

**DISEASE PREVENTION**

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## **Management 1997 of chronic obstructive pulmonary disease. Working Group of the Swiss Society of Pneumology.**

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Schweiz Med Wochenschr (Switzerland) May 3 1997, 127 (18) p766-82

COPD is a disorder characterized by expiratory flow limitation that does not change markedly over periods of several months' observation. When the diagnosis is suspected, COPD patients should be submitted to full assessment and initiation of therapy. Initial assessment includes a complete history, a detailed physical examination, pulmonary function tests, a chest X-ray, and blood tests. Therapy of COPD aims at reducing symptoms, preventing exacerbations and preserving optimal lung function. Many COPD patients have a bronchospastic component and usually show some response to bronchodilator therapy. Anticholinergics, beta 2-agonists or theophylline are used as monotherapy or in combination. A subgroup of patients with COPD may benefit from oral long-term corticosteroid therapy. At prime diagnosis of COPD, a trial of oral steroid under optimal bronchodilator therapy is warranted in order to identify steroid responders early in the course of the disease. Stopping smoking is the most effective preventive measure and should be combined with complementary approaches such as eviction of environmental irritants, vaccines and prescription of antioxidants. Long-term oxygen therapy is beneficial in chronically hypoxemic patients. Respiratory rehabilitation uses a multidisciplinary approach aiming at decreasing dyspnea, increasing exercise tolerance and improving quality of life. Nocturnal home noninvasive mechanical ventilatory assistance can improve arterial blood gas tensions in patients with respiratory failure, but the long-term effect on survival is still under investigation. In selected patients, surgery (bullectomy, lung volume reduction, lung transplantation) may greatly improve pulmonary function. ( 29 Refs.)

## **Chemoprevention of colorectal tumors: role of lactulose and of other agents.**

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Scand J Gastroenterol Suppl (Norway) 1997, 222 p72-5

Chemoprevention can be defined as an attempt at cancer control in which the occurrence of the disease is prevented by the administration of one (or more) chemical compounds. Main problems in chemoprevention studies are the choice of a suitable drug, the choice of an appropriate intermediate or definitive end point, and the definition of the population which should be investigated. Main classes of chemopreventive agents include vitamins, non-steroid antiinflammatory drugs, minerals such as calcium or selenium, and other antioxidants such as N-acetylcysteine. Chemoprevention is particularly appealing in colorectal cancer, either because these lesions develop through a multistep process, or owing to the concept of "field carcinogenesis". Between 1985 and 1990 we carried out a controlled study in which antioxidant vitamins or lactulose were used in an attempt to prevent the recurrence of colorectal polyps after their endoscopic removal. Among the 209 patients who could be evaluated, polyps recurred in 5.7% of the individuals who were given vitamins (A, C and E), 14.7% of patients given lactulose and 35.9% of untreated controls ( $\chi^2 = 17.1$ ,  $P < 0.001$ ). The study suggested that either antioxidant vitamins or lactulose could be effective in reducing the recurrence rate of adenomatous polyps. In a subsequent on-going study, lower doses of the same vitamins were tested versus N-acetylcysteine (60a

40% reduction of the recurrence of polyps (versus controls) in individuals given N-acetylcysteine, while the effect of lower doses of vitamins was less appreciable. Definitive results of the study should be available by the end of 1998.

## **Biochemical basis of selenomethionine-mediated inhibition during 2-acetylaminofluorene-induced hepatocarcinogenesis in the rat.**

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Department of Pharmaceutical Technology, Jadavpur University, Calcutta, India.

Eur J Cancer Prev (England) Dec 1996, 5 (6) p455-63

Supplementation of selenium in the form of selenomethionine (8 ppm) in drinking water daily has been found to be highly effective in reducing cancer incidence in male Sprague-Dawley rats fed 2-acetylaminofluorene (2-AAF) (0.05%) in the basal diet daily for 16 weeks. Selenomethionine treatment before initiation, during initiation or during the selection/promotion phases of hepatocarcinogenesis has been found to be effective in elevating hepatic microsomal cytochrome b5, cytochrome P-450 contents, triphosphopyridine nucleotide-cytochrome c-reductase and cytosolic aryl hydrocarbon hydroxylase activities to a statistically significant level measured either in the hyperplastic nodules or in the non-nodular surrounding liver parenchyma compared with 2-AAF control rats. Moreover, selenomethionine treatment throughout the study also decreased the cytosolic 1-chloro-2,4-dinitrobenzene conjugated glutathione-S-transferase and microsomal UDP-glucuronyl transferase activities to a significant level when compared with 2-AAF control rats. Furthermore, direct correlations between hyperplastic nodules and non-nodular liver areas were observed with the hepatic selenium content and also with the rates and patterns of hepatic drug metabolism. Selenomethionine was also found to protect and improve the histopathological indices without any toe haematoxylin and eosin staining. Our results establish the fact that selenium is particularly protective in limiting the action of 2-AAF during the initiation phase of hepatocarcinogenesis.

## **Application of molecular epidemiology to lung cancer chemoprevention.**

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J Cell Biochem Suppl (United States) 1996, 25 p63-8

Molecular epidemiology has made great progress in detecting and documenting carcinogenic exposures and host susceptibility factors, in an effort to explain interindividual variation in disease. Interindividual differences in genetic and acquired factors including nutritional status. Elevated risk of lung cancer has been associated with polymorphisms of metabolic genes such as CYP1A1 and GSTM1. On the other hand, numerous studies have demonstrated that diets rich in fruits and vegetables are protective against cancer, and have correlated high levels of antioxidants in the blood with decreased risk. As a first step in identifying susceptible individuals, we have assessed the combined effect of genetic factors and nutritional status on DNA adducts in a population of healthy smokers. Plasma retinol, beta-carotene, alpha-tocopherol, and zeaxanthin were inversely correlated with DNA damage, especially in subjects lacking the "protective" GSTM1 gene. Research is ongoing using biomarkers to determine the effect of supplementation with antioxidants/vitamins on DNA damage, especially in population subsets with putative "at risk" genotypes. Information on mechanisms of interactions between exposure, micronutrients, and other susceptibility factors is important in the development of effective practical interventions. (33 Refs.)

## **Effects of dietary vitamin C and E supplementation on the copper mediated oxidation of HDL and on HDL mediated cholesterol efflux.**

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Atherosclerosis (Ireland) Nov 15 1996, 127 (1) p19-26

Copper mediated oxidative modification of high density lipoprotein (HDL) diminishes its capacity to promote cholesterol efflux from cells in culture. In the present study, HDL was isolated from eight subjects before and after a 10 day administration of the antioxidant vitamins C and E. After incubation HDL (1.25 mg protein/ml) with 10 microM copper for 0-4 h or with 0-20 microM copper for 4 h, thiobarbituric acid reactive substances (TBARS) production was significantly decreased following vitamin administration suggesting that the vitamins decreased the susceptibility of HDL to oxidation. However, two other assays of

lipoprotein oxidation, trinitrobenzene sulfonic acid reactivity and conjugated diene formation, did not show a consistent effect of vitamin administration. To study cholesterol efflux, J774 macrophages were labeled with <sup>3</sup>H cholesterol (0.1 microCi/ml, 50 micrograms/ml) and incubated with HDL or oxidized HDL (100 micrograms protein/ml) for 24 h. HDL isolated before vitamins and oxidized in vitro was 39% less effective in mediating efflux compared to unmodified HDL, while HDL isolated after vitamins and oxidized was 22% less effective (before vs. after vitamins,  $P < 0.015$ ). HDL oxidation determined by measuring TBARS production correlated with decreased cholesterol efflux ( $r = 0.37$ ,  $P < 0.050$ ). These data suggest that oxidation of HDL interferes with its role in reverse cholesterol transport and that antioxidant vitamins have a protective effect.

## **Antioxidant actions of beta-carotene in liposomal and microsomal membranes: role of carotenoid-membrane incorporation and alpha-tocopherol.**

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Arch Biochem Biophys (United States) Feb 15 1997, 338 (2) p244-50

beta-Carotene and other carotenoids are widely regarded as biological antioxidants. However, recent clinical trials indicate that beta-carotene supplements are not effective in disease prevention and raise questions about the biological significance of carotenoid antioxidant actions. To further explore this evaluated the antioxidant actions of beta-carotene in liposomal and biological membrane systems. In dilinoleoylphosphatidylcholine liposomes in which 0.35 mol % beta-carotene was incorporated into the bilayer during liposome preparation, the carotenoid inhibited lipid peroxidation initiated by 10 mM azobis[amidinopropane HCl] (AAPH). In carotenoid-free liposome suspensions to which the same amount of beta-carotene was added, no antioxidant effect was observed. Supplementation of rat liver microsomes with beta-carotene in vitro yielded microsomes containing 1.7 nmol beta-carotene mg<sup>-1</sup> and 0.16 nmol alpha-tocopherol mg<sup>-1</sup> microsomal protein. In beta-carotene supplemented microsomes incubated with 10 mM AAPH under an air atmosphere, lipid peroxidation did not occur until alpha-tocopherol was depleted by approximately 60%. beta-Carotene exerted no apparent antioxidant effect and was not significantly depleted in the incubations. Similar results were obtained when the incubation was done at 3.8 torr O<sub>2</sub>. In liver microsomes from Mongolian gerbils fed beta-carotene-supplemented diets, beta-carotene levels were 16-37% of alpha-tocopherol levels. The kinetics of AAPH-induced lipid peroxidation were no different in beta-carotene-supplemented microsomes than in microsomes from unsupplemented animals, although the kinetics of beta-carotene and alpha-tocopherol depletion were similar. The results indicate that beta-carotene is ineffective as an antioxidant when added to preformed lipid bilayer membranes and that alpha-tocopherol is a much more effective membrane antioxidant than beta-carotene, regardless of the method of carotenoid-membrane incorporation. These results support a reevaluation of the proposed antioxidant role for beta-carotene in biological membranes.

## **Comparative study of the effect of 21-aminosteroid and alpha-tocopherol on models of acute oxidative renal injury.**

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Free Radic Biol Med (United States) 1996, 21 (5) p691-7

21-Aminosteroids have incited a great deal of interest owing to its ability to inhibit lipid peroxidation and prevent organ damage. The main mechanism by which 21-aminosteroids idation is similar to the naturally occurring chain-breaking antioxidant alpha-tocopherols. Therefore, to determine whether 21-aminosteroids offer any advantage over alpha-tocopherol, we compared their effects on an in vivo and in vitro models of renal injury. 21-Aminosteroid (U-74006 F) at 3 mg/kg or alpha-tocopherol succinate at 10 mg/kg was administered intravenously once before bilateral renal ischemia and again before reperfusion. Acute administration 21-aminosteroid but not alpha-tocopherol, was attended by suppression of ischemia reperfusion-induced renal lipid peroxidation and injury. However, 4 weeks of dietary enrichment of rats with alpha-tocopherol (1000 IU/kg) was effective in suppressing these ischemia reperfusion-induced changes. In cell culture system, concurrent presence of 21-aminosteroid but not alpha-tocopherol abrogated H<sub>2</sub>O<sub>2</sub>-induced renal epithelial lipid peroxidation and injury. However, alpha-tocopherol was completely effective when cells were incubated with it for 14 h. Further, only the cells incubated with vitamin E for 14 h-but not for 1 or 3 h-had a significant increase in vitamin E content, which suggests that a delay in prompt cellular up take of vitamin E may explain its lack of acute effects. Thus, unlike alpha-tocopherol, 21-aminosteroid appears readily and completely available for its chain-breaking antioxidant activity both in vitro and in vivo. 21-Aminosteroids may, therefore, offer a therapeutic advantage over alpha-tocopherols in acute injury settings.

## **Possible prevention of postangioplasty restenosis by ascorbic acid.**

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Am J Cardiol (United States) Dec 1 1996, 78 (11) p1284-6

In this preliminary study to assess the possibility of using ascorbic acid to prevent post-percutaneous transluminal coronary angiography (PTCA) restenosis, the incidence of restenosis was significantly less in 50 patients receiving 500 mg/day of oral ascorbic acid than idant, appeared to be possibly effective in attenuating post-PTCA restenosis.

## **Effectiveness of antioxidants (vitamin C and E) with and without sunscreens as topical photoprotectants.**

Darr D; Dunston S; Faust H; Pinnell S  
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Acta Derm Venereol (Norway) Jul 1996, 76 (4) p264-8

Considerable interest has been recently generated concerning the use of natural compounds, anti-oxidants in particular, in photoprotection. Two of the best known anti-oxidants are vitamins C and E, both of which have been shown to be somewhat effective in different models of photodamage. Very little has been reported, however, on the effectiveness of a combination of the two (known to be biologically the more relevant situation); nor have there been detailed studies on the ability of these antioxidants to augment commercial sunscreen protection against UV damage. We report that (in swine skin) vitamin C is capable of additive protection against acute UVB damage (sunburn cell formation) when combined with a UVB sunscreen. A combination of both vitamins E and C provided very good protection from a UVB insult, the bulk of the protection attributable to vitamin E. However, vitamin C is significantly better than vitamin E at protecting against a UVA-mediated phototoxic insult in this animal model, while the combination is only slightly more effective than vitamin C alone. When vitamin C or a combination of vitamin C and E is formulated with a commercial UVA sunscreen (oxybenzone), an apparently greater than additive protection is noted against the phototoxic damage. These results confirm the utility of anti-oxidants as photoprotectants but suggest the importance of combining the compounds with known sunscreens to maximize photoprotection.

## **Curcumin protects against 4-hydroxy-2-trans-nonenal-induced cataract formation in rat lenses.**

Awasthi S; Srivatava SK; Piper JT; Singhal SS; Chaubey M; Awasthi YC  
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Am J Clin Nutr (United States) Nov 1996, 64 (5) p761-6

Age-related cataractogenesis is a significant health problem worldwide. Oxidative stress has been suggested to be a common underlying mechanism of cataractogenesis, and augmentation of the antioxidant defenses of the ocular lens has been shown to prevent or delay cataractogenesis. The present studies were designed to test the efficacy of curcumin, an antioxidant present in the commonly used spice turmeric, in preventing cataractogenesis in an in vitro rat model. Rats were maintained on an AIN-76 diet (ICN Pharmaceuticals Inc, Cleveland) for 2 wk, after which they were given a daily dose of corn oil alone or 75 mg curcumin/kg in corn oil for 14 d. Their lenses were removed and cultured for 72 h in vitro in the presence or absence of 100  $\mu$ mol 4-hydroxy-2-nonenal (4-HNE)/L, a highly electrophilic product of lipid peroxidation. The results of these studies showed that 4-HNE caused opacifications of cultured lenses as indicated by the measurements of transmitted light intensity using digital image analysis. However, the lenses from curcumin-treated rats were much more resistant to 4-HNE-induced opacification than were lenses from control animals. Curcumin treatment caused a significant induction of the glutathione S-transferase (GST) isozyme rGST8-8 in rat lens epithelium. Because rGST8-8 utilizes 4-HNE as a preferred substrate, we suggest that the protective effect of curcumin may be mediated through the induction of this GST isozyme. These studies suggest thaumin may be an effective protective agent against cataractogenesis induced by lipid peroxidation.

## **Prevention of asthma.**

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Environmental factors which have changed in the last decade or so appear to be largely responsible for the increase in the prevalence of asthma in affluent countries. It should, therefore, be possible to design interventions to reverse these recent trends and reduce the incidence of asthma. Primary preventive strategies have the potential not only to reduce acquisition of sensitization to common allergens and the risk that symptoms will develop subsequently, but also to reduce morbidity in those who already have persistent disease. There is accumulating epidemiological evidence that a dietary excess of sodium and omega-6 fatty acids, a dietary deficiency of antioxidant vitamins and omega-3 fatty acids, reduced rates of breastfeeding and exposure to allergens and environmental tobacco smoke are all involved in the aetiology of asthma. The modification of these factors has the potential to reduce the incidence and thus the prevalence of this disease. Environmental intervention should be particularly effective in children who have inherited or acquired characteristics which put them at high risk of developing asthma. With the evidence now available, it seems reasonable to assume that interventions which are based on our current knowledge of risk factors could achieve a 50% reduction in the prevalence of asthma in the next generation of children. (185 Refs.)

### **Role of oxidant stress in the adult respiratory distress syndrome: evaluation of a novel antioxidant strategy in a porcine model of endotoxin-induced acute lung injury.**

Gonzalez PK; Zhuang J; Doctrow SR; Malfroy B; Benson PF; Menconi MJ; Fink MP  
Department of Surgery, Beth Israel Hospital, Boston, Massachusetts 02215, USA.  
Shock (United States) 1996, 6 Suppl 1 pS23-6

/Reactive oxygen metabolites (ROMs) are thought to play a key role in the pathogenesis of the adult respiratory distress syndrome (ARDS). Accordingly, the use of ROM scavengers, such as N-acetyl-cysteine or dimethylthiourea, as therapeutic adjuncts to prevent oxidant-mediated damage to the lung have been evaluated extensively in animal models of ARDS. Results with this approach have been quite variable among studies. Another strategy that has been examined in animal models of ARDS is the administration of various enzymes, particularly superoxide dismutase (SOD) or catalase (CAT), in an effort to promote the conversion of ROMs to inactive metabolites. In theory, this strategy should be more effective than the use of ROM scavengers since a single molecule of a catalytically active molecule can neutralize a large number of molecules of a reactive species, whereas most scavengers act in a stoichiometric fashion to neutralize radicals on a mole-for-mole basis. This notion is supported by studies showing that prophylactic treatment with CAT provides impressive protection against acute lung injury induced in experimental animals by the administration of lipopolysaccharide (LPS). Results with SOD have been more variable. Recently, we have utilized a porcine model of LPS-induced ARDS to investigate the therapeutic potential of EUK-8, a novel, synthetic, low molecular salen-manganese complex that exhibits both SOD-like and CAT-like activities in vitro. Using both pre- and post-treatment designs, we have documented that treatment with EUK-8 significantly attenuates many of the features of LPS-induced acute lung injury, including arterial hypoxemia, pulmonary hypertension, decreased dynamic pulmonary compliance, and pulmonary edema. These findings support the view that salen-manganese complexes warrant further nt or prevention of sepsis-related ARDS in humans. (54 Refs.)

### **The new paradigm for coronary artery disease: altering risk factors, atherosclerotic plaques, and clinical prognosis.**

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Mid America Heart Institute, Kansas City, Missouri, USA.  
Mayo Clin Proc (United States) Oct 1996, 71 (10) p957-65

The old paradigm states that the greater the stenosis, the greater the risk of cardiac events. Revascularization procedures are the only effective approach to improving prognosis associated with coronary artery disease. In contrast, on the basis of the new paradigm, the nature of the plaque determines the risk of acute cardiovascular events. Dangerous plaques have a lipid-rich core with surrounding inflammation and a thin friable overlying fibrous cap, but they usually appear innocuous on angiography. Effective risk factor modification stabilizes the dangerous plaques and is associated with prompt improvement in endothelial dysfunction and a substantial decrease in the risk of acute cardiovascular events and death. (66 Refs.)

### **Synergism between N-acetylcysteine and doxorubicin in the prevention of tumorigenicity and metastasis in murine models.**

De Flora S; D'Agostini F; Masiello L; Giunciuglio D; Albini A  
Institute of Hygiene and Preventive Medicine, University of Genoa, Italy.  
Int J Cancer (United States) Sep 17 1996, 67 (6) p842-8

The thiol N-acetylcysteine (NAC) is a promising cancer chemopreventive agent which acts through a variety of mechanisms, including its nucleophilic and antioxidant properties. We have recently shown that NAC inhibits type-IV collagenase activity as well as invasion, tumor take and metastasis of malignant cells in mice. NAC is also known to attenuate the cardiotoxicity of the cytostatic drug doxorubicin (DOX, Adriamycin). The present study was designed to evaluate whether the combination of NAC and DOX treatments in mice injected with cancer cells could affect their tumorigenic and metastatic properties. Six separate experiments were carried out, using a total of 291 adult female mice. In experimental metastasis assays, in which B16-F10 melanoma cells were injected i.v. into (CD-1)BR nude mice, DOX significantly reduced the number of lung metastases when administered i.v. at a dose of 10 mg/kg body weight, 3 days after the i.v. injection of cancer cells. NAC inhibited lung metastases when added to the medium of cancer cells before their i.v. injection. The combined treatment with DOX and NAC, under various experimental conditions, was highly effective, showing a synergistic reduction in the number of metastases. In tumorigenicity and spontaneous metastasis assays, in which B16-BL6 melanoma cells were injected s.c. into the footpad of C57BL/6 mice, DOX decreased the number of lung metastases when given i.p. at 2 mg/kg body weight. Oral NAC exerted significant protective effects, and considerably prolonged survival of mice. The combined treatment with DOX and NAC again showed synergistic effects on the frequency and weight of primary tumors and local recurrences, and completely prevented the formation of lung metastases in the experiment in which these end-points were evaluated at fixed times. While injection of DOX 7 days after implantation of cancer cells failed to improve the cancer-protective effects of NAC, its injection after 1 day resulted in a synergism between DOX (given parenterally) and NAC (given with drinking water) in preventing tumorigenicity and metastases. The indications of these animal studies warrant further evaluation in clinical trials.

### **Prevention of dopamine-induced cell death by thiol antioxidants: possible implications for treatment of Parkinson's disease.**

Offen D; Ziv I; Sternin H; Melamed E; Hochman A  
Department of Neurology, Beilinson Medical Center, Petah-Tiqva, Israel.  
Exp Neurol (United States) Sep 1996, 141 (1) p32-9

We have recently shown that dopamine (DA) can trigger apoptosis, an active program of cellular self-destruction, in various neuronal cultures and proposed that inappropriate activation of apoptosis by DA and or its oxidation products may initiate nigral cell loss in Parkinson's disease (PD). Since DA toxicity may be mediated via generation of oxygen-free radical species, we examined whether DA-induced cell death in PC12 cells may be inhibited by antioxidants. We have found that the thiol containing compounds, reduced glutathione (GSH), N-acetyl-cysteine (NAC), and dithiothreitol (DTT) were markedly protective, while vitamins C and E had lesser or no effect. The thiol antioxidants and vitamin C but not vitamin E, prevented dopamine autooxidation and production of dopamine-melanin. Their protective effect has also manifested by inhibiting DA-induced apoptosis; DNA fragmentation was prevented as was shown histochemically by the in situ end-labeled DNA technique (TUNEL). Intracellular GSH and other thiols constitute an important natural defense against oxidative stress. We have found that depletion of cellular GSH by the addition of phoron, a substrate of glutathione transferase, and buthionine sulfoximine (BSO), an inhibitor of gamma-glutamyl transpeptidase, significantly enhanced DA toxicity. Cotreatment with NAC rescued the cells from the toxic effect of BSO+DA, and phoron+ DA, while addition of GSH provided only partial protection from BSO+DA toxicity. Our data indicate that the thiol family antioxidants, but not vitamins C and E, are highly effective in rescuing cells from DA-induced apoptosis. Further study of the mechanisms underlying the unique protective capacity of thiol antioxidants may lead to the development of new neuroprotective therapeutic strategies for PD.

### **Effect of flavonoids on the outcome of myocardial mitochondrial ischemia/reperfusion injury.**

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Department of Chemical Pathology, University of the Orange Free State, Bloemfontein, Republic of South Africa.  
Res Commun Mol Pathol Pharmacol (United States) Jan 1996, 91 (1) p65-75

There is evidence that flavonoid intake correlates inversely with coronary heart disease risk. Flavonoids are widely distributed in food and drinks and act as antioxidants and iron chelators. The aim of this study was to determine whether pycnogenol (a flavonoid extracted from the bark of *Pinus pinaster*) and catechin could minimise the myocardial mitochondrial damage due to ischemia/reperfusion. Using the rat heart model of ischemia/reperfusion we found that pycnogenol had no significant effect on the resultant damage, while catechin suppressed the observed elevation of low molecular weight iron during ischemia/reperfusion which

might explain the significantly reduced mitochondrial injury when using catechin in the perfusate. Our results suggest that some flavonoids might be effective in minimizing ischaemic/reperfusion injury and would require further detailed investigation.

## **[The dose-dependent effects of a combination of different classes of antioxidants exemplified by dibunol and beta-carotene]**

Minenkova EA; Barsel' VA; Pichugin VV; Gagarina AB; Evteeva NM; Paramonova Mlu; Maikova GG  
Izv Akad Nauk Ser Biol (Russia) Mar-Apr 1996, (2) p147-52

In order to enhance antioxidant protection of the organism in various pathological states, effective combinations of antioxidants have been developed that interact with various types of free radicals. On two experimental models,--acute alcohol intoxication and calcium chloride arrhythmia of rats, the prophylactic activity of antioxidant combinations was established for certain doses, rather than for monotherapy. The possibility of obtaining high protective effects at relatively low concentrations of the components in the complex preparation was shown. An increase of antioxidant concentration in the preparation could decrease its efficiency. The highest efficiency in the complex preparations, as compared with in each component taken separately, was observed in the case of calcium chloride arrhythmia when dibunol and beta-carotene were combined at concentrations of 10 mg/kg and in the case of acute alcohol intoxication (1 and 0.25 mg/kg, respectively). Enhanced efficiency of combined antioxidant therapy opens up the way to the production of new active complex preparations with minimum toxic side effects and complications.

## **Oxidative damage and defense.**

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Am J Clin Nutr (United States) Jun 1996, 63 (6) p985S-990S

Increased production of reactive oxygen species is a feature of most, if not all, human disease, including cardiovascular disease and cancer. Dietary antioxidants may guard against human diseases associated with free radical damage to cellular DNA, lipids, and proteins. Ascorbic acid is an effective water-soluble antioxidant, and epidemiologic studies suggest that increased ascorbate nutrition is associated with reduced risk of some degenerative diseases, especially cancer and eye cataracts. Population studies have also shown that high vitamin E intakes are associated with decreased risk of coronary heart disease, possibly as a result of inhibition of atherogenic forms of oxidized low-density lipoprotein. Recent data suggest that beta-carotene provides protection against lipid peroxidation in humans, as well as provitamin A activity. Yet, present data are not sufficient to quantitate micronutrient requirements needed to protect against oxidative damage. The antioxidant roles of many food constituents, such as polyphenols, have not been clarified. Most antioxidants can act as prooxidants under certain conditions, and more research is needed to determine the occurrence and importance of this in vivo. The few controlled intervention trials carried out so far have shown mixed results as to the potential of antioxidant supplements for reducing the incidence of chronic diseases. Definitive recommendations on antioxidant intakes for disease prevention must await evidence from controlled studies and intervention trials, some currently in progress. Overall, the present data suggest that protection against oxidative damage and related disease is best served by the variety of antioxidant substances found in fruit and vegetables. (43 Refs.)

## **Dietary fiber and the chemopreventive modelation of colon carcinogenesis.**

Alabaster O; Tang Z; Shivapurkar N  
Institute for Disease Prevention, George Washington University Medical Center, Washington DC, USA.  
Mutat Res (Netherlands) Feb 19 1996, 350 (1) p185-97

Comparative international epidemiological data indicate that the difference between the highest and lowest colon cancer incidence is approximately 10-fold. This suggests that the dominant causes of colon cancer are the dominant environmental cause being the typical diet of Western industrialized countries. Many epidemiological and experimental studies have suggested an important role for dietary fiber in the prevention of colon cancer. Using the Fischer-344 rat as the experimental model, data clearly demonstrate a strong protective effect of a diet that is low in fat, high in fiber and high in calcium (low-risk diet). Such a diet prevents the development of both preneoplastic aberrant crypt foci (ACF) and colon tumors. Recent experiments have also demonstrated a direct relationship between a ras point mutation in ACF at different stages of rat colon carcinogenesis, and a ras point mutation that is subsequently present in colon tumors. Using wheat bran as the model dietary fiber source, its effects were compared to the effects of psyllium, phytic acid, vitamin E, beta-carotene, folic acid, alone or in combination, for their ability to prevent colon cancer

in rats on high-risk Western-style diets. Our studies clearly demonstrated the ability of wheat bran to reduce ACF and colon tumors in rats that consumed high-fat, Western-style diets. Although phytic acid, which is a constituent of wheat bran, alone demonstrated strong cancer-preventive potential, our experiments provided evidence for the cancer-preventive effect of the crude fiber fraction that is independent of the effect of phytic acid. The synergistic combination of wheat bran with the soluble fiber psyllium led to enhanced protection; while the combination of wheat bran with beta-carotene showed only an additive effect. Beta-carotene appeared to show higher protection than wheat bran at an intake level that is nutritionally relevant to humans, suggesting the possibility of using beta-carotene to enhance the effects of dietary fiber in high-risk Western populations. Using ACF as an intermediate endpoint, it was also shown that vitamin E and beta-carotene appear to inhibit progression of ACF to colon cancer, while wheat bran and folic acid appeared to have weak cancer-preventive potential at this late stage of carcinogenesis. In conclusion, wheat bran alone, or in combination with psyllium, appears to have greater potential to inhibit earlier phases of carcinogenesis, while beta-carotene and vitamin E may also inhibit later stages of carcinogenesis. Despite considerable epidemiological and experimental evidence that increasing the fiber and lowering the fat content of the Western diet could substantially reduce the risk of cancer and heart disease, the real challenge is to find effective ways to educate and motivate people to overcome their intrinsic cultural resistance to such changes in their eating habits.

## **Selenium: a quest for better understanding.**

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Altern Ther Health Med (United States) Jul 1996, 2 (4) p59-62, 65-7

Selenium is an essential trace element in nutrition for the prevention of disease in humans. Epidemiological studies indicate an association between low nutritional selenium status and increased risks of cardiomyopathy, cardiovascular disease, and carcinogenesis in various sites of the body. The role of selenium supplementation in the prevention and treatment of AIDS-related pathology has been considered. Selenoproteins discovered in mammalian cells may account for the essentiality of selenium in the body's antioxidant defense; thyroid hormone function; immune system function, particularly the cellular immunity; formation of sperm; and functioning of the prostate gland. The seleno-organic compounds, primarily L-(+)-selenomethionine, generally are recognized as safe and effective forms of selenium supplementation. The nutritionally recommended dose of elemental selenium is estimated at 50 to 200 mg per day. There is, however, increased discussion of a pharmacological dose of selenium, significantly higher than the nutritional dose of the microelement, to treat active conditions. One way of increasing the tissue levels of selenium is to combine its ingestible form with a nutrientlability enhancing compound. (87 Refs.)

## **[The Mediterranean diet in the prevention of arteriosclerosis]**

Jossa F; Mancini M93  
Recenti Prog Med (Italy) Apr 1996, 87 (4) p175-81

It is well-known that mortality from coronary heart disease (CHD) is much lower in Italy and the Mediterranean countries than in Northern Europe and United States. Diet is one of the major environmental factors playing an important etiological role in different CHD incidence rates in these areas. The Seven Countries Study demonstrated that the average consumption of saturated fatty acids and cholesterol was directly related to CHD death rates, these being higher in Northern Europe and United States and lower in the Mediterranean countries and the Far East. Olive oil, particularly rich in oleic acid, could play a beneficial role in CHD prevention, as reported in the Italian Nine Communities Study carried out in the early 80s. Another multicenter study, the Intersalt Study, has clearly shown lower blood pressure in participants with lower intake of both sodium and alcohol and higher intake of potassium. Recent findings have also shown that two helping of fish per week and antioxidant vitamins, particularly vitamin E and beta carotene, are related to lower CHD incidence rate in the Mediterranean area compared to other countries. In conclusion, based on the reported findings, the Mediterranean diet represents an useful and effective mean for the prevention of CHD.

## **Change for coronary artery disease. What to tell patients.**

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Postgrad Med (United States) Feb 1996, 99 (2) p89-92, 95-6, 102-6

Heart-healthy living is a wise choice for anyone, but it assumes even greater importance in persons who have or are at risk for

coronary artery disease. Such patients need to know which measures have proved most effective in the prevention and treatment of the disease. This article reviews the data regarding risk factor reduction and offers recommendations for effective lifestyle modifications. (34 Refs.)

## **Population nutrient intake approaches dietary recommendations: 1991 to 1995 Framingham Nutrition Studies.**

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Boston University School of Public Health, MA 02118, USA.  
J Am Diet Assoc (United States) Jul 1997, 97 (7) p742-9

**OBJECTIVE:** To estimate population nutrient intake levels and to assess adherence to current dietary recommendations for health promotion and disease prevention.

**DESIGN:** Cross-sectional analysis of nutrient intake estimated from 3-day food records. Median macronutrient and micronutrient intake levels for men, women, and the total population are reported along with the proportions of men and women who achieved intakes compatible with nutrient goals defined by published guidelines.

**SETTING:** Adult participants (2,520: 1,375 women and 1,145 men) in the Framingham Offspring-Spouse Study surveyed between 1991 and 1995. Statistic Analyses were used to test for gender differences in the proportions of persons who had intakes that met nutrient guidelines.

**RESULTS:** Population intake levels of certain key nutrients, including total and saturated fat, appear to be approaching recommended levels. High proportions of the Framingham population (70% or more) met current recommendations for intakes of protein, polyunsaturated and monounsaturated fat, cholesterol, alcohol, vitamins C and B-12, and folacin. About half or fewer met guidelines for carbohydrate; total and saturated fat; fiber; beta carotene; vitamins A, E, and B-6; calcium; and sodium. Important gender differences in the proportion of those meeting nutrient guidelines were observed for 12 of the 18 nutrients examined, including carbohydrate; total, saturated, and monounsaturated fat; cholesterol; fiber; sodium; calcium; and several vitamins.

**CONCLUSIONS:** Although progress has been made toward achieving population adherence to preventive nutrition recommendations, large proportions of adults fall short of guidelines for some key nutrients. Differences in adherence rates between men and women suggest areas for gender-specific, targeted nutrition messages and behavioral interventions.

## **The antioxidant potential of the Mediterranean diet.**

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Eur J Cancer Prev (England) Mar 1997, 6 Suppl 1 pS15-9

The Mediterranean diet not only produces favourable effects on blood lipids but also protects against oxidative stress. Oxidative damage is thought to represent one of the mechanisms leading to chr. Many studies suggest that a link exists between fruit and vegetables in the diet or the amounts of plasma antioxidant vitamins (ascorbic acid, tocopherol and carotenoids) and risk of death from cancer or coronary heart diseases. Although a large emphasis has been given to different components of the diet, attention has recently shifted to the diet as a whole. The Mediterranean diet is able to modulate oxidative stress through complex mechanisms and not just the high antioxidant compound content. The preference for fresh fruit and vegetables in the Mediterranean diet will result in a higher consumption of raw foods, a lower production of cooking-related oxidants and a consequent decreased waste of nutritional and endogenous antioxidants. The high intake of antioxidant and fibre helps to scavenge even the small amount of oxidants or oxidized compounds.

## **[Atherogenic factors in the diet of the Costa Rican population, 1991]**

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Arch Latinoam Nutr (Venezuela) Mar 1996, 46 (1) p27-32

The present study analyzes the atherogenic factors of the diet of the Costa Rican population in various population and geographic groups. Data utilized was obtained from the Second National Survey on Apparent Food Consumption, 1991. Results found that on the national level consumption of fats, in relation to total caloric intake was higher than recommended levels. Likewise, the percentage of saturated fats exceed the established recommendations for prevention cardiovascular disease, and the intake of polyunsaturated fats was inferior to recommended levels. P/S ratio was 0.3, a value within the range considered to be atherogenic. Cholesterol intake is considered to be adequate. Cholesterol-Saturated-Index (CSI) of the majority of the diets studied was high, as reported in similar situation in other countries where cardiovascular disease is likewise the first cause of death. Dietary fiber was found to be in the lower levels of the AI values, while intake of vitamin A is deficient. The principal source of three types of fat in the diet, as well as vitamin E, was shortening made from palm oil, which in spite of not being a rich source of unsaturated fatty acid, the consumption of it is high. Egg is the main source of cholesterol and dietary fiber is primarily obtained from beans. In conclusion, the Costa Rican diet presents a nutritional imbalance which can be considered an atherogenic risk factor for cardiovascular disease.

## **Vitamin C intake and cardiovascular disease risk factors in persons with non-insulin-dependent diabetes mellitus. From the Insulin Resistance Atherosclerosis Study and the San Luis Valley Diabetes Study.**

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Prev Med (United States) May-Jun 1997, 26 (3) p277-83

**BACKGROUND:** Persons with non-insulin-dependent diabetes mellitus (NIDDM) are at increased risk for cardiovascular disease, partly due to concomitant worsening of traditional risk factors including dyslipidemia and hypertension. Based on evidence from small, controlled clinical trials, we hypothesized that increased intake of vitamin C would be associated with improved cardiovascular disease (CVD) risk factor status among community-dwelling persons with NIDDM.

**METHODS:** In separate but parallel statistical analyses, hypotheses were evaluated among persons with NIDDM confirmed by WHO criteria from the Insulin Resistance Atherosclerosis Study (IRAS, n = 520) and from the San Luis Valley Diabetes Study (SLVDS, n = 422). For IRAS, diet and vitamin supplement use was assessed by food frequency interview and for SLVDS, by 24-hr dietary recall interview.

**RESULTS:** Mean vitamin C intake (mg/day) was 275 for IRAS and 133 for SLVDS, including supplements. In cross-sectional regression models from each data set, vitamin C intake was not associated with systolic or diastolic blood pressure nor with HDL-C, LDL-C, or triglycerides (P values > 0.10; adjusted for calories, demographic and lifestyle variables, obesity, diabetes duration, and medications). In prospective analyses including 285 SLVDS participants, baseline vitamin C intake was not related to any of these CVD risk factors measured an average of 4 years later nor to change in CVD risk factor status during the follow-up period.

**CONCLUSIONS:** We conclude that, across a wide range of intake, vitamin C does not appear to be associated with improved CVD risk factor status among community-dwelling persons with diabetes.

## **The effect of dietary fat, antioxidants, and pro-oxidants on blood lipids, lipoproteins, and atherosclerosis.**

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J Am Diet Assoc (United States) Jul 1997, 97 (7 Suppl) pS31-41

A number of primary and secondary prevention trials, including angiographic studies, have indicated that a decrease in dietary saturated fat and cholesterol produces a decrease in the blood levels of cholesterol and low-density lipoprotein (LDL) cholesterol, leading to a decrease in coronary artery disease (CAD). Increasing evidence indicates that the oxidation of LDL in human beings is atherogenic. Of the three major antioxidants, vitamin E, beta carotene, and vitamin C, the evidence is strongest that vitamin E (at a minimum dose of 100 IU/day) has a strong and independent inverse association with CAD. Selenium and flavonoids also have antioxidant properties, but their association with CAD in human beings is equivocal. Two prooxidants, homocysteine and iron, have been found to be associated with CAD. Blood homocysteine levels can be lowered significantly by an increase in dietary folic acid. Clinical trials are needed to assess expeditiously the effect of antioxidants, particularly vitamin E, and of folic acid on CAD and

atherosclerosis. The substitution of monounsaturated fat for saturated fat lowers LDL and makes it less susceptible to oxidation without decreasing high-density lipoprotein (HDL) cholesterol. Studies in transgenic mice indicate that apolipoprotein A-I, the major protein of HDL, may inhibit the oxidation of LDL. Dietary trans fatty acids at the level consumed by many Americans can increase LDL cholesterol and may decrease HDL cholesterol. Individuals who have CAD or have family members who have premature CAD have delayed clearance of dietary fat, as judged by studies of postprandial triglyceride metabolism. The importance of decreasing dietary saturated fat and cholesterol is well established, but a number of other factors appear to influence the risk of CAD significantly and provide important areas for future investigation to improve prevention and treatment through better nutrition. (75 Refs.)

## **Reliability of a food frequency questionnaire to assess dietary antioxidant intake.**

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Ophthalmic Epidemiol (Netherlands) Mar 1997, 4 (1) p33-9

**OBJECTIVE:** Epidemiologic evidence of a role for antioxidants in the prevention of chronic disease has been inconclusive, in part due to the difficulty of measuring past diets of free-living populations. The purpose of the current study was to examine the reliability of a 19-item, self-administered, semiquantitative, food frequency questionnaire to assess intake of the major dietary antioxidants.

**METHODS:** Reliability was established by administering the food frequency questionnaire a second time by telephone. The subjects comprised 151 participants in the Melbourne Visual Impairment Project, a study of the distribution and determinants of eye disease in Melbourne residents aged 40 and over.

**RESULTS:** Spearman correlation coefficients ranged from 0.39 for spinach to 0.76 for yoghurt, and all were highly significant (all  $p = 0.001$ ). The reliability of the instrument was not influenced by gender, English speaking ability, or the number of days between the first and second administration of the questionnaire. uency questionnaire to be highly reliable. It should be useful for anyone involved in the study of the relationship of dietary antioxidant intake to health outcomes in large populations where limitations of time and money prohibit the collection of more detailed dietary intake information.

## **Oxidative stress hypothesis in Alzheimer's disease.**

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Free Radic Biol Med (United States) 1997, 23 (1) p134-47

The major hurdle in understanding Alzheimer's disease (AD) is a lack of knowledge about the etiology and pathogenesis of selective neuron death. In recent years, considerable data have accrued indicating that the brain in AD is under increased oxidative stress and this may have a role in the pathogenesis of neuron degeneration and death in this disorder. The direct evidence supporting increased oxidative stress in AD is: (1) increased brain Fe, Al, and Hg in AD, capable of stimulating free radical generation; (2) increased lipid peroxidation and decreased polyunsaturated fatty acids in the AD brain, and increased 4-hydroxynonenal, an aldehyde product of lipid peroxidation in AD ventricular fluid; (3) increased protein and DNA oxidation in the AD brain; (4) diminished energy metabolism and decreased cytochrome c oxidase in the brain in AD; (5) advanced glycation end products (AGE), malondialdehyde SOD-1 in neurofibrillary tangles and AGE, heme oxygenase-1, SOD-1 in senile plaques; and (6) studies showing that amyloid beta peptide is capable of generating free radicals. Supporting indirect evidence comes from a variety of in vitro studies showing that free radicals are capable of mediating neuron degeneration and death. Overall, these studies indicate that free radicals are possibly involved in the pathogenesis of neuron death in AD. Because tissue injury itself can induce reactive oxygen species (ROS) generation, it is not known whether this is a primary or secondary event. Even if free radical generation is secondary to other initiating causes, they are deleterious and part of a cascade of events that can lead to neuron death, suggesting that therapeutic efforts aimed at removal of ROS or prevention of their formation may be beneficial in AD. ( 155 Refs.)

## **Alcohol, ischemic heart disease, and the French paradox.**

Constant J

Many studies have shown either an inverse relation between alcohol intake and ischemic heart disease or a U-shaped curve in which the equivalent of two drinks per day of any kind of alcohol is associated with a decreased incidence of coronary disease compared with no drinks, while higher doses result in an increased risk of infarction and stroke. Although the cardioprotective effects of most alcoholic beverages are probably due to an elevation of high-density lipoprotein as well as the ability of alcohol to prevent platelet aggregation and increased fibrinolysis, there is an increased favorable effect of red wine. The unique cardioprotective properties of red wine reside in the action of flavonoids which are absent in white wine (with the exception of champagne) and sparse in beer (with the exception of dark beers). The best research flavonoids are resveritrol and quercetin, which confer antioxidant properties more potent than alpha-tocopherol. Grape juice has about half the amount of flavonoids by volume as does red wine. (51 Refs.)

### **Dietary antioxidants and Parkinson disease. The Rotterdam Study.**

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Arch Neurol (United States) Jun 1997, 54 (6) p762-5

**OBJECTIVE:** To investigate whether high dietary intake of antioxidants decreases the risk of Parkinson disease (PD).

**SETTING:** The community-based Rotterdam Study, the Netherlands.

**DESIGN:** The cross-sectional study formed part of a large community-based study in which all participants were individually screened for parkinsonism and were administered a semiquantitative food frequency questionnaire. The study population consisted of 5342 independently living individuals without dementia between 55 and 95 years of age, including 31 participants with PD (Hoehn-Yahr stages 1-3).

**RESULTS:** The odds ratio for PD was 0.5 (95% confidence interval [CI], 0.2-0.9) per 10-mg daily dietary vitamin E intake, 0.6 (95% CI, 0.3-1.3) per 1-mg beta carotene intake, 0.9 (95% CI, 0.4-1.9) per 100-mg vitamin C intake, and 0.9 (95% CI, 0.7-1.2) per 10-mg flavonoids intake, all adjusted for age, sex, smoking habits, and energy intake. The association with vitamin E intake was dose dependent (P for trend = .03). To assess whether the association was different in participants with more advanced disease, we excluded those with PD who had a Hoehn-Yahr stage of 2.5 or 3. This did not fundamentally alter the results.

**CONCLUSION:** Our data suggest that a high intake of dietary vitamin E may protect against the occurrence of PD.

### **Anti-oxidants and coronary heart disease [letter]**

Walker AR; Labadarios D  
S Afr Med J (South Africa) Jan 1997, 87 (1 Suppl) p103

No abstract.

### **Randomised trial of alpha-tocopherol and beta-carotene supplements on incidence of major coronary events in men with previous myocardial infraction**

Rapola JM; Virtamo J; Ripatti S; Huttunen JK; Albanes D; Taylor PR; Heinonen OP  
National Public Health Institute, Helsinki, Finland.  
Lancet (England) Jun 14 1997, 349 (9067) p1715-20

**BACKGROUND:** Epidemiological data suggest that the intake of antioxidants such as alpha-tocopherol (vitamin E) and beta-carotene has an inverse correlation with the incidence of coronary heart disease. The results from clinical trials of antioxidant supplementation in people with known coronary heart disease are inconclusive.

**METHODS:** We studied the frequency of major coronary events in 1862 men enrolled in the alpha-tocopherol beta-carotene Cancer Prevention Study (smokers aged between 50 and 69 years) who had a previous myocardial infarction. In this randomised, double-blind, placebo-controlled study, men had received dietary supplements of alpha-tocopherol (50 mg/day), beta-carotene (20 mg/day), both, or placebo. The median follow-up was 5.3 years. The endpoint of this substudy was the first major coronary event after randomisation. Analyses were by intention to treat.

**FINDINGS:** 424 major coronary events (non-fatal myocardial infarction and fatal coronary heart disease) occurred during follow-up. There were no significant differences in the number of major coronary events between any supplementation group and the placebo group (alpha-tocopherol 94/466; beta-carotene 113/461; alpha-tocopherol and beta-carotene 123/497; placebo 94/438 [log-rank test,  $p = 0.25$ ]). There were significantly more deaths from fatal coronary heart disease in the beta-carotene (74/461, multivariate-adjusted relative risk 1.75 [95% CI 1.16-2.64],  $p = 0.007$ ) and combined alpha-tocopherol and beta-carotene groups (67/497, relative risk 1.58 [1.05-2.40],  $p = 0.038$ ), but there was no significant increase in the alpha-tocopherol supplementation group (54/466, relative risk 1.33 [0.86-2.05],  $p = 0.20$ ).

**INTERPRETATION:** The proportion of major coronary events in men with a previous myocardial infarction who smoke was not decreased with either alpha-tocopherol or beta-carotene supplements. In fact, the risk of fatal coronary heart disease increased in the groups that received either beta-carotene or the combination of alpha-tocopherol and beta-carotene; there was a non-significant trend of increased deaths in the alpha-tocopherol group. We do not recommend the use of alpha-tocopherol or beta-carotene supplements in this group of patients.

## **Anti-oxidant therapy for ischaemic heart disease: where do we stand?**

Stephens N  
Department of Cardiology, Northwick Park Hospital, Harrow, UK.  
Lancet (England) Jun 14 1997, 349 (9067) p1710-1

No abstract.

## **Lower ischemic heart disease incidence and mortality among vitamin supplement users.**

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Can J Cardiol 1996 Oct;12(10):930-4

**OBJECTIVE:** This study assessed the relationship between vitamin supplement use and the occurrence of ischemic heart disease (IHD).

**DESIGN:** A cohort study was conducted between 1985 and 1991 in Quebec City. In 1985, 2313 men provided baseline information on vitamin supplement use and IHD risk factors. Incidence of IHD events was ascertained over the first five years of follow-up. Cox regression models were used to assess the relation between vitamin supplement use and occurrence of IHD events while controlling for confounders.

**MAIN RESULTS:** Vitamin supplement use was consistently associated with a lower incidence of IHD. The adjusted rate ratios and their 95% confidence intervals were: 0.31 (0.09-0.99) for IHD death, 0.53 (0.24-1.11) for MI, 0.76 (0.44-1.65) for angina and 0.73 (0.44-1.22) for a first IHD event. The associations were stronger for IHD death and myocardial infarction, two events assessed with high validity. The inverse association with IHD was more consistent for vitamin E than for any other vitamin.

**CONCLUSION:** This study suggests that the inverse association between vitamin supplement use and IHD is real. The causal nature of the association can only be demonstrated in the context of a randomised intervention trial such as the HOPE study. .

## **Association of serum vitamin levels, LDL susceptibility to oxidation, and autoantibodies against MDA-LDL with carotid atherosclerosis. A case-control study. The ARIC Study Investigators. Atherosclerosis Risk in Communities.**

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Arterioscler Thromb Vasc Biol (United States) Jun 1997, 17 (6) p1171-7

Oxidative modification of LDL is believed to be a crucial step in atherosclerosis. Thus, antioxidant vitamins may have a role in the prevention of coronary disease. We examined the cross-sectional association of serum vitamin levels, the susceptibility of LDL to hemin-induced oxidation (lag phase to conjugated diene formation), and the malondialdehyde-LDL (MDA-LDL) to native LDL radioacomatic early atherosclerosis. The participants in this observational study were 231 asymptomatic age-, sex-, race-, and field center-matched case-control pairs selected from the Atherosclerosis Risk in Communities (ARIC) study cohort on the basis of B-mode carotid artery ultrasonograms obtained from 1986 through 1989. Cases exceeded the 90th percentile of IMT, and control subjects were below the 75th percentile of IMT for all arterial segments. Biochemical analyses were performed on fasting frozen (-70 degrees C) serum specimens collected from 1990 through 1992. In conditional logistic regression adjusting for age, blood storage time, total cholesterol, and log-triglyceride concentrations, serum beta-cryptoxanthin and lutein plus zeaxanthin levels were inversely related to the extent of atherosclerosis (odds ratio [OR] per 1-SD increase: 0.75, 95% confidence interval [CI]: 0.59-0.94; and OR per 1-SD increase: 0.76, 95% CI: 0.59-0.95, respectively). Increases in alpha-carotene and lycopene were associated with nonsignificantly lower odds of being a case, whereas beta-carotene, retinol, and alpha-tocopherol were unrelated to IMT. Although not reaching statistical significance, the lag phase and autoantibodies against MDA-LDL were positively associated with asymptomatic atherosclerosis. After adjustment for potential confounders, only the inverse association of lutein plus zeaxanthin with asymptomatic atherosclerosis was maintained. This study supports a modest inverse association between circulating levels of some carotenoids, particularly lutein plus zeaxanthin, and carotid IMT. These findings suggest that these carotenoid compounds (regarded as biomarkers of fruit and vegetable intake) may be important in early stages of atherosclerosis.

## **Validity of diagnoses of major coronary events in national registers of hospital diagnoses and deaths in Finland.**

Rapola JM; Virtamo J; Korhonen P; Haapakoski J; Hartman AM; Edwards BK; Heinonen OP  
National Public Health Institute, Helsinki, Finland.  
Eur J Epidemiol (Netherlands) Feb 1997, 13 (2) p133-8

We validated diagnoses of acute myocardial infarction (AMI) and death from coronary heart disease (CHD) found in the Finnish National Hospital Discharge Register and the Register of Causes of Death from a sample of the 29,133 men participating in the Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study. The cases were traced to hospitals and institutes performing medico-legal death cause examinations and all relevant information was collected. The cardiac events were re-evaluated according to the diagnostic criteria of the Finnish contribution to the WHO MONICA project, i.e. the FINMONICA criteria. Altogether 408 cases of non-fatal AMI (n = 217) and death from CHD (n = 191) were reviewed. In the re-evaluation 94% of them (95% confidence interval 92-96%) were diagnosed as either definite (57%) or possible (37%) AMI. Non-fatal cases were more often classified definite AMI in the review, whereas fatal cases were more often classified possible AMI. Age or trial supplementation group did not affect classification, and no secular trend was observed. In conclusion, the diagnoses of AMI and death from CHD in the registers were highly predictive of a true major coronary event defined by strict criteria, thus their use in endpoint assessment in epidemiological studies and clinical trials is justified. ni

## **Vitamin C and cardiovascular disease: a systematic review.**

Ness AR; Powles JW; Khaw KT  
Institute of Public Health, University Forvie Site, Cambridge, UK.  
J Cardiovasc Risk (England) Dec 1996, 3 (6) p513-21

**BACKGROUND:** Laboratory studies suggest that antioxidants, such as Vitamin C, are important inhibitors of atherosclerotic lesions. Most epidemiological reviews have considered all antioxidants together. This review seeks to clarify the current state of knowledge specifically concerned with vitamin C.

**METHODS:** All ecological studies, case-control studies, prospective studies and trials in humans that examined the association between vitamin C intake or blood levels of vitamin C and cardiovascular disease were included. Relevant references were located search for articles published from 1966 to 1996, by an EMBASE search for articles published from 1980 to 1996, by searching personal bibliographies, books and reviews and from citations in located articles.

**RESULTS:** For coronary heart disease four of seven ecological studies, one of four case-control studies and three of 12 cohort

studies found a significant protective association with vitamin C intake or status. For strokes two of two ecological studies, none of one case-control study and two of seven cohort studies found a significant protective association. For total circulatory disease, two of three cohort studies reported a significant protective association.

**CONCLUSIONS:** The evidence, albeit limited, is consistent with vitamin C having protective effect against stroke whereas the evidence that vitamin C is protective against coronary heart disease is less consistent. The lack of an association for coronary heart disease could be explained in terms of there being a true lack of effect, dietary measurement error, a threshold effect, and effect of seasonal variations in intake, an interaction with other dietary constituents or a relatively short duration of follow-up. (63 Refs.)

### **Glutathione transferases catalyse the detoxication of oxidized metabolites (o-quinones) of catecholamines and may serve as an antioxidant system preventing degenerative cellular processes.**

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Biochem J (England) May 15 1997, 324 ( Pt 1) p25-8

o-Quinones are physiological oxidation products of catecholamines that contribute to redox cycling, toxicity and apoptosis, i.e. the neurodegenerative processes underlying Parkinson's disease and schizophrenia. The present study shows that the cyclized o-quinones aminochrome, dopachrome, adrenochrome and noradrenochrome, derived from dopamine, dopa, adrenaline and noradrenaline respectively, are efficiently conjugated with glutathione in the presence of human glutathione transferase (GST) M2-2. The oxidation product of adrenaline, adrenochrome, is less active as a substrate for GST M2-2, and more efficiently conjugated by GST M1-1. Evidence for expression of GST M2-2 in substantia nigra of human brain was obtained by identification of the corresponding PCR product in a cDNA library. Glutathione conjugation of these quinones is a detoxication reaction that prevents a role involving elimination of reactive chemical species originating from the oxidative metabolism of catecholamines. In particular, GST M2-2 has the capacity to provide protection relevant to the prevention of neurodegenerative diseases.

### **Chemopreventive effects of green and black tea on pulmonary and hepatic carcinogenesis.**

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Department of Pharmacology and Toxicology, Indiana University School of Medicine, Indianapolis 46202-5196, USA.  
Fundam Appl Toxicol (United States) Feb 1996, 29 (2) p244-50

The chemopreventive effects of decaffeinated green and black tea treatment on liver and lung tumorigenesis were examined in carcinogen-treated mice. Male C3H mice were given decaffeinated green or decaffeinated black tea in their drinking water prior to, during, and after treatment with diethylnitrosamine (50 micrograms/kg bw, i.p., once per week for 8 weeks). After 40 weeks of tea treatment, mice were sampled and examined for pulmonary and hepatic tumors. Mice treated with both DENA and tea displayed a significant decrease in the mean number of lung and liver tumors compared to DENA-only treated animals. Mice that received 0.63 or 1.25% green tea or 1.25% black tea exhibited a reduction in liver tumor numbers of 54, 50, and 63%, respectively from that multiplicity of lung adenomas. Mice receiving DENA and either 0.63 or 1.25% green tea or 1.25% black tea showed a decrease in the mean number of lung tumors of 40, 46, and 34%, respectively, from DENA-only treated mice. While a possible association between the chemopreventive activity of tea on lung tumor response and the concentration of (-) epigallocatechin gallate (EGCG) in the tea was suggested, no apparent relationship between EGCG concentration and liver tumor response was seen, however. These results show a dose-dependent chemoprevention of both lung and liver tumors by both black and green tea in diethylnitrosamine-treated C3H mice.

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