

LE Magazine March 2001

ABSTRACTS

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Prostate cancer

Association between alpha-tocopherol, gamma-tocopherol, selenium, and subsequent prostate cancer.

BACKGROUND: Selenium and alpha-tocopherol, the major form of vitamin E in supplements, appear to have a protective effect against prostate cancer. However, little attention has been paid to the possible role of gamma-tocopherol, a major component of vitamin E in the U.S. diet and the second most common tocopherol in human serum. A nested case-control study was conducted to examine the associations of alpha-tocopherol, gamma-tocopherol, and selenium with incident prostate cancer. **METHODS:** In 1989, a total of 10 456 male residents of Washington County, MD, donated blood for a specimen bank. A total of 117 of 145 men who developed prostate cancer and 233 matched control subjects had toenail and plasma samples available for assays of selenium, alpha-tocopherol, and gamma-tocopherol. The association between the micronutrient concentrations and the development of prostate cancer was assessed by conditional logistic regression analysis. All statistical tests were two-sided. **RESULTS:** The risk of prostate cancer declined, but not linearly, with increasing concentrations of alpha-tocopherol (odds ratio (highest versus lowest fifth) = 0.65; 95% confidence interval = 0.32-1.32; P:(trend) =.28). For gamma-tocopherol, men in the highest fifth of the distribution had a fivefold reduction in the risk of developing prostate cancer than men in the lowest fifth (P:(trend) =.002). The association between selenium and prostate cancer risk was in the protective direction with individuals in the top four fifths of the distribution having a reduced risk of prostate cancer compared with individuals in the bottom fifth (P:(trend) =.27). Statistically significant protective associations for high levels of selenium and alpha-tocopherol were observed only when gamma-tocopherol concentrations were high. **CONCLUSIONS:** The use of combined alpha- and gamma- tocopherol supplements should be considered in upcoming prostate cancer prevention trials, given the observed interaction between alpha-tocopherol, gamma-tocopherol, and selenium.

J Natl Cancer Inst 2000 Dec 20;92(24):2018-2023

Under-used form of vitamin E may be the most protective against prostate cancer.

Scientists at the Johns Hopkins School of Public Health have found that higher blood levels of gamma-tocopherol, a form of vitamin E not usually included in vitamin supplements, is associated with a lower risk of developing prostate cancer than is alpha-tocopherol, the synthetic form of vitamin E most commonly found in supplements. Although seldom studied, gamma-tocopherol is a natural form of vitamin E routinely found in the U.S. diet, notably in soy foods. The study also revealed that high concentrations of gamma-tocopherol appear to boost the prostate cancer-fighting abilities of both alpha-tocopherol and the micronutrient selenium. The study appears in the December 20, 2000 issue of the Journal of the National Cancer Institute, where it is accompanied by an editorial.

“Given gamma-tocopherol's positive interactions with both alpha-tocopherol and selenium,” says Kathy J. Helzlsouer, MD, MHS, professor, Epidemiology, the Johns Hopkins School of Public Health, and the lead investigator of the study, “its use should be considered in upcoming prostate cancer prevention trials.” A previous intervention trial, designed to look at the effects of supplemental alpha-tocopherol on the risk of lung cancer among smokers, had observed that the men taking the supplements had a lower risk of developing prostate cancer. Little attention, however, has been paid to other forms of vitamin E such as gamma-tocopherol, which studies in cells suggest may have even stronger antioxidant properties than alpha-tocopherol. The present study is the first to simultaneously investigate the association between the risk of prostate cancer and concentrations of alpha-tocopherol, gamma-tocopherol, and selenium. It is also the first to simultaneously consider the association between the risk of prostate cancer and concentrations of these micronutrients when they are supplied primarily from normal dietary intake (i.e., not from supplements). In a countywide campaign in 1989, researchers from the Johns Hopkins School of Public Health collected and froze blood samples from a total of 10,456 male residents of Washington County, Md., for future study. At the time of blood donation, participants gave information about their medical and smoking histories; all supplements and medications taken within the past 48 hours; and their height and weight, both currently and at age 21. Each participant was also asked to mail in a nail clipping from the big toe so that selenium levels could be assessed. Among the men who gave a blood sample and nail clipping in 1989, 110 went on to develop prostate cancer between January 1990 and September 1996. Each of these men with prostate

cancer were matched with two controls, men who had remained cancer-free. Serum levels of alpha-tocopherol and gamma-tocopherol, as well as toenail selenium levels, were measured and compared between the two groups. The researchers then compared all three micronutrients' concentrations, both singly and in combination, with each man's risk of developing prostate cancer. Median concentrations of both alpha-tocopherol and gamma-tocopherol were lower among the men with prostate cancer than among the control subjects, but these differences were statistically significant only for gamma-tocopherol. Compared with the men with the lowest levels of gamma-tocopherol, men with the highest levels had a fivefold reduction in their risk of developing prostate cancer. What is more, gamma-tocopherol appeared to boost the protective effects of both alpha-tocopherol and selenium. That is, compared with individuals with low concentrations of all three micronutrients, high concentrations of selenium and alpha-tocopherol were associated with a statistically significant decreased risk of prostate cancer only when high concentrations of gamma-tocopherol were also present.

The authors note that since alpha-tocopherol supplementation may lower gamma-tocopherol concentrations in plasma and tissues, supplementation with combined alpha- and gamma-tocopherol may be called for in future prostate cancer prevention trials. Support for this study was provided by a Public Health Service grant from the National Cancer Institute at the National Institutes of Health, and by grants from the Department of Defense.

JOHNS HOPKINS SCHOOL OF PUBLIC HEALTH, December 19, 2000

Vegetable/Mineral consumption

Dietary intake of whole grains.

OBJECTIVE: The objective of this study was to provide national estimates of whole-grain intake in the United States, identify major dietary sources of whole grains and compare food and nutrient intakes of whole-grain consumers and nonconsumers. **METHODS:** Data were collected from 9,323 individuals age 20 years and older in USDA's 1994-96 Continuing Survey of Food Intakes by Individuals through in-person interviews on two non-consecutive days using a multiple-pass 24-hour recall method. Foods reported by respondents were quantified in servings as defined by the Food Guide Pyramid using a new database developed by the USDA. Whole-grain and nonwhole-grain servings were determined based on the proportion, by weight, of the grain ingredients in each food that were whole grain and nonwhole grain. Sampling weights were applied to provide national probability estimates adjusted for differential rates of selection and nonresponse. Then, tests were used to assess statistically significant differences in intakes of nutrients and food groups by whole-grain consumers and nonconsumers. **RESULTS:** According to the 1994-96 survey, U.S. adults consumed an average of 6.7 servings of grain products per day; 1.0 serving was whole grain. Thirty-six percent averaged less than one whole-grain serving per day based on two days of intake data, and only eight percent met the recommendation to eat at least three servings per day. Yeast breads and breakfast cereals each provided almost one-third of the whole-grain servings, grain-based snacks provided about one-fifth, and less than one-tenth came from quick breads, pasta, rice, cakes, cookies, pies, pastries and miscellaneous grains. Whole-grain consumers had significantly better nutrient profiles than nonconsumers, including higher intakes of vitamins and minerals as percentages of 1989 Recommended Dietary Allowances and as nutrients per 1,000 kilocalories, and lower intakes of total fat, saturated fat and added sugars as percentages of food energy. Consumers were significantly more likely than nonconsumers to meet Pyramid recommendations for the grain, fruit and dairy food groups. **CONCLUSION:** Consumption of whole-grain foods by U.S. adults falls well below the recommended level. A large proportion of the population could benefit from eating more whole grain, and efforts are needed to encourage consumption.

J Am Coll Nutr 2000 Jun;19(3 Suppl):331S-38S

Effect of increasing dietary folate on red-cell folate: implications for prevention of neural tube defects.

BACKGROUND: Recommendations by the UK Department of Health suggest that protection from neural tube defects (NTD) can be achieved through intakes of an extra 400 microgram daily of folate/folic acid as natural food, foods fortified with folic acid, or supplements. The assumption is that all three routes of intervention would have equal effects on folate status. **METHODS:** We assessed the effectiveness of these suggested routes of intervention in optimising folate status. 62 women were recruited from the University staff and students to take part in a 3-month intervention study. Participants were randomly assigned to one of the following five groups: folic acid supplement (400 microgram/day; I); folic-acid-fortified foods (an additional 400 microgram/day; II); dietary folate (an additional 400 microgram/day; III); dietary advice (IV), and control (V). Responses to intervention were assessed as changes in red-cell folate between pre-intervention and post-intervention values. **FINDINGS:** 41 women completed the intervention study. Red-cell folate concentrations increased significantly over the 3 months in the groups taking folic acid supplements (group I) or food fortified with folic acid (group II) only ($p < 0.01$ for both groups). By contrast, although aggressive intervention with dietary folate (group III) or dietary advice (group IV) significantly increased intake of food folate ($p < 0.001$ and $p < 0.05$, respectively), there was no significant change in folate status. **INTERPRETATION:** We have shown that compared with supplements and fortified food, consumption of extra folate as natural food folate is relatively ineffective at increasing folate status. We believe that advice to women to consume folate-rich foods as a means to optimise folate status is misleading.

Lancet 1996 Mar 9;347(9002):657-9

BACKGROUND: High intake of folate may reduce risk for colon cancer, but the dosage and duration relations and the impact of dietary compared with supplementary sources are not well understood. **OBJECTIVE:** To evaluate the relation between folate intake and incidence of colon cancer. **DESIGN:** Prospective cohort study. **SETTING:** 88,756 women from the Nurses' Health Study who were free of cancer in 1980 and provided updated assessments of diet, including multivitamin supplement use, from 1980 to 1994. **PATIENTS:** 442 women with new cases of colon cancer. **MEASUREMENTS:** Multivariate relative risk (RR) and 95% CIs for colon cancer in relation to energy-adjusted folate intake. **RESULTS:** Higher energy-adjusted folate intake in 1980 was related to a lower risk for colon cancer (RR, 0.69 [95% CI, 0.52 to 0.93] for intake > 400 microg/d compared with intake < or = 200 microg/d) after controlling for age; family history of colorectal cancer; aspirin use; smoking; body mass; physical activity; and intakes of red meat, alcohol, methionine, and fiber. When intake of vitamins A, C, D, and E and intake of calcium were also controlled for, results were similar. Women who used multivitamins containing folic acid had no benefit with respect to colon cancer after 4 years of use (RR, 1.02) and had only nonsignificant risk reductions after 5 to 9 (RR, 0.83) or 10 to 14 years of use (RR, 0.80). After 15 years of use, however, risk was markedly lower (RR, 0.25 [CI, 0.13 to 0.51]), representing 15 instead of 68 new cases of colon cancer per 10,000 women 55 to 69 years of age. Folate from dietary sources alone was related to a modest reduction in risk for colon cancer, and the benefit of long-term multivitamin use was present across all levels of dietary intakes. **CONCLUSIONS:** Long-term use of multivitamins may substantially reduce risk for colon cancer. This effect may be related to the folic acid contained in multivitamins.

Ann Intern Med 1998 Oct 1;129(7):517-24

Plasma pyridoxal 5'-phosphate concentration and dietary vitamin B6 intake in free-living, low-income elderly people.

Free-living, elderly persons (aged greater than or equal to 60 y, n = 198) were recruited to determine the effects of age, sex, health status, dietary vitamin B6 intakes, and B6 supplement use on plasma pyridoxal 5'-phosphate (PLP). Vitamin B6 intakes were determined from 3-d diet records; supplementation was based on self-reported brand and frequency data. Fasting blood samples were analyzed for PLP. Subjects were primarily low-income Caucasians. There was no linear relationship between dietary vitamin B6 intake, age, sex or health status, and PLP while accounting for supplemental vitamin B6 use. PLP, however, was negatively correlated with age (p less than 0.001) in individuals with PLP values between 32 and 90 nmol/L. Vitamin B6 status was low (PLP less than 32 nmol/L) in 32% of this elderly population (n = 198) and could be attributed to low dietary vitamin B6 intakes and/or the presence of health problems reported to alter vitamin B6 status. This research suggests that low vitamin B6 status is prevalent in low-income, elderly persons, especially those with multiple health problems.

Am J Clin Nutr 1989 Aug;50(2):339-45

Plasma total homocysteine response to oral doses of folic acid and pyridoxine hydrochloride (vitamin B6) in healthy individuals. Oral doses of vitamin B6 reduce concentrations of serum folate.

Plasma total homocysteine response was compared in four groups of healthy individuals given orally divided doses of vitamin supplementations for a duration of 5 weeks. The vitamin supplements; A, 0.3 mg folic acid; B, 120 mg vitamin B6; C, combination of 0.3 mg folic acid and 120 mg vitamin B6 or D, 0.6 mg folic acid reduced the concentrations of plasma total homocysteine 20, 17, 32 and 24%, respectively. However, the intergroup comparisons did not show a significant difference in the effects of vitamin supplements. Multivariate analysis with correction for differences in pre-supplement values indicated a significant effect of vitamin B6 supplementation on plasma total homocysteine and serum folate. Our data show that plasma total homocysteine concentrations are reduced with low to medium divided doses of folic acid alone or in combination with vitamin B6.

Scand J Clin Lab Invest 1999 Apr;59(2):139-46

Folate and vitamin B6 from diet and supplements in relation to risk of coronary heart disease among women.

CONTEXT: Hyperhomocysteinemia is caused by genetic and lifestyle influences, including low intakes of folate and vitamin B6. However, prospective data relating intake of these vitamins to risk of coronary heart disease (CHD) are not available. **OBJECTIVE:** To examine intakes of folate and vitamin B6 in relation to the incidence of nonfatal myocardial infarction (MI) and fatal CHD. **DESIGN:** Prospective cohort study. **SETTING AND PATIENTS:** In 1980, a total of 80,082 women from the Nurses' Health Study with no previous history of cardiovascular disease, cancer, hypercholesterolemia, or diabetes completed a detailed food frequency questionnaire from which we derived usual intake of folate and vitamin B6. **MAIN OUTCOME MEASURE:** Nonfatal MI and fatal CHD confirmed by World Health Organization criteria. **RESULTS:** During 14 years of follow-up, we documented 658 incident cases of nonfatal MI and 281 cases of fatal CHD. After controlling for cardiovascular risk factors, including smoking and hypertension and intake of alcohol, fiber, vitamin E, and saturated, polyunsaturated, and trans fat, the relative risks (RRs) of CHD between extreme quintiles were 0.69 (95% confidence interval [CI], 0.55-0.87) for folate (median intake, 696 microg/d vs 158 microg/d) and 0.67 (95% CI, 0.53-0.85) for vitamin B6 (median intake, 4.6 mg/d vs 1.1 mg/d). Controlling for the same variables, the RR was 0.55 (95% CI, 0.41-0.74) among women in the highest quintile of both folate and vitamin B6 intake compared with the opposite extreme. Risk of CHD was reduced among women who regularly used multiple vitamins (RR=0.76; 95% CI, 0.65-0.90), the major source of folate

and vitamin B6, and after excluding multiple vitamin users, among those with higher dietary intakes of folate and vitamin B6. In a subgroup analysis, compared with nondrinkers, the inverse association between a high-folate diet and CHD was strongest among women who consumed up to 1 alcoholic beverage per day (RR =0.69; 95% CI, 0.49-0.97) or more than 1 drink per day (RR=0.27; 95% CI, 0.13-0.58). CONCLUSION: These results suggest that intake of folate and vitamin B6 above the current recommended dietary allowance may be important in the primary prevention of CHD among women.

JAMA 1998 Feb 4;279(5):359-64

Age differences in vitamin B6 status of 617 men.

The effect of age on vitamin B6 metabolism was studied in 617 community-dwelling subjects, ages 18 to 90. These are, for the most part, clinically healthy, educated men whose intake of nutrients is not limited by economic factors. Plasma pyridoxal phosphate (PLP) was used as the primary criterion of vitamin B6 status. About one-third of the subjects were taking supplementary vitamins on their own initiative. The amount of pyridoxine-HCl varied from 0.1 to 105 mg/day. The average plasma PLP of the men not taking a supplement (N = 414) was 12.3 +/-0.3 ng/ml, with 25% of the values below 7.5 ng/ml and 7% below 5 ng/ml. There was a statistically significant decrease in plasma PLP with age of 0.9 ng/ml per decade. For those taking a supplement, the average plasma PLP was 20.5 +/- 1.0 ng/ml, with only 8% of the values below 7.5 ng/ml and none below 5 ng/ml. Glutamic-oxaloacetic transaminase activity in plasma (PGOT) and erythrocytes (EGOT) was determined on all subjects. The ratio of EGOT with in vitro stimulation by PLP to EGOT actual (alpha-EGOT) was also studied. These studies provide the most extensive normative data on vitamin B6 status available on men in the adult years of life.

Am J Clin Nutr 1976 Aug;29(8):847-53

Dietary sources of nutrients among US adults, 1989 to 1991.

OBJECTIVE: To identify major food sources of 27 nutrients and dietary constituents for US adults. DESIGN: Single 24-hour dietary recalls were used to assess intakes. From 3,970 individual foods reported, 112 groups were created on the basis of similarities in nutrient content or use. Food mixtures were disaggregated using the US Department of Agriculture (USDA) food grouping system. SUBJECTS/SETTING: A nationally representative sample of adults aged 19 years or older (n = 10,638) from USDA's 1989-91 Continuing Survey of Food Intakes by Individuals. ANALYSES PERFORMED: For each of 27 dietary components, the contribution of each food group to intake was obtained by summing the amount provided by the food group for all respondents and dividing by total intake from all food groups for all respondents. RESULTS: This article updates previous work and is, to the authors' knowledge the first to provide such data for carotenenes, vitamin B12, magnesium, and copper. Beef, yeast bread, poultry, cheese, and milk were among the top 10 sources of energy, fat, and protein. The following other major sources also contributed more than 2% to energy intakes: carbohydrate: yeast bread, soft drinks/soda, cakes/cookies/, quick breads/doughnuts, sugars/syrups/jams, potatoes (white), ready-to-eat cereal, and pasta; protein: pasta; and fat: margarine, salad dressings/mayonnaise, and cakes/cookies/quick breads/doughnuts. Ready-to-eat cereals, primarily because of fortification, were among the top 10 food sources for 18 of 27 nutrients. APPLICATIONS/CONCLUSIONS: These analyses are the most current regarding food sources of nutrients and, because of disaggregation of mixtures, provide a truer picture of contributions of each food group.

J Am Diet Assoc 1998 May;98(5):537-47

Folate intake and food sources in the US population.

Dietary data from 24-h recalls collected in the Second National Health and Nutrition Examination Survey (NHANES II) were analyzed to determine intake and food sources of folate in US adults between ages 19 and 74 y. Mean daily folate intake was 242 +/- 2.8 micrograms (means +/- SEM) for all adults, 281 +/- 3.6 micrograms for males, and 207 +/- 2.9 micrograms for females. Daily intake per 1000 kcal was 130 +/- 1.3 micrograms for all adults 122 +/- 1.3 micrograms for males, and 137 +/- 1.7 micrograms for females. Based on the Recommended Dietary Allowance of 400 micrograms/d, our results suggest that folate intake in the United States is low, particularly among women and blacks. Intake by age, education, and poverty index is discussed. Orange juice, white breads, dried beans, green salad, and ready-to-eat breakfast cereals are the major food sources of folate on a given day, contributing 37% of total folate intake.

Am J Clin Nutr 1989 Sep;50(3):508-16

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Cimetidine

Randomized trial of preoperative cimetidine in patients with colorectal carcinoma with quantitative assessment of tumor-associated lymphocytes.

BACKGROUND: Previous studies have suggested that cimetidine, a histamine-2 receptor antagonist with immunostimulatory effects, may improve survival in patients with colorectal carcinoma. This effect may be apparent by an increase in the number of peritumoral lymphocytes. A prospective, double blind, randomized, placebo-controlled trial of a short course of preoperative treatment with cimetidine in patients with colorectal carcinoma was performed to assess the effect of cimetidine on survival and on the number of peritumoral lymphocytes. **METHODS:** One hundred and twenty-five patients who were scheduled to undergo elective colon or rectal excision for carcinoma were randomized to receive either placebo or cimetidine preoperatively for 5 days. In addition to standard histopathology, immunohistochemistry and computer video image analysis were used to assess the number of peritumoral lymphocytes in an objective manner. Interim survival analysis according to the Kaplan-Meier method was performed. **RESULTS:** A trend toward a survival advantage in the group of patients receiving cimetidine (800 mg twice daily) compared with the placebo group was observed ($P = 0.20$, log rank test) that was most marked in patients with replication error negative tumors ($P = 0.04$). Similarly, in these two groups there was a trend toward an increase in the number of patients with a conspicuous lymphocytic infiltration ($P = 0.10$, chi-square test). However, there was no difference in the number of peritumoral lymphocytes as measured by image analysis. **CONCLUSIONS:** Based on the results of the current study, a short course of preoperative treatment with cimetidine does appear to have an effect on patient survival; however, the exact mechanism is unknown. The failure of this study to demonstrate a clear increase in the local lymphocyte response does not exclude an immunologic mechanism of action.

Cancer 1999 Apr 15;85(8):1658-63

Efficacy of cimetidine in treatment of Herpes zoster in the first 5 days from the moment of disease manifestation.

221 patients with Herpes zoster have undergone the treatment. They were given cimetidine in the daily dose 3 x 200 mg and 1 x 400 mg to night. It was proved that the efficacy of the Herpes zoster treatment by cimetidine is inversely proportional to the time of the disease duration. The authors suggest to use cimetidine in the treatment of Herpes zoster virus infections even during the prodromal period.

Pol Tyg Lek 1996 Jun;51(23-26):338-9

Oral cimetidine for the management of genital and perigenital warts in children.

PURPOSE: It is believed that most warts are self-limiting and generally require little or no treatment. When numerous or almost complete infestation of the perineum, genital area and groin is encountered it can be distressing and a difficult problem to treat in children. Multiple treatments with caustic agents are sometimes necessary, and treatment of perigenital warts may require use of anesthesia for multiple procedures. Cimetidine is a histamine receptor antagonist that has been used mainly to treat peptic ulcer disease. Recently it has been reported to be useful for the treatment of mucocutaneous candidiasis, herpes simplex, herpes zoster and verruca because of its immunomodulatory effects. Several studies have been published indicating its effectiveness in the treatment of warts. **MATERIALS AND METHODS:** We treated 4 children with extensive condylomata acuminata of the genital and perigenital areas with high doses of cimetidine in an attempt to eradicate the condyloma and avoid recurrence in 2 and as primary treatment in 2. All patients were treated with 30 to 40 mg./kg. cimetidine daily in 3 divided doses during a 3-month period. **RESULTS:** All patients are free of condyloma at 24 months following treatment. **CONCLUSIONS:** Our results show that cimetidine is useful for primary and adjunctive treatment of condyloma in young children. It also appears to be effective as first line therapy.

J Urol 2000 Sep;164(3 Pt 2):1074-5

In vitro cell-mediated immune reactions in herpes zoster patients treated with cimetidine.

In a double-blind placebo-control study the immunomodulating effect of cimetidine treatment for one week and placebo was investigated for cell-mediated immune reactions of 22 patients with herpes zoster (HZ). The mitogen induced leukocyte migration inhibition test (LMIT) and the in vitro proliferation of the patients' lymphocytes to exogenous IL-2 were used. Before any treatment, the mitogen induced leukocyte migration inhibition capacity (LMIC) of HZ patients was found to be significantly reduced ($p < 0.02$) as compared to healthy blood bank donors (controls). After one week, within the same treatment, the LMIC was significantly improved ($p < 0.01$). The patients' lymphoproliferative response to IL-2, before any treatment, was not significantly different from that of controls ($p < 0.05$). However, significantly higher values ($p < 0.001$) were found in patients tested 7 days after the disease onset as compared to those tested after 12 days. One-week cimetidine treatment significantly improved ($p < 0.05$) the lymphoproliferative response to IL-2 of initially low responders and had no effect on higher responder patients. In contrast to this, after one week of placebo treatment, a significant decrease in the patients' lymphoproliferative response to IL-2 could be observed as compared to patients' initial responses ($p < 0.05$) or to those of controls ($p < 0.05$). Although the number of cases is very small. The data suggest that after cimetidine treatment, as compared to placebo, healing from skin rash and pain was achieved in a significantly shorter time ($p < 0.01$).

Asian Pac J Allergy Immunol 1994 Jun;12(1):51-8

Cimetidine as an immunomodulator in the treatment of herpes zoster.

As there is evidence of a possible immunoregulatory role for H₂-histamine receptor antagonists, we carried out a prospective randomized trial to evaluate the in vivo and in vitro effect of cimetidine, an H₂-blocker, in the treatment of herpes zoster infection. Cimetidine treatment shortened the median interval until the first decrease in pain, the median interval until the complete resolution of pain and promoted faster complete healing of skin lesions than symptomatic treatment. The immunological trends observed in vitro support an important role for histamine in the induction of immunosuppression, as measured by the response to the mitogen phytohemagglutinin. This effect of histamine was antagonized by cimetidine.

J Neuroimmunol 1989 Mar;22(1):69-76

Cimetidine: an immunomodulator.

Suppressor T lymphocytes possess histamine₂ (H₂) receptors and contribute significantly to the function of the immune system. Experimentally, cimetidine, an H₂-receptor antagonist, has been shown to enhance a variety of immunologic functions both in vivo and in vitro because of its inhibitory effects on suppressor-cell function. Successful tumor immunotherapy, as well as some protection from infection, has been reported in experimental animals. Patients receiving cimetidine have been shown to exhibit enhanced cell-mediated immunity as evaluated by increased response to skin-test antigens, restoration of sensitivity following development of acquired tolerance, and increased responses of lymphocytes to mitogen stimulation. Preliminary reports also indicate that cimetidine may offer therapeutic benefits for patients with Varicella zoster and Herpes simplex infections, as well as those suffering from mucocutaneous candidiasis and common variable hypogammaglobulinemia. These immunoregulatory effects are dose-related but are not always consistent. Because of its inhibitory effect on suppressor function, cimetidine treatment may be deleterious in patients with organ transplant and autoimmune disorders. Cimetidine should be used as an immunomodulator on an experimental basis only.

DICP 1990 Mar;24(3):289-95

Cimetidine therapy for warts: a placebo-controlled, double-blind study.

BACKGROUND: Cimetidine, an H₂-receptor antagonist, has been used successfully to treat patients with mucocutaneous candidiasis, common variable immunodeficiency, herpes simplex, and herpes zoster because of its immunomodulatory effects. Recently, some trials have suggested that cimetidine may also be useful for the treatment of warts. **OBJECTIVE:** The aim of the present study was to determine whether cimetidine is effective in the treatment of warts. **METHODS:** Seventy patients with multiple warts were included in a placebo-controlled, double-blind study. Patients were randomly allocated to treatment groups equally. The groups received cimetidine, 25 to 40 mg/kg daily, or placebo for 3 months. Patients were examined at monthly intervals. **RESULTS:** At the end of the therapy, 28 cimetidine-treated and 26 placebo-treated patients were examined to determine the efficacy of treatment. Cure rates obtained were 32% (9 of 28) in the cimetidine-treated group and 30.7% (8 of 26) in the placebo-treated group. No significant difference was found between cimetidine and placebo in effectiveness ($p = 0.85$). **CONCLUSION:** Our results show that cimetidine is no more effective than placebo in the treatment of patients with common warts.

J Am Acad Dermatol 1996 Jun;34(6):1005-7

Cimetidine in the treatment of herpesvirus infections.

In August 1977 a patient developed herpes zoster just before she commenced a course of cimetidine (Tagamet; Smith, Kline & French) for a chronic gastric ulcer. She experienced both rapid relief of the ulcer symptoms and, rather unexpectedly, dramatic

relief of the herpetic pain and rapid disappearance of the eruption. On the basis of this observation cimetidine was prescribed to 21 patients with herpes zoster. The results continued to be encouraging in all but 3 patients. The trial was therefore extended to other herpesvirus infections. In all but 1 of 7 patients with herpes labialis the blisters were aborted, and in 1 patient with herpes keratitis the result was also encouraging, the attacks being markedly shortened in duration and reduced in frequency. The results of this preliminary trial warrant a systematic scientific inquiry into the potential role of cimetidine in the treatment of herpesvirus infection, as well as a study of the mechanisms involved.

S Afr Med J 1980 Jul 19;58(3):112-6

Viral infections in severely immunocompromised cancer patients.

Immunocompromised cancer patients are susceptible to infection by many viral pathogens. The most serious morbidity results from active infection by members of the herpes virus family. Reactivation of latent virus occurs as a sequela of cytotoxic therapy and deficiency of cell-mediated immunity, especially cytotoxic responses, the major host protective defense. Herpes simplex virus and varicella zoster virus infections are problematic in patients with all types of cancer; cytomegalovirus infections cause life-threatening morbidity in bone marrow transplant patients. Several antiviral agents are highly active against these pathogens and different strategies of using them have resulted in reduced morbidity and mortality. Ultimately, the resolution of these infections is dependent on the control of the malignancy and the ability of the patient to mount an adequate immune response.

Support Care Cancer 1994 Nov;2(6):355-68

Herpes zoster: treatment with cimetidine.

The active phase of herpes zoster can be predicted from the length of time it takes for all the vesicles to erupt. A case is reported in which cimetidine therapy appeared to reduce the expected length of the active phase from 35 days or longer to 10 days.

Can Med Assoc J 1983 Dec 15;129(12):1284-5

Immunomodulatory properties of cimetidine in ARC patients.

The immunomodulatory potency of cimetidine, a histamine H₂ receptor antagonist, was investigated in 33 AIDS-related complex (ARC) patients performing detailed immunological and clinical evaluations. Cimetidine was administered orally in daily doses of 1200 mg for a period of 5 months with an interruption of therapy after the first 3 months for an interval of 3 weeks. Significant (P less than 0.05) elevations of immunoglobulins (IgG, IgA), complement C4, B-lymphocytes, and OKT4+ (helper/inducer) cells were found after cimetidine intake. The in vitro lymphocyte proliferative response to plant mitogens was significantly increased, and the in vivo cell-mediated hypersensitivity reaction assessed by intradermal application of seven recall antigens improved significantly. These effects were both reversible with the discontinuation of cimetidine and reproducible with repeated administration of the drug. Clinical data such as performance status, body weight, and fever were influenced favorably (P less than 0.05) by cimetidine. The frequency of diarrhea and the lymph node size were also diminished significantly. The data suggest that cimetidine may at least partially restore immunofunctions in AIDS-related complex.

Clin Immunol Immunopathol 1988 Jul;48(1):50-60

Effect of cimetidine on herpes zoster infection.

Cimetidine was administered to two patients for herpes zoster infection. An acute pain-relieving effect was observed. The patients were followed for 11 and 14 months without developing postherpetic neuralgia. Possible mechanisms for prevention of postherpetic neuralgia by cimetidine are discussed.

Drug Intell Clin Pharm 1987 Oct;21(10):803-5

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Synthetic Estrogen/Heart Disease

Effect of postmenopausal hormones on inflammation-sensitive proteins: the Postmenopausal Estrogen/Progestin Interventions (PEPI) Study.

BACKGROUND: Observational studies in healthy women suggest postmenopausal hormone therapy reduces risk of coronary events. In contrast, in a recent clinical trial of women with coronary disease, a subgroup analysis demonstrated increased risk during the early months of therapy. Because higher levels of inflammation factors predict vascular disease outcomes, the effect of hormones on these factors is of interest. **METHODS AND RESULTS:** Four inflammation-sensitive factors, C-reactive protein, soluble E-selectin, von Willebrand factor antigen, and coagulation factor VIIIc were measured at baseline, 12, and 36 months in 365 participants of the Postmenopausal Estrogen/Progestin Interventions (PEPI) Trial, a randomized, placebo-controlled trial of the effects of 4 hormone preparations on cardiovascular disease risk factors. Compared with placebo, all 4 active preparations resulted in a large sustained increase in the concentration of C-reactive protein and a decrease in soluble E-selectin ($P=0.0001$). There were no effects of treatment on concentrations of von Willebrand factor or factor VIIIc. There were no differences in effects among treatment arms. Relative to placebo, when combining active treatment arms, final concentrations of C-reactive protein were 85% higher whereas E-selectin was 18% lower compared with baseline. **CONCLUSIONS:** Postmenopausal hormones rapidly increased the concentration of the inflammation factor C-reactive protein. Such an effect may be related to adverse early effects of estrogen therapy. In contrast, hormones reduced the concentration of soluble E-selectin, and this might be considered an anti-inflammatory effect. Because PEPI was not designed to assess clinical endpoints, studies of the impact of hormone-mediated changes in inflammation on risk of subsequent coronary events are needed.

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Both raloxifene and estrogen reduce major cardiovascular risk factors in healthy postmenopausal women: A 2-year, placebo-controlled study.

Currently raloxifene, a selective estrogen receptor modulator, is being investigated as a potential alternative for postmenopausal hormone replacement to prevent osteoporosis and cardiovascular disease. We compared the 2-year effects of raloxifene on a wide range of cardiovascular risk factors with those of placebo and conjugated equine estrogens (CEE). Analyses were based on 56 hysterectomized but otherwise healthy postmenopausal women aged 54. 8 ± 3.5 (mean \pm SD) years who entered this double-blind study and who were randomly assigned to raloxifene hydrochloride 60 mg/d ($n=15$) or 150 mg/d ($n=13$), placebo ($n=13$), or CEEs 0.625 mg/d ($n=15$). At baseline and after 6, 12, and 24 months of treatment, we assessed serum lipids, blood pressure, glucose metabolism, C-reactive protein, and various hemostatic parameters. Compared with placebo, both raloxifene and CEEs lowered the level of low density lipoprotein cholesterol by 0.53 to 0.79 mmol/L (all $P<0.04$) and lowered, at 24 months, the level of fibrinogen by 0.71 to 0.86 g/L (all $P<0.05$). The effects of raloxifene and CEEs did not differ significantly. In contrast to raloxifene, from 6 months on CEEs increased high density lipoprotein cholesterol by 0.25 to 0.29 mmol/L and reduced plasminogen activator inhibitor-1 antigen by 30.6 to 48.6 ng/mL (all $P<0.02$ versus both placebo and raloxifene). CEEs transiently increased C-reactive protein by 1.0 mg/L at 6 months ($P<0.05$ versus placebo) and prothrombin-derived fragment F1+2 by 0.79 nmol/L at 12 months ($P<0.001$ versus placebo). Finally, from 12 months on, CEEs increased triglycerides by 0.33 to 0.56 mmol/L (all $P<0.05$ versus both placebo and raloxifene). Our findings suggest that in healthy postmenopausal women, raloxifene and estrogen monotherapy have similar beneficial effects on low density lipoprotein cholesterol and fibrinogen levels. These treatments differ, however, in their effects on high density lipoprotein cholesterol, triglycerides, and plasminogen activator inhibitor-1 and possibly in their effects on prothrombin fragment F1+2 and C-reactive protein.

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Randomized trial of estrogen plus progestin for secondary prevention of coronary heart disease in postmenopausal women. Heart and Estrogen/Progestin Replacement Study (HERS) Research Group.

CONTEXT: Observational studies have found lower rates of coronary heart disease (CHD) in postmenopausal women who take estrogen than in women who do not, but this potential benefit has not been confirmed in clinical trials. **OBJECTIVE:** To determine if estrogen plus progestin therapy alters the risk for CHD events in postmenopausal women with established coronary disease. **DESIGN:** Randomized, blinded, placebo-controlled secondary prevention trial. **SETTING:** Outpatient and community settings at 20

US clinical centers. PARTICIPANTS: A total of 2763 women with coronary disease, younger than 80 years, and postmenopausal with an intact uterus. Mean age was 66.7 years. INTERVENTION: Either 0.625 mg of conjugated equine estrogens plus 2.5 mg of medroxyprogesterone acetate in 1 tablet daily (n = 1380) or a placebo of identical appearance (n = 1383). Follow-up averaged 4.1 years; 82% of those assigned to hormone treatment were taking it at the end of 1 year, and 75% at the end of 3 years. MAIN OUTCOME MEASURES: The primary outcome was the occurrence of nonfatal myocardial infarction (MI) or CHD death. Secondary cardiovascular outcomes included coronary revascularization, unstable angina, congestive heart failure, resuscitated cardiac arrest, stroke or transient ischemic attack, and peripheral arterial disease. All-cause mortality was also considered. RESULTS: Overall, there were no significant differences between groups in the primary outcome or in any of the secondary cardiovascular outcomes: 172 women in the hormone group and 176 women in the placebo group had MI or CHD death (relative hazard [RH], 0.99; 95% confidence interval [CI], 0.80-1.22). The lack of an overall effect occurred despite a net 11% lower low-density lipoprotein cholesterol level and 10% higher high-density lipoprotein cholesterol level in the hormone group compared with the placebo group (each $P < .001$). Within the overall null effect, there was a statistically significant time trend, with more CHD events in the hormone group than in the placebo group in year 1 and fewer in years 4 and 5. More women in the hormone group than in the placebo group experienced venous thromboembolic events (34 vs 12; RH, 2.89; 95% CI, 1.50-5.58) and gallbladder disease (84 vs 62; RH, 1.38; 95% CI, 1.00-1.92). There were no significant differences in several other end points for which power was limited, including fracture, cancer, and total mortality (131 vs 123 deaths; RH, 1.08; 95% CI, 0.84-1.38). CONCLUSIONS: During an average follow-up of 4.1 years, treatment with oral conjugated equine estrogen plus medroxyprogesterone acetate did not reduce the overall rate of CHD events in postmenopausal women with established coronary disease. The treatment did increase the rate of thromboembolic events and gallbladder disease. Based on the finding of no overall cardiovascular benefit and a pattern of early increase in risk of CHD events, we do not recommend starting this treatment for the purpose of secondary prevention of CHD. However, given the favorable pattern of CHD events after several years of therapy, it could be appropriate for women already receiving this treatment to continue.

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Changes in micronutrient concentrations following anti-inflammatory treatment in patients with gastrointestinal cancer.

Circulating concentrations of vitamin antioxidants (retinol, alpha-tocopherol, lutein, lycopene, alpha- and beta-carotene) and trace elements (zinc, copper, iron and selenium) plus carrier proteins (albumin, transferrin, ceruloplasmin) in gastrointestinal cancer patients (n = 12) with an inflammatory response (as demonstrated by an elevated C-reactive protein concentration) were compared with a control group (n = 12). Further, the effect of moderating the inflammatory response, using the anti-inflammatory agent ibuprofen, on these measurements was examined in the cancer group. The control and cancer groups were similar in terms of age, sex, and body mass index. However, the cancer group had significantly higher C-reactive protein concentrations ($P < 0.001$). Concentrations of vitamin antioxidants and trace elements (and carrier proteins) were significantly lower ($P < 0.001$), except copper (ceruloplasmin) which was significantly higher ($P < 0.05$). After anti-inflammatory treatment, there were small but significant increases in lutein, lycopene, and beta-carotene ($P < 0.05$) and in iron and selenium ($P < 0.05$), whereas ceruloplasmin decreased ($P < 0.05$). The micronutrient concentrations in the cancer patients remained different from those in the control subjects. These results support the concept that the magnitude of inflammation plays an important role in the regulation of circulating concentrations of vitamin antioxidants and trace elements in patients with gastrointestinal cancer.

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Plasma concentration of C-reactive protein in patients with high estrogen levels.

The monitoring of inflammatory activity in patients with a high level of estrogen is controversial because the significance of a raised estradiol level on C-reactive protein (CRP) concentrations is a debated question. This prompted us to assay CRP by a sensitive Elisa in a sample of 30 patients with ovarian stimulation for in vitro fertilization, thus with high levels of estradiol. For 15 of these women, six to nine plasma samples were analyzed allowing a kinetic study of plasma levels of CRP, estradiol and sex steroid-binding plasma protein (SBP). No significant correlation was found between the concentrations of estradiol and CRP for the 30 patients. In the kinetic study, as mean estradiol levels rose exponentially from 50 to 1400 ng/l between day 5 and 14, the CRP level tended to vary markedly from one patient to another and sometimes from day to day, but there was never any relation with estradiol level. Furthermore, CRP did not significantly modify the slope of the regression line between estradiol concentration and the day of the menstrual cycle. In contrast, the effect of estradiol on SBP was clear, which supports the absence of estradiol effect on CRP level.

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Hormone replacement therapy and sensitive C-reactive protein concentrations in women with type-2 diabetes.

C-reactive protein concentrations as a marker of inflammation predicts vascular risk and is raised in type-2 diabetes. In a 6-month double-blind placebo controlled trial, a combination of transdermal oestradiol 80 microg with continuous oral norethisterone 1 mg significantly reduced C-reactive protein concentrations in postmenopausal women with type-2 diabetes.

Increased C-reactive protein levels during short-term hormone replacement therapy in healthy postmenopausal women.

OBJECTIVE: To study the short-term effect of unopposed oestradiol (E2) and sequentially combined hormone replacement therapy (E2 + P) on C-reactive protein (CRP) in healthy postmenopausal women. **DESIGN:** Prospective, randomised, placebo-controlled 12-week study. Sixty healthy, normotensive, non-hysterectomised postmenopausal women received either placebo (N = 16) or daily 2 mg micronised oestradiol, either unopposed (N = 16, E2 group) or sequentially combined with a progestagen on 14 days of each cycle (N = 28, E2+P group). Data were collected at baseline and at 4 and 12 weeks. **RESULTS:** CRP levels increased significantly during the 12 weeks in the E2 and the E2+P groups compared to placebo. No differences were found between the E2 group and the E2+P group [E2 and E2+P group together (N = 44) versus placebo: P = 0.01; E2 versus E2+P: P = 0.75]. To give a quantitative estimate of the increase, the median change calculated from baseline in both treatment groups together was +87% (P = 0.02) at 4 weeks, and +114% (P = 0.08) at 12 weeks, as compared to the placebo group. **CONCLUSION:** In healthy postmenopausal women, short-term treatment with E2 or E2+P was associated with a rapid rise in CRP concentrations. These observations raise the possibility that the increased risk of cardiovascular events is related to an initial increase in CRP levels after starting hormone replacement therapy.

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The effects of hormone replacement therapy and raloxifene on C-reactive protein and homocysteine in healthy postmenopausal women: a randomized, controlled trial.

C-Reactive protein and homocysteine are independent risk factors for the development of cardiovascular disease. This study compared the effects of hormone replacement therapy (HRT) and raloxifene on serum C-reactive protein and homocysteine levels as markers of cardiovascular risk in healthy postmenopausal women. Healthy postmenopausal women (n = 390) were enrolled in a double blind, randomized, placebo-controlled, 6-month trial at eight out-patient sites in the United States. Women were randomly assigned to receive continuous combined HRT (0.625 mg/day conjugated equine estrogen and 2.5 mg/day medroxyprogesterone acetate), raloxifene (60 or 120 mg/day), or placebo for 6 months. C-Reactive protein and homocysteine were measured in baseline and 6-month serum samples. HRT increased C-reactive protein levels by 84% (P<0.001), whereas raloxifene (60 and 120 mg/day) had no significant effect (-6% and -4%, respectively; P>0.2). Raloxifene (60 and 120 mg/day) significantly lowered serum levels of homocysteine by 8% (P = 0.014) and 6% (P = 0.024), respectively, similar to the 7% (P = 0.014) reduction obtained with HRT. We conclude that HRT and raloxifene lower serum homocysteine levels to a comparable extent in postmenopausal women. Whereas cardiovascular risk predicted by C-reactive protein in healthy postmenopausal women is not influenced by raloxifene, the relationship between elevated C-reactive protein levels with HRT and cardiovascular disease events requires further study.

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