

Health Benefits of Nutritional Supplements

Selected Abstracts

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Updated: April 24, 2001

Forward

The importance of nutrition for human health has long been recognized. Prior to 1960, interest in this field largely focused on the etiology and prevention of acute nutrient deficiency diseases such as scurvy, rickets, and pellagra. Some 50 essential nutrients (vitamins, minerals, antioxidants, cofactors, essential amino acids, essential fatty acids) were identified, and recommended daily intakes for those essential nutrients (e.g. Recommended Dietary Allowances or RDAs) were developed. These recommendations, in turn, proved to be valuable in eradicating acute nutrient deficiency diseases.

During the past 20-30 years, attention has shifted to the role of diet and nutrition in the pathogenesis of chronic degenerative diseases. Heart disease, some cancers, osteoporosis, type II diabetes, and macular degeneration are all known to have dietary risk factors, many of which involve chronic nutrient deficiencies. Importantly, these associations have been much more difficult to study, in large measure because of the time frames involved. Chronic degenerative diseases develop over decades (lifetimes), and it is extremely challenging to conduct research programs for such extended periods. Nevertheless, advances in epidemiological and clinical research have helped us learn a great deal about the impacts (positive and negative) of diet and essential nutrient intakes on long-term health.

During the past decade, the scientific and healthcare communities have paid increasing attention to the role of nutritional supplements (as components of diet) in preventing and treating chronic disease. Hundreds of scientific studies have been conducted and published. These studies span a broad range of health issues. They have employed a wide variety of methodologies. And they have produced both positive and negative results. In some areas (e.g. the role of calcium and vitamin D supplements in slowing the progression of osteoporosis, and the role of folic acid supplements in preventing certain birth defects), results have been consistent, and benefits have been well accepted. In other areas (e.g. the role of antioxidant supplementation in preventing heart disease), results have been less consistent, and conclusions remain controversial. In any event, research on the health benefits of nutritional supplements is progressing, and evidence continues to mount that nutritional supplements offer a convenient and cost effective means for promoting health, over both the short- and long-terms.

The following is a collection of abstracts from about 100 scientific papers describing research on the health benefits of nutritional supplements. This collection is not exhaustive. Papers were selected on the basis of scientific merit and relevance to the field. The majority describes positive results, but in some, negative results are reported. Our objective in compiling this list was to provide readers with a good cross section of the scientific literature so that they could develop a sense for the current state of research in this field and draw their own conclusions concerning the role of supplementation in healthcare. References for many more papers are given in our bibliography entitled *Health Benefits of Nutritional Supplements: Selected Readings* .

For convenience, the abstracts have been sorted by health issue; namely Cardiovascular Health, Cancer Prevention, Strong Bones, Healthy Pregnancies/Healthy Babies, Sound Metabolism, Robust Immune Function, Acute Vision, and Other.

Cancer Prevention

Calcium supplements for the prevention of colorectal adenomas. Calcium Polyp Prevention Study Group.

Baron JA, Beach M, Mandel JS, van Stolk RU, Haile RW, Sandler RS, Rothstein R, Summers RW, Snover DC, Beck GJ, Bond JH, Greenberg ER. 1999. N Engl J Med 340(2):101-7

BACKGROUND AND METHODS: Laboratory, clinical, and epidemiologic evidence suggests that calcium may help prevent colorectal adenomas. We conducted a randomized, double-blind trial of the effect of supplementation with calcium carbonate on the recurrence of colorectal adenomas. We randomly assigned 930 subjects (mean age, 61 years; 72 percent men) with a recent history of colorectal adenomas to receive either calcium carbonate (3 g [1200 mg of elemental calcium] daily) or placebo, with follow-up colonoscopies one and four years after the qualifying examination. The primary end point was the proportion of subjects in whom at least one adenoma was detected after the first follow-up endoscopy but up to (and including) the second follow-up examination. Risk ratios for the recurrence of adenomas were adjusted for age, sex, lifetime number of adenomas before the study, clinical center, and length of the surveillance period. **RESULTS:** The subjects in the calcium group had a lower risk of recurrent adenomas. Among the 913 subjects who underwent at least one study colonoscopy, the adjusted risk ratio for any recurrence of adenoma with calcium as compared with placebo was 0.85 (95 percent confidence interval, 0.74 to 0.98; P=0.03). The main analysis was based on the 832 subjects (409 in the calcium group and 423 in the placebo group) who completed both follow-up examinations. At least one adenoma was diagnosed between the first and second follow-up endoscopies in 127 subjects in the calcium group (31 percent) and 159 subjects in the placebo group (38 percent); the adjusted risk ratio was 0.81 (95 percent confidence interval, 0.67 to 0.99; P=0.04). The adjusted ratio of the average number of adenomas in the calcium group to that in the placebo group was 0.76 (95 percent confidence interval, 0.60 to 0.96; P=0.02). The effect of calcium was independent of initial dietary fat and calcium intake. **CONCLUSIONS:** Calcium supplementation is associated with a significant - though moderate - reduction in the risk of recurrent colorectal adenomas.

Regression of oral leukoplakia with alpha-tocopherol: a community clinical oncology program chemoprevention study.

Benner SE, Winn RJ, Lippman SM, Poland J, Hansen KS, Luna MA, Hong WK. 1993.
J Natl Cancer Inst 85(1):44-7

BACKGROUND: Oral leukoplakia is an important model for developing chemoprevention approaches for lesions in the upper aerodigestive tract. These lesions most often result from exposure to carcinogens such as tobacco and alcohol and may precede development of invasive cancer. The potent antioxidant alpha-tocopherol (vitamin E) has prevented the development of cancers of the oral cavities in animal models. **PURPOSE:** The objectives of this study were to evaluate the toxicity and efficacy of alpha-tocopherol in patients with oral leukoplakia and to assess the feasibility of performing chemoprevention trials through the network of the Community Clinical Oncology Program (CCOP). **METHODS:** A single-arm phase II study using the nontoxic agent alpha-tocopherol to treat oral premalignant leukoplakia was performed at seven institutions affiliated with the CCOP through The University of Texas M. D. Anderson Cancer Center. Patients with symptomatic leukoplakia or dysplasia were treated orally with alpha-tocopherol (400 IU) twice daily for 24 weeks. Follow-up was performed at 6, 12, and 24 weeks after the start of treatment to assess toxicity and response, and serum alpha-tocopherol levels were determined at baseline and at 6 and 24 weeks. **RESULTS:** Of the 43 patients who have completed 24 weeks of treatment, 20 (46%) had clinical responses and nine (21%) had histologic responses. Mean serum alpha-tocopherol levels were 16.1 micrograms/mL at baseline and increased to 34.29 micrograms/mL after 24 weeks of treatment. Patient-recorded drug calendars, as well as serum drug levels, indicated excellent patient compliance; an average of 95% of the prescribed pills were taken. Treatment was extremely well tolerated; no grade 3 or 4 toxic effects were reported. **CONCLUSIONS:** Administration of alpha-tocopherol resulted in both clinical and histologic responses in premalignant leukoplakia lesions. The study also demonstrated that chemoprevention trials can be performed through the CCOP. The major problems were that a high percentage of patients were not assessable for response, some patients withdrew because expenses were not reimbursable, and there was limited participation within the CCOP network. These problems may reflect difficulties inherent in the implementation of multi-institutional chemoprevention trials. **IMPLICATIONS:** The efficacy of alpha-tocopherol alone and in combination with other chemopreventive agents for carcinogenesis in the upper aerodigestive tract should be explored in future trials.

Reduced risk of colon cancer with high intake of vitamin E: the Iowa Women's Health Study.

Bostick RM, Potter JD, McKenzie DR, Sellers TA, Kushi LH, Steinmetz KA, Folsom AR. 1993. *Cancer Res* 53(18):4230-7

Antioxidant micronutrients, including vitamin E, vitamin C, the carotenoids, and selenium, defend the body against free radicals and reactive oxygen molecules, suggesting a potential for these dietary components in cancer prevention. To investigate whether high intakes of antioxidant micronutrients protect against colon cancer in humans, we analyzed data from a prospective cohort study of 35,215 Iowa women aged 55-69 years and without a history of cancer who completed a dietary questionnaire in 1986. Through 1990, 212 incident cases of colon cancer were documented. Adjusted for age, total vitamin E intake was inversely associated with the risk of colon cancer (P for trend < 0.0001); the relative risk for the highest compared to the lowest quintile was 0.32 [95% confidence interval (95% CI) 0.19, 0.54]. Further adjustment for total energy intake and other risk factors in proportional hazards regression had little effect on these estimates. The association was not uniform across age groups: the multivariate relative risk of colon cancer for the highest compared to the lowest quintile of total vitamin E intake was 0.16 (95% CI 0.04, 0.70) for those 55-59 years old, 0.37 (95% CI 0.12, 1.16) for those 60-64 years old, and 0.93 (95% CI 0.27, 3.25) for those 65-69 years old. Multivariate-adjusted relative risks among women with higher total intakes of vitamins A and C and beta-carotene, and among users of selenium supplements, were not significantly different from 1.0. These prospective data provide evidence that a high intake of vitamin E may decrease the risk of colon cancer, especially in persons under 65 years of age.

Effects of selenium supplementation for cancer prevention in patients with carcinoma of the skin. A randomized controlled trial. Nutritional Prevention of Cancer Study Group.

Clark LC, Combs GF Jr, Turnbull BW, Slate EH, Chalker DK, Chow J, Davis LS, Glover RA, Graham GF, Gross EG, Krongrad A, Leshner JL Jr, Park HK, Sanders BB Jr, Smith CL, Taylor JR. 1996. JAMA 276(24):1957-63

OBJECTIVE: To determine whether a nutritional supplement of selenium will decrease the incidence of cancer. **DESIGN:** A multicenter, double-blind, randomized, placebo-controlled cancer prevention trial. **SETTING:** Seven dermatology clinics in the eastern United States. **PATIENTS:** A total of 1312 patients (mean age, 63 years; range, 18-80 years) with a history of basal cell or squamous cell carcinomas of the skin were randomized from 1983 through 1991. Patients were treated for a mean (SD) of 4.5 (2.8) years and had a total follow-up of 6.4 (2.0) years. **INTERVENTIONS:** Oral administration of 200 microg of selenium per day or placebo. **MAIN OUTCOME MEASURES:** The primary end points for the trial were the incidences of basal and squamous cell carcinomas of the skin. The secondary end points, established in 1990, were all-cause mortality and total cancer mortality, total cancer incidence, and the incidences of lung, prostate, and colorectal cancers. **RESULTS:** After a total follow-up of 8271 person-years, selenium treatment did not significantly affect the incidence of basal cell or squamous cell skin cancer. There were 377 new cases of basal cell skin cancer among patients in the selenium group and 350 cases among the control group (relative risk [RR], 1.10; 95% confidence interval [CI], 0.95-1.28), and 218 new squamous cell skin cancers in the selenium group and 190 cases among the controls (RR, 1.14; 95% CI, 0.93-1.39). Analysis of secondary end points revealed that, compared with controls, patients treated with selenium had a nonsignificant reduction in all-cause mortality (108 deaths in the selenium group and 129 deaths in the control group [RR; 0.83; 95% CI, 0.63-1.08]) and significant reductions in total cancer mortality (29 deaths in the selenium treatment group and 57 deaths in controls [RR, 0.50; 95% CI, 0.31-0.80]), total cancer incidence (77 cancers in the selenium group and 119 in controls [RR, 0.63; 95% CI, 0.47-0.85]), and incidences of lung, colorectal, and prostate cancers. Primarily because of the apparent reductions in total cancer mortality and total cancer incidence in the selenium group, the blinded phase of the trial was stopped early. No cases of selenium toxicity occurred. **CONCLUSIONS:** Selenium treatment did not protect against development of basal or squamous cell carcinomas of the skin. However, results from secondary end-point analyses support the hypothesis that supplemental selenium may reduce the incidence of, and mortality from, carcinomas of several sites. These effects of selenium require confirmation in an independent trial of appropriate design before new public health recommendations regarding selenium supplementation can be made.

Decreased incidence of prostate cancer with selenium supplementation: results of a double-blind cancer prevention trial.

Clark LC, Dalkin B, Krongrad A, Combs GF Jr, Turnbull BW, Slate EH, Witherington R, Herlong JH, Janosko E, Carpenter D, Borosso C, Falk S, Rounder J. 1998.
Br J Urol 81(5):730-4

OBJECTIVE: To test if supplemental dietary selenium is associated with changes in the incidence of prostate cancer. **PATIENTS AND METHOD:** A total of 974 men with a history of either a basal cell or squamous cell carcinoma were randomized to either a daily supplement of 200 microg of selenium or a placebo. Patients were treated for a mean of 4.5 years and followed for a mean of 6.5 years. **RESULTS:** Selenium treatment was associated with a significant (63%) reduction in the secondary endpoint of prostate cancer incidence during 1983-93. There were 13 prostate cancer cases in the selenium-treated group and 35 cases in the placebo group (relative risk, RR=0.37, P=0.002). Restricting the analysis to the 843 patients with initially normal levels of prostate-specific antigen (≤ 4 ng/mL), only four cases were diagnosed in the selenium-treated group and 16 cases were diagnosed in the placebo group after a 2 year treatment lag, (RR=0.26 P=0.009). There were significant health benefits also for the other secondary endpoints of total cancer mortality, and the incidence of total, lung and colorectal cancer. There was no significant change in incidence for the primary endpoints of basal and squamous cell carcinoma of the skin. In light of these results, the 'blinded' phase of this trial was stopped early. **CONCLUSIONS:** Although selenium shows no protective effects against the primary endpoint of squamous and basal cell carcinomas of the skin, the selenium-treated group had substantial reductions in the incidence of prostate cancer, and total cancer incidence and mortality that demand further evaluation in well-controlled prevention trials.

Vitamin supplement use and reduced risk of oral and pharyngeal cancer.

Gridley G, McLaughlin JK, Block G, Blot WJ, Gluch M, Fraumeni JF Jr. 1992.
Am J Epidemiol 135(10):1083-92

Use of vitamin and mineral supplements was assessed in a population-based case-control study of oral and pharyngeal cancer, conducted during 1984-1985 in four areas of the United States. There was no association with intake of multivitamin products, but users of supplements of individual vitamins, including vitamins A, B, C, and E, were at lower risk after controlling for the effects of tobacco, alcohol, and other risk factors for these cancers. After further adjustment for use of other supplements, vitamin E was the only supplement that remained associated with a significantly reduced cancer risk. The adjusted odds ratio of oral and pharyngeal cancer for "ever regularly used" vitamin E was 0.5 (95% confidence interval 0.4-0.6). To the authors' knowledge, this is the first epidemiologic study to show a reduced oral cancer risk with vitamin E use. Although it is not clear that the lower risk among consumers of vitamin E supplements is due to the vitamin per se, the findings are consistent with experimental evidence and should prompt further research on the role of vitamin E and other micronutrients as inhibitors of oral and pharyngeal cancer.

Vitamin and mineral supplement use is associated with reduced risk of prostate cancer.

Kristal AR, Stanford JL, Cohen JH, Wicklund K, Patterson RE. 1999.
Cancer Epidemiol Biomarkers Prev 8(10):887-92

This population-based, case-control study in King County, Washington examined supplement use in 697 incident prostate cancer cases (ages 40-64) identified from the Puget Sound Surveillance, Epidemiology and End Results program registry and 666 controls recruited from the same overall population using random-digit dialing sampling. Participants reported their frequency of use of three types of multivitamins and single supplements of vitamins A, C, and E, calcium, iron, and zinc over the 2 years before diagnosis. Logistic regression analyses controlled for age, race, education, family history of prostate cancer, body mass index, number of prostate-specific antigen tests in the previous 5 years, and dietary fat intake. Adjusted odds ratios (95% confidence limits) for the contrast of > or =7/week versus no use were as follows: multivitamins, 0.96 (0.73, 1.26); vitamin A, 0.59 (0.32, 1.06); vitamin C, 0.77 (0.57, 1.04); vitamin E, 0.76 (0.54, 1.08); calcium, 1.04 (0.61, 1.78); iron, 0.50 (0.13, 1.76); and zinc, 0.55 (0.30, 1.00). Odds ratios differed little when cases were stratified by stage of disease at diagnosis or by histopathological grade. There were significant dose-response effects for zinc and ordered dose-response trends for vitamins C and E. Overall, these results suggest that multivitamin use is not associated with prostate cancer risk, but use of individual supplements of zinc, vitamin C, and vitamin E may be protective. Further study is needed to investigate the direct role of these dietary supplements, as well as the role of lifestyle variables associated with supplement use, on prostate cancer risk.

Lack of effect of a low-fat, high-fiber diet on the recurrence of colorectal adenomas. Polyp Prevention Trial Study Group.

Schatzkin A, Lanza E, Corle D, Lance P, Iber F, Caan B, Shike M, Weissfeld J, Burt R, Cooper MR, Kikendall JW, Cahill J. 2000.
Polyp Prevention Trial Study Group. N Engl J Med 342(16):1149-55

BACKGROUND: We tested the hypothesis that dietary intervention can inhibit the development of recurrent colorectal adenomas, which are precursors of most large-bowel cancers. **METHODS:** We randomly assigned 2079 men and women who were 35 years of age or older and who had had one or more histologically confirmed colorectal adenomas removed within six months before randomization to one of two groups: an intervention group given intensive counseling and assigned to follow a diet that was low in fat (20 percent of total calories) and high in fiber (18 g of dietary fiber per 1000 kcal) and fruits and vegetables (3.5 servings per 1000 kcal), and a control group given a standard brochure on healthy eating and assigned to follow their usual diet. Subjects entered the study after undergoing complete colonoscopy and removal of adenomatous polyps; they remained in the study for approximately four years, undergoing colonoscopy one and four years after randomization. **RESULTS:** A total of 1905 of the randomized subjects (91.6 percent) completed the study. Of the 958 subjects in the intervention group and the 947 in the control group who completed the study, 39.7 percent and 39.5 percent, respectively, had at least one recurrent adenoma; the unadjusted risk ratio was 1.00 (95 percent confidence interval, 0.90 to 1.12). Among subjects with recurrent adenomas, the mean (+/-SE) number of such lesions was 1.85 +/- 0.08 in the intervention group and 1.84 +/- 0.07 in the control group. The rate of recurrence of large adenomas (with a maximal diameter of at least 1 cm) and advanced adenomas (defined as lesions that had a maximal diameter of at least 1 cm or at least 25 percent villous elements or evidence of high-grade dysplasia, including carcinoma) did not differ significantly between the two groups. **CONCLUSIONS:** Adopting a diet that is low in fat and high in fiber, fruits, and vegetables does not influence the risk of recurrence of colorectal adenomas.