

ABSTRACTS

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Breast cancer/vitamin E

Does lack of tocopherols and tocotrienols put women at increased risk of breast cancer?

Breast cancer is the leading site of new cancers in women and the second leading cause (after lung cancer) of cancer mortality in women. Observational studies that have collected data for dietary exposure to alpha-tocopherol with or without the other related tocopherols and tocotrienols have suggested that vitamin E from dietary sources may provide women with modest protection from breast cancer. However, there is no evidence that vitamin E supplements confer any protection whatever against breast cancer. Observational studies that have assessed exposure to vitamin E by plasma or adipose tissue concentrations of alpha-tocopherol have failed to provide consistent support for the idea that alpha-tocopherol provides any protection against breast cancer. In addition, evidence from studies in experimental animals suggest that alpha-tocopherol supplementation alone has little effect on mammary tumors. In contrast, studies in breast cancer cells indicate that alpha-, gamma-, and delta-tocotrienol, and to a lesser extent delta-tocopherol, have potent antiproliferative and proapoptotic effects that would be expected to reduce risk of breast cancer. Many vegetable sources of alpha-tocopherol also contain other tocopherols or tocotrienols. Thus, it seems plausible that the modest protection from breast cancer associated with dietary vitamin E may be due to the effects of the other tocopherols and the tocotrienols in the diet. Additional studies will be required to determine whether this may be the case, and to identify the most active tocopherol/tocotrienol.

J Nutr Biochem 2002 Jan;13(1):2-20

Diet and the risk of breast cancer in a case-control study: does the threat of disease have an influence on recall bias?

It has been suggested that recall bias may explain the discrepant results between case-control and cohort studies on diet and the risk of breast cancer. Two control groups were used for this case-control study of 25 to 75-year-old breast cancer cases (n = 310). The first group consisted of population controls drawn from the Finnish National Population Register (n = 454). The second group consisted of women who were referred to the same examinations as were the cases because of clinical suspicion of breast disease but who were later diagnosed as healthy (referral controls; n = 506). Because the diagnosis was unknown at the time of interview, it was possible to assess by comparing the two control groups whether the self-reporting of diet changed under the threat of disease. Dietary habits were examined using a validated, self-administered food-frequency questionnaire. Premenopausal women misreported their consumption of liquid milk products, tea and sugar. Reporting bias was also associated with the intake of fat and vitamins. Postmenopausal women misreported consumption of milk products. When recall bias was taken into consideration, milk was associated with increased risk of premenopausal breast cancer, whereas high consumption of poultry or high intake of monounsaturated fatty acids, n-3 fatty acids, n-6 fatty acids and vitamin E were related to lower risk. The study suggested that oil, milk, cheese, coffee and beta-carotene may act as protective factors in postmenopausal women, whereas butter and cream may be risk factors for breast cancer. In summary, it is possible that some food items may be overreported or underreported under the threat of disease in health-conscious population. However, most of the results in this study were not modified by recall bias.

J Clin Epidemiol 1999 May;52(5):429-39

Interaction of family history of breast cancer and dietary antioxidants with breast cancer risk (New York, United States).

We sought to determine if specific dietary antioxidants may be particularly effective in reducing breast cancer risk for women reporting family history (FH) of breast cancer in a first-degree relative. Interviews regarding usual diet, health and family histories were conducted with 262 premenopausal and 371 postmenopausal women with incident, primary breast cancer from western New York (United States). These women were frequency-matched by age and county of residence with community controls. Among premenopausal women, there was a significant interaction between FH and alpha-tocopherol; alpha-tocopherol was associated with significantly decreased risk among FH+ women (adjusted fourth-quartile odds ratio [OR] = 0.01, 95 percent confidence interval [CI] = 0.0-0.3). This association was much weaker for FH- women [OR = 0.7, CI = 0.4-1.2]. For FH- women, a significant inverse association was observed between beta-carotene and premenopausal breast-cancer risk (OR = 0.4, CI = 0.3-0.5), but not for FH+ women (OR = 0.5, CI = 0.1-4.0). Similar relationships, although not as strong, were noted among postmenopausal women.

Although limited by small numbers, these results suggest that biologic mechanisms of tumorigenesis may differ in FH+ and FH- women, and that alpha-tocopherol may be a potential chemopreventive agent for women with a family history of breast cancer, particularly premenopausal women.

Cancer Causes Control 1995 Sep;6(5):407-15

Premenopausal breast cancer risk and intake of vegetables, fruits and related nutrients.

BACKGROUND: Given the international variations in breast cancer incidence rates and the changes in breast cancer incidence among migrant populations, it has been hypothesized that diet is a factor influencing risk of this disease. Many studies indicate that a diet high in vegetables and fruits may protect against breast cancer. **PURPOSE:** We conducted a case-control study of diet, including the intake of non-food supplements, and premenopausal breast cancer risk. We evaluated in detail usual intake of vegetables and fruits (each measured as the total reported grams consumed for all queried vegetables and fruit), vitamins C and E, folic acid, individual carotenoids and dietary fiber with its components. **METHODS:** Case patients (n=297) were identified through pathology records from hospitals in Erie and Niagara counties in western New York. They consisted of premenopausal women 40 years of age or older who were diagnosed with breast cancer from November 1986 through April 1991. Control subjects (n=311), frequency-matched to case patients on the basis of age and county of residence, were randomly selected from New York State Department of Motor Vehicles records. In-person interviews included detailed reports of usual diet in the period 2 years before the interview. Unconditional logistic regression was used to estimate odds ratios (ORs) and 95% confidence intervals (CIs). **RESULTS:** There was a reduction in risk associated with high intake of several nutrients. With the lowest quartile of intake as the referent, adjusted ORs for the highest quartile of intake for specific nutrients were as follows: vitamin C (OR=0.53; 95% CI=0.33-0.86), alpha-tocopherol (OR=0.55; 95% CI=0.34-0.88), folic acid (OR=0.50; 95% CI=0.31-0.82), alpha-carotene (OR=0.67; 95% CI=0.42-1.08) and beta-carotene (OR=0.46; 95% CI=0.28-0.74), lutein + zeaxanthin (OR=0.47; 95% CI=0.28-0.77), and dietary fiber from vegetables and fruits (OR=0.48; 95% CI=0.30-0.78). No association with risk was found for beta-cryptoxanthin, lycopene, or grain fiber. Fruits were weakly associated with a reduction in risk (fourth quartile OR=0.67; 95% CI=0.42-1.09). No association was found between breast cancer risk and intake of vitamins C and E and folic acid taken as supplements. A strong inverse association between total vegetable intake and risk was observed (fourth quartile OR=0.46; 95% CI=0.28-0.74). This inverse association was found to be independent of vitamin C, alpha-tocopherol, folic acid, dietary fiber, and alpha-carotene. Adjusting for beta-carotene or lutein + zeaxanthin somewhat attenuated the inverse association with vegetable intake. **CONCLUSIONS:** In this population, intake of vegetables appears to decrease premenopausal breast cancer risk. This effect may be related, in part, to beta-carotene and lutein + zeaxanthin in vegetables. It appears, however, that, of the nutrients and food components examined, no single dietary factor explains the effect. Evaluated components found together in vegetables may have a synergistic effect on breast cancer risk; alternatively, other unmeasured factors in these foods may also influence risk.

J Natl Cancer Inst 1996 Mar 20;88(6):340-8

The role of fat, animal protein and some vitamin consumption in breast cancer: a case control study in southern France.

The role of the consumption of fat, animal protein and vitamins on breast-cancer risk was investigated in a hospital-based case-control study of 924 patients (409 cases and 515 controls) in Montpellier (France). A dietary history questionnaire, administered by interview, comprising 55 key food items as well as beverage consumption, and including food frequencies and portion sizes, was used to measure the intake of total fat and its constituents, animal protein, retinol, beta-carotene, vitamin E and alcohol consumption. The questionnaire also elicited information on relevant medical history and personal characteristics. All food items which showed significantly elevated odds ratio (high-fat cheese, desserts and chocolate and processed pork meat) in a multivariate analysis contained a high proportion of animal fat. This is reflected in the nutrient analysis, which showed a significant linear trend as well as an elevated odds ratio for the highest tertile of consumption of total fat [OR3 = 1.6 (1.1-2.2)], animal fat [OR3 = 1.6 (1.1-2.2)], saturated fat [OR3 = 1.9 (1.3-2.6)] and mono-unsaturated fat [OR3 = 1.7 (1.2-2.5)]. For post-menopausal women, there is a particularly strong association with saturated fat [OR3 = 3.3 (1.4-7.8)] in a multivariate analysis including all other significant nutrients. There is no evidence of an increase of risk with the intake of animal protein and no evidence of risk reduction with increased consumption of vegetables, beta-carotene or vitamin E. Along with some recent studies, our results give support to the hypothesis that dietary fat is a risk factor in breast carcinogenesis.

Int J Cancer 1991 Apr 22;48(1):1-9

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Efficacy of the various forms of vitamin E

Effects of tocotrienols on life span and protein carbonylation in *Caenorhabditis elegans*.

To assess the efficiency of tocotrienols against oxidative damage, we have demonstrated in a model-system nematode, *Caenorhabditis elegans*, that tocotrienol administration reduced the accumulation of protein carbonyl (a good indicator of oxidative damage during aging) and consequently extended the mean life span (LS), but not the maximum LS. Conversely, alpha-tocopherol acetate did not affect these parameters. As a way to evaluate the protective ability of tocotrienols against oxidative stress, the life spans of animals administered tocotrienols before or after exposure to ultraviolet B-induced oxidative stress were measured. Ultraviolet B irradiation shortened the mean LS of animals, whereas preadministration of tocotrienols recovered the mean LS to that of unirradiated animals. Interestingly, postadministration also extended the mean LS more than that of unirradiated animals, and administration through the LS conferred greater protection. Thus, the administration of tocotrienols to animals results in a reduction of oxidative stress risks. These data indicated that tocotrienols merit further investigation as possible agents for antiaging and oxidative stress prevention. In addition, they suggest that *C. elegans* will continue to provide provocative clues into the mechanisms of aging.

J Gerontol A Biol Sci Med Sci 2000 Jun;55(6):B280-5

Effects of vitamin E on lipid peroxidation in healthy persons.

CONTEXT: Oxidative stress may play a role in the development or exacerbation of many common diseases. However, results of prospective controlled trials of the effects of antioxidants such as vitamin E are contradictory. OBJECTIVE: To assess the effects of supplemental vitamin E on lipid peroxidation in vivo in healthy adults. DESIGN: Randomized, double-blind, placebo-controlled trial conducted March 1999 to June 2000. SETTING: A general clinical research center in a tertiary referral academic medical center. PARTICIPANTS: Thirty healthy men and women aged 18 to 60 years. INTERVENTIONS: Participants were randomly assigned to receive placebo or alpha-tocopherol dosages of 200, 400, 800, 1200 or 2000 IU/d for 8 weeks (n = 5 in each group), followed by an 8-week washout period. MAIN OUTCOME MEASURES: Three indices of lipid peroxidation, urinary 4-hydroxynonenal (4-HNE) and 2 isoprostanes, iPF(2alpha)-III and iPF(2alpha)-VI, measured by gas vs 168 (22.3) pg/mg of creatinine for subjects taking placebo; 165 (19.6) vs 234 (30.1) pg/mg for those taking 200 IU/d of vitamin E; and 195 (26.7) vs 213 (40.6) pg/mg for subjects taking 2000 IU/d. Corresponding iPF(2alpha)-VI levels were 1.43 (0.6) vs 1.62 (0.4) ng/mg of creatinine for subjects taking placebo; 1.64 (0.3) vs 1.24 (0.8) ng/mg for those taking 200 IU/d of vitamin E; and 1.83 (0.3) vs 1.94 (0.9) ng/mg for those taking 2000 IU/d. Baseline vs week 8 levels of 4-HNE were 0.5 (0.04) vs 0.4 (0.05) ng/mg of creatinine for subjects taking placebo; 0.4 (0.06) vs 0.5 (0.02) ng/mg with 200 IU/d of vitamin E; and 0.2 (0.02) vs 0.2 (0.1) ng/mg with 2000 IU/d. CONCLUSIONS: Our results question the rationale for vitamin E supplementation in healthy individuals. Specific quantitative indices of oxidative stress in vivo should be considered as entry criteria and for dose selection in clinical trials of antioxidant drugs and vitamins in human disease.

JAMA 2001 Mar 7;285(9):1178-82

Antioxidant effects of tocotrienols in patients with hyperlipidemia and carotid stenosis.

Antioxidants may have a role in the prevention of atherosclerosis. In the present trial, we investigated the antioxidant properties of Palm Vitee, a gamma-tocotrienol-, and alpha-tocopherol enriched fraction of palm oil, in patients with carotid atherosclerosis. Serum lipids, fatty acid peroxides, platelet aggregation and carotid artery stenosis were measured over an 18-month period in fifty patients with cerebrovascular disease. Change in stenosis was measured with duplex ultrasonography. Ultrasound scans were done at six months, twelve months, and yearly thereafter. Bilateral duplex ultrasonography revealed apparent carotid atherosclerotic regression in seven and progression in two of the 25 tocotrienol patients, while none of the control group exhibited regression and ten of 25 showed progression (P < 0.002). Serum thiobarbituric acid reactive substances, an ex vivo indicator of maximal platelet peroxidation, decreased in the treatment group from 1.08 +/- 0.70 to 0.80 +/- 0.55 microM/L (P < 0.05) after 12 mon, and in the placebo group, they increased nonsignificantly from 0.99 +/- 0.80 to 1.26 +/- 0.54 microM/L. Both tocotrienol and placebo groups displayed significantly attenuated collagen-induced platelet aggregation responses (P < 0.05) as compared with entry values. Serum total cholesterol, low density lipoprotein cholesterol, and triglyceride values remained unchanged in both groups, as did the plasma high density lipoprotein cholesterol values. These findings suggest that antioxidants, such as tocotrienols, may influence the course of carotid atherosclerosis.

Dietary antioxidant vitamins and death from coronary heart disease in postmenopausal women.

BACKGROUND: The role of dietary antioxidant vitamins in preventing coronary heart disease has aroused considerable interest because of the knowledge that oxidative modification of low-density lipoprotein may promote atherosclerosis. **METHODS.** We studied 34,486 postmenopausal women with no cardiovascular disease who in early 1986 completed a questionnaire that assessed, among other factors, their intake of vitamins A, E and C from food sources and supplements. During approximately seven years of follow-up (ending December 31, 1992), 242 of the women died of coronary heart disease. **RESULTS.** In analyses adjusted for age and dietary energy intake, vitamin E consumption appeared to be inversely associated with the risk of death from coronary heart disease. This association was particularly striking in the subgroup of 21,809 women who did not consume vitamin supplements (relative risks from lowest to highest quintile of vitamin E intake, 1.0, 0.68, 0.71, 0.42 and 0.42; P for trend 0.008). After adjustment for possible confounding variables, this inverse association remained (relative risks from lowest to highest quintile, 1.0, 0.70, 0.76, 0.32 and 0.38; P for trend, 0.004). There was little evidence that the intake of vitamin E from supplements was associated with a decreased risk of death from coronary heart disease, but the effects of high-dose supplementation and the duration of supplement use could not be definitely addressed. Intake of vitamins A and C did not appear to be associated with the risk of death from coronary heart disease. **CONCLUSIONS.** These results suggest that in postmenopausal women the intake of vitamin E from food is inversely associated with the risk of death from coronary heart disease and that such women can lower their risk without using vitamin supplements. By contrast, the intake of vitamins A and C was not associated with lower risks of dying from coronary disease.

N Engl J Med 1996 May 2;334(18):1156-62

Apoptosis and cell-cycle arrest in human and murine tumor cells are initiated by isoprenoids.

Diverse classes of phytochemicals initiate biological responses that effectively lower cancer risk. One class of phytochemicals, broadly defined as pure and mixed isoprenoids, encompasses an estimated 22,000 individual components. A representative mixed isoprenoid, gamma-tocotrienol, suppresses the growth of murine B16(F10) melanoma cells, and with greater potency, the growth of human breast adenocarcinoma (MCF-7) and human leukemic (HL-60) cells. beta-Ionone, a pure isoprenoid, suppresses the growth of B16 cells and with greater potency, the growth of MCF-7, HL-60 and human colon adenocarcinoma (Caco-2) cells. Results obtained with diverse cell lines differing in ras and p53 status showed that the isoprenoid-mediated suppression of growth is independent of mutated ras and p53 functions. beta-Ionone suppressed the growth of human colon fibroblasts (CCD-18Co) but only when present at three-fold the concentration required to suppress the growth of Caco-2 cells. The isoprenoids initiated apoptosis and, concomitantly arrested cells in the G1 phase of the cell cycle. Both suppress 3-hydroxy-3-methylglutaryl CoA reductase activity. beta-Ionone and lovastatin interfered with the posttranslational processing of lamin B, an activity essential to assembly of daughter nuclei. This interference, we postulate, renders neosynthesized DNA available to the endonuclease activities leading to apoptotic cell death. Lovastatin-imposed mevalonate starvation suppressed the glycosylation and translocation of growth factor receptors to the cell surface. As a consequence, cells were arrested in the G1 phase of the cell cycle. This rationale may apply to the isoprenoid-mediated G1-phase arrest of tumor cells. The additive and potentially synergistic actions of these isoprenoids in the suppression of tumor cell proliferation and initiation of apoptosis coupled with the mass action of the diverse isoprenoid constituents of plant products may explain, in part, the impact of fruit, vegetable and grain consumption on cancer risk.

J Nutr 1999 Apr;129(4):804-13

Macular degeneration

Identification and quantitation of carotenoids and their metabolites in the tissues of the human eye.

There is increasing evidence that the macular pigment carotenoids, lutein and zeaxanthin, may play an important role in the prevention of age-related macular degeneration, cataract, and other blinding disorders. Although it is well known that the retina and lens are enriched in these carotenoids, relatively little is known about carotenoid levels in the uveal tract and in other ocular tissues. Also, the oxidative metabolism and physiological functions of the ocular carotenoids are not fully understood. Thus, we have set out to identify and quantify the complete spectrum of dietary carotenoids and their oxidative metabolites in a systematic manner in all tissues of the human eye in order to gain better insight into their ocular physiology. Human donor eyes were dissected, and carotenoid extracts from ocular tissues [retinal pigment epithelium/choroid (RPE/choroid), macula, peripheral retina, ciliary body, iris, lens, vitreous, cornea, and sclera] were analyzed by high-performance liquid chromatography (HPLC). Carotenoids were identified and quantified by comparing their chromatographic and spectral profiles with those of authentic standards. Nearly all ocular structures examined with the exception of vitreous, cornea, and sclera had quantifiable levels of dietary (3R,3'R,6'R)-lutein, zeaxanthin, their geometrical (E / Z) isomers, as well as their metabolites, (3R,3'S,6'R)-lutein (3'-epilutein) and 3-hydroxy-beta,epsilon-caroten-3'-one. In addition, human ciliary body revealed the presence of monohydroxycarotenoids and hydrocarbon carotenoids, while only the latter group was detected in human RPE/choroid. Uveal structures (iris, ciliary body, and RPE/choroid) account for approximately 50% of the eye's total carotenoids and approximately 30% of the lutein and zeaxanthin. In the iris, these

pigments are likely to play a role in filtering out phototoxic short-wavelength visible light, while they are more likely to act as antioxidants in the ciliary body. Both mechanisms, light screening and antioxidant, may be operative in the RPE/choroid in addition to a possible function of this tissue in the transport of dihydroxycarotenoids from the circulating blood to the retina. This report lends further support for the critical role of lutein, zeaxanthin, and other ocular carotenoids in protecting the eye from light-induced oxidative damage and aging.

Exp Eye Res 2001 Mar;72(3):215-23

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Influence of lutein supplementation on macular pigment, assessed with two objective techniques.

PURPOSE: Macular pigment (MP) may protect against age-related macular degeneration. This study was conducted to determine the extent of changes in the macular pigment density as a consequence of oral supplementation with lutein. A second purpose was to compare two objective measurement techniques. **METHODS:** In the first technique, reflectance maps were made with a scanning laser ophthalmoscope. Digital subtraction of log reflectance maps and comparison between the foveal area and a 14 degrees temporal site provided MP density estimates. In the second technique, spectral fundus reflectance of the fovea was measured with a fundus reflectometer and analyzed with a detailed optical model, to arrive at MP density values. Eight subjects participated in this study. They took 10 mg lutein per day for 12 weeks. Plasma lutein concentration was measured at 4-week intervals. **RESULTS:** After 4 weeks, mean blood level of lutein had increased from 0.18 to 0.90 microM. It stayed at this level throughout the intake period and declined to 0.28 microM 4 weeks after termination. Measurement of the density of MP showed a within-subject variation of 10% with MP maps and 17% with spectral reflectance analysis. MP density showed a mean linear 4-week increase of 5.3% ($P < 0.001$) and 4.1% ($P = 0.022$), respectively. **CONCLUSIONS:** Supplementation with lutein significantly increased the density of the MP. Analyzing reflectance maps with a scanning laser ophthalmoscope provided very reliable estimates of MP.

Invest Ophthalmol Vis Sci 2000 Oct;41(11):3322-6

Lutein and zeaxanthin concentrations in rod outer segment membranes from perifoveal and peripheral human retina.

PURPOSE: In addition to acting as an optical filter, macular (carotenoid) pigment has been hypothesized to function as an antioxidant in the human retina by inhibiting the peroxidation of long-chain polyunsaturated fatty acids. However, at its location of highest density in the inner (prereceptor) layers of the foveal retina, a specific requirement for antioxidant protection would not be predicted. The purpose of this study was to determine whether lutein and zeaxanthin, the major carotenoids comprising the macular pigment, are present in rod outer segment (ROS) membranes where the concentration of long-chain polyunsaturated fatty acids, and susceptibility to oxidation, is highest. **METHODS:** Retinas from human donor eyes were dissected to obtain two regions: an annular ring of 1.5- to 4-mm eccentricity representing the area centralis excluding the fovea (perifoveal retina) and the remaining retina outside this region (peripheral retina). ROS and residual (ROS-depleted) retinal membranes were isolated from these regions by differential centrifugation and their purity checked by polyacrylamide gel electrophoresis and fatty acid analysis. Lutein and zeaxanthin were analyzed by high-performance liquid chromatography and their concentrations expressed relative to membrane protein. Preparation of membranes and analysis of carotenoids were performed in parallel on bovine retinas for comparison to a nonprimate species. Carotenoid concentrations were also determined for retinal pigment epithelium harvested from human eyes. **RESULTS:** ROS membranes prepared from perifoveal and peripheral regions of human retina were found to be of high purity as indicated by the presence of a dense opsin band on protein gels. Fatty acid analysis of human ROS membranes showed a characteristic enrichment of docosahexaenoic acid relative to residual membranes. Membranes prepared from bovine retinas had protein profiles and fatty acid composition similar to those from human retinas. Carotenoid analysis showed that lutein and zeaxanthin were present in ROS and residual human retinal membranes. The combined concentration of lutein plus zeaxanthin was 70% higher in human ROS than in residual membranes. Lutein plus zeaxanthin in human ROS membranes was 2.7 times more concentrated in the perifoveal than the peripheral retinal region. Lutein and zeaxanthin were consistently detected in human retinal pigment epithelium at relatively low concentrations. **CONCLUSIONS:** The presence of lutein and zeaxanthin in human ROS membranes raises the possibility that they function as antioxidants in this cell compartment. The finding of a higher concentration of these carotenoids in ROS of the perifoveal retina lends support to their proposed protective role in age-related macular degeneration.

Invest Ophthalmol Vis Sci 2000 Apr;41(5):1200-9

The role of oxidative stress in the pathogenesis of age-related macular degeneration.

Age-related macular degeneration (AMD) is the leading cause of blind registration in the developed world, and yet its pathogenesis remains poorly understood. Oxidative stress, which refers to cellular damage caused by reactive oxygen intermediates (ROI), has been implicated in many disease processes, especially age-related disorders. ROIs include free radicals, hydrogen peroxide, and singlet oxygen, and they are often the byproducts of oxygen metabolism. The retina is particularly susceptible to oxidative stress because of its high consumption of oxygen, its high proportion of polyunsaturated fatty acids, and its exposure to visible light. In vitro studies have consistently shown that photochemical retinal injury is attributable to oxidative stress and that the antioxidant vitamins A, C, and E protect against this type of injury. Furthermore, there is strong evidence suggesting that lipofuscin is derived, at least in part, from oxidatively damaged photoreceptor outer segments and that it is itself a photoreactive substance. However, the

relationships between dietary and serum levels of the antioxidant vitamins and age-related macular disease are less clear, although a protective effect of high plasma concentrations of alpha-tocopherol has been convincingly demonstrated. Macular pigment is also believed to limit retinal oxidative damage by absorbing incoming blue light and/or quenching ROIs. Many putative risk-factors for AMD have been linked to a lack of macular pigment, including female gender, lens density, tobacco use, light iris color and reduced visual sensitivity. Moreover, the Eye Disease Case-Control Study found that high plasma levels of lutein and zeaxanthin were associated with reduced risk of neovascular AMD. The concept that AMD can be attributed to cumulative oxidative stress is enticing, but remains unproven. With a view to reducing oxidative damage, the effect of nutritional antioxidant supplements on the onset and natural course of age-related macular disease is currently being evaluated.

Surv Ophthalmol 2000 Sep-Oct;45(2):115-34

Protein oxidation and loss of protease activity may lead to cataract formation in the aged lens.

Over 95% of the dry mass of the eye lens consists of specialized proteins called crystallins. Aged lenses are subject to cataract formation, in which damage, cross-linking, and precipitation of crystallins contribute to a loss of lens clarity. Cataract is one of the major causes of blindness, and it is estimated that over 50,000,000 people suffer from this disability. Damage to lens crystallins appears to be largely attributable to the effects of UV radiation and/or various active oxygen species (oxygen radicals, $1O_2$, H_2O_2 , etc.). Photooxidative damage to lens crystallins is normally retarded by a series of antioxidant enzymes and compounds. Crystallins which experience mild oxidative damage are rapidly degraded by a system of lenticular proteases. However, extensive oxidation and cross-linking severely decrease proteolytic susceptibility of lens crystallins. Thus, in the young lens the combination of antioxidants and proteases serves to prevent crystallin damage and precipitation in cataract formation. The aged lens, however, exhibits diminished antioxidant capacity and decreased proteolytic capabilities. The loss of proteolytic activity may actually be partially attributable to oxidative damage which proteases (like any other protein) can sustain. We propose that the rate of crystallin damage increases as antioxidant capacity declines with age. The lower protease activity of aged lens cells may be insufficient to cope with such rates of crystallin damage, and denatured crystallins may begin to accumulate. As the concentration of oxidatively denatured crystallins rises, cross-linking reactions may produce insoluble aggregates which are refractive to protease digestion. Such a scheme could explain many events which are known to contribute to cataract formation, as well as several which have appeared to be unrelated.

Free Radic Biol Med 1987;3(6):371-7

Macular pigment optical density in a midwestern sample.

OBJECTIVE: To assess the distribution of the macular pigments (MPs) lutein (L) and zeaxanthin (Z) in a healthy sample more representative of the general population than past studies and to determine which dietary factors and personal characteristics might explain the large interindividual differences in the density of these MPs. **DESIGN:** Prevalence study in a self-selected population. **PARTICIPANTS:** Two hundred eighty healthy adult volunteers, consisting of 138 men and 142 women, between the ages of 18 and 50 years, recruited from the general population. **METHODS:** MP optical density was measured psychophysically at 460 nm by use of a 1 degree test field. Serum was analyzed for carotenoid and vitamin E content with reversed-phase high-performance liquid chromatography. Usual intakes of nutrients over the past year were determined by means of a food frequency questionnaire. **MAIN OUTCOME MEASURES:** MP optical density. **RESULTS:** Mean MP optical density measured 0.211 +/- 0.13, which is approximately 40% lower than the average reported in smaller, less representative studies. MP density was 44% lower in the bottom versus the top quintile of serum L and Z concentrations. Similarly, MP density was 33% lower in the bottom compared with the top quintile of L and Z intake. MP density was 19% lower in blue-grey-eyed subjects than in subjects with brown-black irises. When all variables were considered together in a general linear model of determinants of MP, statistically significant ($P < 0.05$) relationships were found between MP density and serum L and Z, dietary L and Z intake, fiber intake, and iris color. **CONCLUSIONS:** These data suggest that MP values in this healthy adult population are lower than in smaller select samples. Moreover, these data indicate that MP is related to serum L and Z, dietary L and Z intake, fiber intake, and iris color.

Ophthalmology 2001 Apr;108(4):730-7

The potential role of dietary xanthophylls in cataract and age-related macular degeneration.

The carotenoid xanthophylls, lutein and zeaxanthin, accumulate in the eye lens and macular region of the retina. Lutein and zeaxanthin concentrations in the macula are greater than those found in plasma and other tissues. A relationship between macular pigment optical density, a marker of lutein and zeaxanthin concentration in the macula, and lens optical density, an antecedent of cataractous changes, has been suggested. The xanthophylls may act to protect the eye from ultraviolet phototoxicity via quenching reactive oxygen species and/or other mechanisms. Some observational studies have shown that generous intakes of lutein and zeaxanthin, particularly from certain xanthophyll-rich foods like spinach, broccoli and eggs, are associated with a significant reduction in the risk for cataract (up to 20%) and for age-related macular degeneration (up to 40%). While the pathophysiology of cataract and age-related macular degeneration is complex and contains both environmental and genetic components, research studies suggest dietary factors including antioxidant vitamins and xanthophylls may contribute to a reduction in the risk of these

degenerative eye diseases. Further research is necessary to confirm these observations.

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Prostate Cancer

U.S. dietary exposures to heterocyclic amines.

Heterocyclic amines (HAs) formed in fried, broiled or grilled meats are potent mutagens that increase rates of colon, mammary, prostate and other cancers in bioassay rodents. Studies of how human dietary HA exposures may affect cancer risks have so far relied on fairly crudely defined HA-exposure categories. Recently, an integrated, quantitative approach to HA-exposure assessment (HAEA) was developed to estimate compound-specific intakes for particular individuals based on corresponding HA-concentration estimates that reflect their meat-type, intake-rate, cooking-method and meat-doneness preferences. This method was applied in the present study to U.S. national Continuing Survey of Food Intakes by Individuals (CSFII) data on meats consumed and cooking methods used by >25,000 people, after adjusting for underreported energy intake and conditional on meat-doneness preferences estimated from additional survey data. The U.S. population average lifetime time-weighted average of total HAs consumed was estimated to be approximately 9 ng/kg/day, with 2-amino-1-methyl-6-phenylimidazo[4,5-b]pyridine (PhIP) estimated to comprise about two thirds of this intake. Pan-fried meats were the largest source of HA in the diet and chicken the largest source of HAs among different meat types. Estimated total HA intakes by male vs. female children were generally similar, with those by (0- to 15-year-old) children approximately 25% greater than those by (16+-year-old) adults. Race-, age- and sex-specific mean HA intakes were estimated to be greatest for African American males, who were estimated to consume approximately 2- and approximately 3-fold more PhIP than white males at ages <16 and 30+ years, respectively, after considering a relatively greater preference for more well-done items among African Americans based on national survey data. This difference in PhIP intakes may at least partly explain why prostate cancer (PC) kills approximately 2-fold more African American than white men, in view of experimental data indicating that PhIP mutates prostate DNA and causes prostate tumors in rats.

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Indole-3-carbinol (I3C) induced cell growth inhibition, G1 cell cycle arrest and apoptosis in prostate cancer cells.

Prostate cancer is one of the most common cancers in men and it is the second leading cause of cancer related death in men in the United States. Recent dietary and epidemiological studies have suggested the benefit of dietary intake of fruits and vegetables in lowering the incidence of prostate cancer. A diet rich in fruits and vegetables provides phytochemicals, particularly indole-3-carbinol (I3C), which may be responsible for the prevention of many types of cancer, including hormone-related cancers such as prostate. Studies to elucidate the role and the molecular mechanism(s) of action of I3C in prostate cancer, however, have not been conducted. In the current study, we investigated whether I3C had any effect against prostate cancer cells and, if so, attempts were made to identify the potential molecular mechanism(s) by which I3C elicits its biological effects on prostate cancer cells. Here we report for the first time that I3C inhibits the growth of PC-3 prostate cancer cells. Induction of G1 cell cycle arrest was also observed in PC-3 cells treated with I3C, which may be due to the observed effects of I3C in the up-regulation of p21(WAF1) and p27(Kip1) CDK inhibitors, followed by their association with cyclin D1 and E and down-regulation of CDK6 protein kinase levels and activity. The induction of p21(WAF1) appears to be transcriptionally upregulated and independent of the p53 responsive element. In addition, I3C inhibited the hyperphosphorylation of the Retinoblastoma (Rb) protein in PC-3 cells. Induction of apoptosis was also observed in this cell line when treated with I3C, as measured by DNA laddering and poly (ADP-ribose) polymerase (PARP) cleavage. We also found an up-regulation of Bax, and down-regulation of Bcl-2 in I3C-treated cells. These effects may also be mediated by the down-regulation of NF-kappaB observed in I3C treated PC-3 cells. From these results, we conclude that I3C inhibits the growth of PC-3 prostate cancer cells by inducing G1 cell cycle arrest leading to apoptosis, and regulates the expression of apoptosis-related genes. These findings suggest that I3C may be an effective chemopreventive or therapeutic agent against prostate cancer.

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Fruit and vegetable intakes and prostate cancer risk.

BACKGROUND: There is extensive and consistent evidence that high fruit and vegetable intakes are associated with decreased risks of many cancers, but results for prostate cancer risk have been inconsistent. We studied the associations of fruit and vegetable intakes with prostate cancer risk in a population-based, case-control study of men under 65 years of age. **METHODS:** Case participants were 628 men from King County (Seattle area), WA, who were newly diagnosed with prostate cancer. Control participants were 602 men recruited from the same underlying population and frequency matched to case participants by age. Self-administered food-frequency questionnaires were used to assess diet over the 3- to 5-year period before diagnosis or recruitment.

Daily nutrient intakes were calculated by use of a nutrient database with recently updated analytic values for carotenoids. Odds ratios for prostate cancer risk associated with foods and nutrients were calculated by use of unconditional logistic regression. RESULTS: No associations were found between fruit intake and prostate cancer risk. The adjusted odds ratio (ORs) for the comparison of 28 or more servings of vegetables per week with fewer than 14 servings per week was 0.65 (95% confidence interval [CI] = 0.45-0.94), with a two-sided P for trend = .01. For cruciferous vegetable consumption, adjusted for covariates and total vegetable intake, the OR for comparison of three or more servings per week with less than one serving per week was 0.59 (95% CI = 0.39-0.90), with a two-sided P for trend = .02. The OR for daily intake of 2000 microg or more lutein plus zeaxanthin compared with an intake of less than 800 microg was 0.68 (95% CI = 0.45-1.00). CONCLUSION: These results suggest that high consumption of vegetables, particularly cruciferous vegetables, is associated with a reduced risk of prostate cancer.

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Mechanisms of anti-carcinogenesis by indole-3-carbinol. Studies of enzyme induction, electrophile-scavenging, and inhibition of aflatoxin B1 activation.

The induction of oxidation and conjugation enzymes, the scavenging of carcinogen electrophiles, and the inhibition of aflatoxin B1 (AFB1) activation were examined as possible mechanisms of anti-carcinogenesis by indole-3-carbinol (I3C). Liver microsomal 7-ethoxycoumarin O-deethylase and 7-ethoxyresorufin O-deethylase activities were not induced significantly in rainbow trout fed diets containing 500-2000 ppm I3C for 8 days compared to trout fed the control diet. Furthermore, no detectable changes in the specific contents of cytochrome P-450 isozymes LM2 and LM4b, as measured by Western-blotting and immunoquantitation, were found in liver microsomes following dietary I3C administration. Dietary I3C had no significant effect on liver microsomal uridine diphosphate-glucuronyl-transferase activity, measured using the substrates 1-naphthol and testosterone, or on cytosolic glutathione S-transferase activity, measured using the substrate styrene oxide. The ability of I3C or its acid reaction products (RXM; generated by the reaction of I3C with HCl) to act as scavengers for the direct alkylating agent AFB1-8,9-Cl2 was examined. Addition of I3C or RXM to in vitro incubations did not inhibit the covalent binding of AFB1-8,9-Cl2 to calf thymus DNA. Kinetic analyses of microsome-mediated binding of AFB1 to DNA in vitro indicated that RXM inhibited the metabolic activation of AFB1. RXM increased the apparent Km for the AFB1-DNA binding reaction without changing the associated Vmax; the apparent Km values at 0, 3.5, 35, and 350 microM RXM were 35, 38, 66 and 86 microM for trout liver microsomes. RXM also inhibited the activation of AFB1 by rat liver microsomes, but I3C was not an effective inhibitor against AFB1-DNA binding mediated by either rat or trout liver microsomes. The results of the present study indicate that inhibition of microsome-activated AFB1 binding to DNA by I3C products may be of significant importance in I3C inhibition of hepatocarcinogenesis in trout and other species. The inhibition of carcinogen activation by I3C is contrasted with the mechanism of anti-carcinogenesis by beta-naphthoflavone, which involves induction of xenobiotic metabolizing enzymes.

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A prospective study of dietary fat and risk of prostate cancer.

BACKGROUND: The strong correlation between national consumption of fat and national rate of mortality from prostate cancer has raised the hypothesis that dietary fat increases the risk of this malignancy. Case-control and cohort studies have not consistently supported this hypothesis. PURPOSE: We examined prospectively the relationship between prostate cancer and dietary fat, including specific fatty acids and dietary sources of fat. We examined the relationship of fat consumption to the incidence of advanced prostate cancer (stages C, D or fatal cases) and to the total incidence of prostate cancer. METHODS: We used data from the Health Professionals Follow-up Study, which is a prospective cohort of 51529 U.S. men, aged 40 through 75, who completed a validated food-frequency questionnaire in 1986. We sent follow-up questionnaires to the entire cohort in 1988 and 1990 to document new cases of a variety of diseases and to update exposure information. As of January 31, 1990, 300 new cases of prostate cancer, including 126 advanced cases, were documented in 47855 participants initially free of diagnosed cancer. The Mantel-Haenszel summary estimator was used to adjust for age and other potentially confounding variables. Multiple logistic regression was used to estimate relative risks (RRs) when controlling simultaneously for more than two covariates. RESULTS: Total fat consumption was directly related to risk of advanced prostate cancer (age- and energy-adjusted RR = 1.79, with 95% confidence interval [CI] = 1.04-3.07, for high versus low quintile of intake; P [trend] = .06). This association was due primarily to animal fat (RR = 1.63; 95% CI = 0.95-2.78; P [trend] = .08), but not vegetable fat. Red meat represented the food group with the strongest positive association with advanced cancer (RR = 2.64; 95% CI = 1.21-5.77; P = .02). Fat from dairy products (with the exception of butter) or fish was unrelated to risk. Saturated fat, monounsaturated fat, and alpha-linolenic acid, but not linoleic acid, were associated with advanced prostate cancer risk; only the association with alpha-linolenic acid persisted when saturated fat, monounsaturated fat, linoleic acid, and alpha-linolenic acid were modeled simultaneously (multivariate RR = 3.43; 95% CI = 1.67-7.04; P [trend] = .002). CONCLUSION: The results support the hypothesis that animal fat, especially fat from red meat, is associated with an elevated risk of advanced prostate cancer. IMPLICATIONS: These findings support recommendations to lower intake of meat to reduce the risk of prostate cancer. The potential roles of carcinogens formed in cooking animal fat and of alpha-linolenic acid in the progression of prostate cancer need to be explored.

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BACKGROUND: Large international variations in rates of prostate cancer incidence and mortality suggest that environmental factors have a strong influence on the development of this disease. The purpose of this study was to identify predictive variables for prostate cancer mortality in data from 59 countries. **METHODS:** Data on prostate cancer mortality, food consumption, tobacco use, socioeconomic factors, reproductive factors, and health indicators were obtained from United Nations sources. Linear regression models were fit to these data. The influence of each variable fit in the regression models was assessed by multiplying the regression coefficient b by the 75th (X_{75}) and 25th (X_{25}) percentile values of the variable. The difference, $bX_{75} - bX_{25}$, is the estimated effect of the variable across its interquartile range on mortality rates measured as deaths per 100000 males aged 45 to 74 years. Reported P values are two-sided. **RESULTS:** Prostate cancer mortality was inversely associated with estimated consumption of cereals ($bX_{75} - bX_{25} = -7.31$ deaths; $P = .001$), nuts and oilseeds ($bX_{75} - bX_{25} = -1.72$ deaths; $P = .003$), and fish ($bX_{75} - bX_{25} = -1.47$ deaths; $P = .001$). In the 42 countries for which we had appropriate data, soy products were found to be significantly protective ($P = .0001$), with an effect size per kilocalorie at least four times as large as that of any other dietary factor. Besides variables related to diet, we observed an association between prostate cancer mortality rates and a composite of other health-related, sanitation, and economic variables ($P = .003$). **CONCLUSIONS:** The specific food-related results from this study are consistent with previous information and support the current dietary guidelines and hypothesis that grains, cereals, and nuts are protective against prostate cancer. The findings also provide a rationale for future study of soy products in prostate cancer prevention trials.

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