95% CL = 0.70, 0.99; P for trend = 0.019), beta-carotene (highest versus lowest quintile: RR = 0.78; 95% CL = 0.66, 0.94; P for trend = 0.021), and lycopene (highest versus lowest quintile: RR = 0.85; 95% CL = 0.73, 1.00; P for trend = 0.064) were inversely associated with risk of ER+PR+breast cancer, but not with other breast cancer groups jointly defined by ER and PR status. Total or supplemental beta-carotene and dietary intakes of lutein+zeaxanthin and beta-cryptoxanthin were not associated with breast cancers defined by ER and PR status. Vitamin E (regardless of source) and dietary vitamin C were not associated with breast cancer. However, total and supplemental vitamin C intake had weak positive associations with breast cancer overall. CONCLUSION: Dietary intake of certain carotenoids might be differentially associated with risk of invasive breast cancers jointly defined by ER and PR status among postmenopausal women.


Purpose: Fatigue is one of the most frequently reported and adverse effects of cancer chemotherapy. The present study tested the hypothesis that women's levels of emotional distress at the time of their initial outpatient chemotherapy treatment would predict the severity of their postinfusion fatigue. Methods: Sixty stage I (32.69%) and II (67.4%) patients with breast cancer (mean age, 44.5 years) who were receiving standard outpatient chemotherapy participated. The independent variable, emotional distress, was assessed for “last night,” “this morning,” and “right now” with a visual analog scale (0 to 100). The dependent variable, post-treatment fatigue (PTF), was assessed (0 to 100) over each of the subsequent 6 days using end-of-day diaries, which also included assessments of distress and nausea (0 to 100). For the statistical analyses, post-treatment fatigue was divided into three phases with means calculated for days 1 through 2 (phase 1), 3 to 4 (phase 2), and 5 to 6 (phase 3). Results: Consistent with the study hypothesis, patents pre-treatment distress level in the clinic was a significant (P < .001) predictor of PTF. There was also a significant (P < .025) interaction with phase, with distress becoming a predictor of PTF after phase 1. Multivariate analysis indicated that prior levels of distress were not independent predictors of PTF. Conclusions: This study is the first to demonstrate time-specific effects of pretreatment distress on PTF. Possible mechanisms of these effects now warrant investigation, as do possible benefits of brief interventions to reduce patient distress immediately before treatment.

**Prostate**


Calcitriol, the hormonally active form of vitamin D, inhibits the growth and development of several cancers. Inflammation has been implicated in the development and progression of many cancers, including prostate cancer (PCa). Recent research from our laboratory suggests that calcitriol exhibits anti-inflammatory actions that may contribute to its inhibitory effects in PCa. We found that calcitriol inhibits the synthesis and actions of pro-inflammatory prostaglandins (PGs) by three mechanisms: (1) inhibition of the expression of cyclooxygenase-2 (COX-2), the enzyme that
synthesizes PGs, (2) induction of the expression of 15-prostaglandin dehydrogenase (15-PGDH), the enzyme that inactivates PGs, and (3) decreasing the expression of prostaglandin E and prostaglandin F PG receptors, which are the mediators of PG signaling. The combination of calcitriol and nonsteroidal anti-inflammatory drugs (NSAIDs) result in a synergistic inhibition of PCa cell growth and offers a potential therapeutic strategy. Acting on a separate anti-inflammatory pathway, calcitriol induces the expression of mitogen-activated protein kinase phosphatase 5 (MKP5), a member of a family of phosphatases that are negative regulators of MAP kinases, causing the selective dephosphorylation and inactivation of the stress-activated protein kinase p38. Because p38 activation may be both procarcinogenic and promote inflammation, this calcitriol action, especially coupled with the inhibition of the PG pathway, may contribute to the chemopreventive activity of calcitriol. We conclude that calcitriol exerts several anti-inflammatory actions in prostate cells, which contribute to its potential as a chemopreventive and therapeutic agent in PCa.

Perabo FG, Von Low EC, Ellinger J, et al. Soy isoflavone genistein in prevention and treatment of prostate cancer. Prostate Cancer & Prostatic Diseases. 2008;11(1):6-12. Dietary habits and incidence of prostate cancer (PCa) are very different in several parts of the world. Among the differences between Eastern and Western diets is the greater intake of soy in the Eastern cultures. This might be one factor contributing to a lower incidence of PCa in Asian men. Many studies using PCa cells and animal studies of chemical carcinogenesis have shown that a wide range of dietary compounds have cancer chemopreventive potential. Therefore, the interest in nutrition-based approaches for prevention and treatment of PCa is increasing. We reviewed all experimental preclinical in vitro and in vivo data as well as clinical trials performed with soy isoflavone genistein for prevention and treatment of PCa. The preclinical data for genistein presented in this review show a remarkable efficacy against PCa cells in vitro with molecular targets ranging from cell cycle regulation to induction of apoptosis. In addition, seemingly well-conducted animal experiments support the belief that genistein might have a clinical activity in human cancer therapy. However, it is difficult to make definite statements or conclusions on clinical efficacy of genistein because of the great variability and differences of the study designs, small patient numbers, short treatment duration and lack of a standardized drug formulation. Although some results from these genistein studies seem encouraging, reliable or long-term data on tumor recurrence, disease progression and survival are unknown. The presented data potentially allow recommending patients the use of genistein as in soy products in a preventive setting. However, at present there is no convincing clinical proof or evidence that genistein might be useful in PCa therapy.

Freedman ND, Park Y, Subar AF, et al. Fruit and vegetable intake and head and neck cancer risk in a large United States prospective cohort study. International Journal of Cancer. 2008 May 15;122(10):2330-2336. Squamous head and neck cancers include cancers of the oral cavity, pharynx and larynx are the sixth leading cause of cancer mortality worldwide, resulting in more than 350,000 deaths annually. Intake of fruit and vegetables may protect against head and neck cancer incidence, although few prospective studies have examined this association. We investigated this relation in 490,802 United States participants of the NIH-AARP Diet and Health cohort using Cox proportional hazard models adjusted for potential confounders. During 2,193,751 person years of follow-up from 1995/1996-2000, 787 participants were diagnosed with head and neck cancer. We found an inverse association between total fruit and vegetable intake and head and neck cancer risk (per serving/day/1,000 calories, Hazard Ratio, 95% Confidence interval: 0.94, 0.89-0.99). In models mutually adjusted for fruit and vegetable intake, the association was stronger for vegetables (fifth vs. first quintile: 0.65, 0.50-0.85) than for fruit (fifth vs. first quintile: 0.87, 0.68-1.11). When further subclassified into botanical groups, those in the highest tertile of leguminosae (dried beans, string beans and peas, 0.80, 0.67-0.96), rosaceae (apples, peach, nectarines, plums, pears and strawberries, 0.60, 0.49-0.73), solanaceae (peppers and tomatoes, 0.82, 0.69-0.98) and umbelliferae (carrots, 0.73, 0.60-0.89) had decreased risk of head and neck cancer, but no significant associations were seen for 9 other botanical groups. Results from this large prospective observational study are consistent with previous case-control studies and support the hypothesis that total fruit and vegetable intake is associated with reduced risk of head and neck cancer.

Thank you to the BC Foundation for Prostate Disease for their generous support. www.BCPROSTATECANCER.org

Pancreatic Cancer

Calton, BA, R. Z. Stolzenberg-Solomon, S. C. Moore, et al. A Prospective Study of Physical Activity and the Risk of Pancreatic Cancer among Women (United States). Background: Several epidemiologic studies have examined the association between physical activity and pancreatic cancer risk; however, the results of these studies are not consistent. Methods: This study examined the associations of total, moderate, and vigorous physical activity to pancreatic cancer in a cohort of 33,530 U.S. women enrolled in the Breast Cancer Detection Demonstration Project (BCDDP). At baseline (1987-1989), information on physical activity over the past year was obtained using a self-administered questionnaire. Cox proportional hazards regression was used to estimate relative risks (RR) and 95% Confidence Interval (CI) for the associations of total, moderate, and vigorous physical activity to pancreatic cancer risk.
confidence intervals of pancreatic cancer risk. Results: 70 incident cases of pancreatic cancer were ascertained during 284,639 person years of follow-up between 1987-1989 and 1995-1998. After adjustment for age, body mass index, smoking status, history of diabetes, and height, increased physical activity was related to a suggestively decreased risk of pancreatic cancer. The RRs for increasing quartiles of total physical activity were 1.0, 0.80, 0.66, 0.52 (95% CI = 0.26, 1.05; ptrend = 0.05). This association was consistent across subgroups defined by body mass index and smoking status. We also observed statistically non-significant reductions in pancreatic cancer risk for women in the highest quartile of moderate (RR = 0.57; 95% CI = 0.26, 1.26) and highest quartile of vigorous physical activity (RR = 0.63; 95% CI = 0.31, 1.28) compared to their least active counterparts. Conclusion: Our study provides evidence for a role of physical activity in protecting against pancreatic cancer.


BACKGROUND: Recent studies of pancreatic cancer suggest a role for hyperinsulinemia in carcinogenesis. Because insulin is secreted in response to elevated blood glucose concentrations, dietary factors that increase these concentrations may be important in pancreatic carcinogenesis. OBJECTIVE: The objective was to examine prospectively the relation between pancreatic cancer risk and dietary glycaemic load (GL), overall glycaemic index (GI), and intake of total carbohydrates and mono- and disaccharides. DESIGN: The Netherlands Cohort Study consisted of 120,852 men and women who completed a baseline questionnaire in 1986. After 13.3 y of follow-up, 406 pancreatic cancer cases were detected, 66% of which were microscopically confirmed. A validated 150-item food-frequency questionnaire, completed at baseline, was used to calculate carbohydrate and mono- and disaccharide intakes and the GL and GI of the diet. RESULTS: Dietary GL, GI, or intake of carbohydrates and mono- and disaccharides were not associated with pancreatic cancer risk in this cohort. Also, the associations were not modified by sex. Our results did not change after the analysis was restricted to microscopically confirmed pancreatic cancer cases or after individuals who reported a history of diabetes at baseline were excluded from the analyses. CONCLUSIONS: Overall, our findings do not support the hypothesis that GL, GI, or intake of carbohydrates and mono- and disaccharides are positively associated with pancreatic cancer risk. This is in agreement with previous prospective studies that investigated the relation between GL and GI and pancreatic cancer risk.

**Antioxidants**

Saiko, P. A. Szakmary, W. Jaeger and T. Szekeres. Resveratrol and its Analogs: Defense Against Cancer, Coronary Disease and Neurodegenerative Maladies Or just a Fad? Mutat Res. 2008 Jan-Feb; 6581-2: 68-94. Resveratrol (3,5,4'-trihydroxy-trans-stilbene; RV), a dietary constituent found in grapes and wine, exerts a wide variety of pharmacological activities. Because the grape skins are not fermented in the production process of white wines, only red wines contain considerable amounts of this compound. RV is metabolized into sulfated and glucuronidated forms within approximately 15min of entering the bloodstream, and moderate consumption of red wine results in serum levels of RV that barely reach the micromolar concentrations. In contrast, its metabolites, which may be the active principle, circulate in serum for up to 9h. RV has been identified as an effective candidate for cancer chemoprevention due its ability to block each step in the carcinogenesis process by inhibiting several molecular targets such as kinases, cyclooxygenases, ribonucleotide reductase, and DNA polymerases. In addition, RV protects the cardiovascular system by a large number of mechanisms, including defense against ischemic-reperfusion injury, promotion of vasorelaxation, protection and maintenance of intact endothelium, anti-atherosclerotic properties, inhibition of low-density lipoprotein oxidation, and suppression of platelet aggregation, thereby strongly supporting its role in the prevention of coronary disease. Promising data within the use of RV have also been obtained regarding progressive neurodegenerative maladies such as Alzheimer's, Huntington's, and Parkinson's diseases. Because neurotoxicity is often related to mitochondrial dysfunction and may be ameliorated through the inclusion of metabolic modifiers and/or antioxidants, RV may provide an alternative (and early) intervention approach that could prevent further damage. RV induces a multitude of effects that depend on the cell type (e.g., NF-kappaB modulation in cancer cells vs. neural cells), cellular condition (normal, stressed, or malignant), and concentration (proliferative vs. growth arrest), and it can have opposing activities. RV affects whole pathways and sets of intracellular events rather than a single enzyme and, therefore, may be an effective therapy to restore homoeostasis. Nonetheless, the question of whether RV or its metabolites can accumulate to bioactive levels in target organs remains to be addressed.

**Nutrition**

Seeram NP. Berry fruits for cancer prevention: current status and future prospects. Journal of Agricultural & Food Chemistry. 2008 Feb 13;56(3):630-635. Overwhelming evidence suggests that edible small and soft-fleshed berry fruits may have beneficial effects against several types of human cancers. The anticancer potential of berries has been related, at least in part, to a multitude of bioactive phytochemicals that these colorful fruits contain, including polyphenols (flavonoids, proanthocyanidins, ellagitannins, gallotannins, phenolic acids, stilbenoids, lignans, and triterpenoids. Studies show that the anticancer effects of berry bioactives are partially mediated through their abilities to counteract, reduce, and also repair damage resulting from oxidative stress and inflammation. In addition, berry bioactives also regulate carcinogen and xenobiotic metabolizing enzymes, various transcription and growth factors, inflammatory cytokines, and subcellular signaling pathways of cancer cell proliferation, apoptosis, and tumor angiogenesis. Berry phytochemicals may also potentially sensitize tumor cells to chemotherapeutic agents by inhibiting pathways that lead to treatment resistance, and berry fruit consumption may provide protection from therapy-associated toxicities. Although a wide variety of berry fruits are consumed worldwide, this paper focuses on those commonly consumed in North America, namely, blackberries, black raspberries, blueberries, cranberries, red raspberries and strawberries. In addition, a large body of studies on singly purified berry bioactives is available, but this paper focuses on studies of "whole berries" per se, that is, as berry extracts and purified fractions, juices, and freeze-dried powders. Potential mechanisms of anticancer action and bioavailability of berry phenolics, as well as gaps in knowledge and recommendations for future berry research, are also briefly discussed.

**Vitamin D/Sunlight**

Bischoff-Ferrari, HA Optimal Serum 25-Hydroxyvitamin D Levels for Multiple Health Outcomes Advances in Experimental Medicine & Biology. 2008 62455-71. Recent evidence suggests that higher vitamin D intakes beyond current recommendations may be associated with better health outcomes. In this chapter, evidence is summarized from different studies that evaluate threshold levels for serum 25(OH)D levels in relation to bone mineral density (BMD), lower extremity function, dental health, risk of falls, admission to nursing home, fractures, cancer prevention and incident hypertension. For all endpoints, the most advantageous serum levels for 25(OH)D appeared to be at least 75 nmol/l (30 ng/ml) and for cancer prevention, desirable 25(OH)D levels are between 90-120 nmol/l (36-48 ng/ml). An
intake of no less than 1000 IU (25 mcg) of vitamin D3 (cholecalciferol) per day for all adults may bring at least 50% of the population up to 75 nmol/l. Thus, higher doses of vitamin D are needed to bring most individuals into the desired range. While estimates suggest that 2000 IU vitamin D3 per day may successfully and safely achieve this goal, the implications of 2000 IU or higher doses for the total adult population need to be addressed in future studies.


Vitamin D is the sunshine vitamin for good reason. During exposure to sunlight, the ultraviolet B photons enter the skin and photosynthesize 7-dehydrocholesterol to previtamin D3 which in turn is isomerized by the body's temperature to vitamin D3. Most humans have depended on sun for their vitamin D requirement. Skin pigment, sunscreen use, aging, time of day, season and latitude dramatically affect previtamin D3 synthesis. Vitamin D deficiency was thought to have been conquered, but it is now recognized that more than 50% of the world's population is at risk for vitamin D deficiency. This deficiency is in part due to the inadequate fortification of foods with vitamin D and the misconception that a healthy diet contains an adequate amount of vitamin D. Vitamin D deficiency causes growth retardation and rickets in children and will precipitate and exacerbate osteopenia, osteoporosis and increase risk of fracture in adults. The vitamin D deficiency has been associated with other serious consequences including increased risk of common cancers, autoimmune diseases, infectious diseases and cardiovascular disease. There needs to be a renewed appreciation of the beneficial effect of moderate sunlight for providing all humans with their vitamin D requirement for health. [References: 93].


To get an optimal vitamin D supplement from the sun at a minimal risk of getting cutaneous malignant melanoma (CMM), the best time of sun exposure is noon. Thus, common health recommendations given by authorities in many countries, that sun exposure should be avoided for three to five hours around noon and postponed to the afternoon, may be wrong and may even promote CMM. The reasons for this are (1) The action spectrum for CMM is likely to be centered at longer wavelengths (UVA, ultraviolet A, 320-400 nm) than that of vitamin D generation (UVB, ultraviolet B, 280-320 nm). (2) Scattering of solar radiation on clear days is caused by small scattering elements, Rayleigh dominated and increases with decreasing wavelengths. A larger fraction of UVA than of UVB comes directly and unscattered from the sun. (3) The human body can be more realistically represented by a vertical cylinder than by a horizontal, planar surface, as done in almost all calculations in the literature. With the cylinder model, high UVA fluorescence rates last about twice as long after noon as high UVB fluorescence rates do. In view of this, short, nonerythemogenic fluence rates do. In view of this, short, nonerythemogenic exposures last about twice as long after noon as high UVB fluence rates do. In view of this, short, nonerythemogenic fluence rates do. In view of this, short, nonerythemogenic exposures around noon should be recommended rather than longer nonerythemogenic exposures in the afternoon. This would give a maximal yield of vitamin D at a minimal CMM risk.


Epidemiological and experimental studies suggest that derivatives of vitamin D may improve prognosis of a number of cancer types. Sun is our most important source of vitamin D. Seasonal variations and latitudinal gradients of calcidiol (the marker of vitamin D status) have been reported. We wanted to investigate if season and latitude play any role for survival from seven different cancer types in Norway. Seasonal and geographical variations of vitamin D were estimated by calculations and were compared with clinical data.

For the survival analyses, 249373 cancer patients were followed for three years after diagnosis and the risk of death was analyzed separately for summer- and winter diagnosis, as well as for two geographical regions with different UV exposures. We found a 15-25% better survival for patients diagnosed during summer and a slight beneficial effect for residents of the high UV region for some of the cancer forms investigated. Based on our results we suggest that calcidiol concentration at the time of cancer diagnosis is related to survival and discuss briefly ways to improve the vitamin D levels in the general population.


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