

# Vitamin News

Vol. VI No. 4

Fall 1999

Vitamins and Human Health ♦ Current Research and Opinion

**B**REAST cancer is the most common form of cancer among American women, with as many as 175 thousand new cases of invasive disease diagnosed annually. According to the American Cancer Society, breast cancer is the second leading cause of cancer deaths in women, after lung cancer, accounting for nearly 45 thousand deaths in the U.S. each year. Although the causes of breast cancer are not known with certainty, epidemiologic studies have shown that several factors increase a woman's risk of developing the disease, including older age, a family history of breast cancer, early onset of menstruation, late menopause, alcohol use, and long-term use of estrogen-replacement therapy. Although early reports suggested a direct association between breast cancer risk and dietary intake of fat, subsequent studies using more powerful research designs failed to confirm these findings. Most nutritionists now agree that fat intake, per se, does not substantially influence breast cancer risk, although adult weight gain, which is related to excessive intake of fat and other energy nutrients, may be involved.<sup>1</sup>

## **Antioxidant Vitamins**

Recent research attention has focused on the association between breast cancer risk and vitamin status, including vitamins C, E, and A, and the carotenoids, a family of vitamin A-like plant pigments that includes beta-carotene, lycopene, and lutein. These nutrients serve predominantly as

## **Vitamins and Breast Cancer**

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cellular antioxidants, neutralizing free radicals and other high-energy oxygen compounds that have been linked to DNA damage and genetic mutations—important steps in the development of cancer. Several small epidemiologic studies have reported inverse relations between breast cancer risk and tissue<sup>2</sup> and plasma concentrations of beta-carotene<sup>3</sup> and lycopene.<sup>4</sup> A similar protective effect of beta-carotene was reported in a larger case-control study of Greek women,<sup>5</sup> although the reduction in risk was only evident among women who were premenopausal when their breast cancer was diagnosed.

Another recent, large epidemiologic study<sup>6</sup> also suggests that the protective effects of antioxidant vitamins may occur in subgroups of women. Researchers at the Harvard School of Public Health used data from over 83 thousand participants in the Nurses' Health Study, a prospective cohort study begun in 1976. After adjusting for other risk factors, they found that intakes of beta-carotene, vitamin A, and lutein each were associated with a 20% reduction in the risk of breast cancer among premenopausal but not postmenopausal women. Among premenopausal women, dietary intakes of carotenoids and vitamins A and C were associated with 60% reductions in breast cancer risk among women with a positive family history of breast cancer but not those without a family history. Similarly, when premenopausal women were grouped according to alcohol

## **Contents**

Vitamins and Breast Cancer .....	1
Plasma Lycopene Levels and Prostate Cancer .....	2
Vitamins E and C Help Preserve Lung Function Following Ozone Exposure .....	3
Supplemental Vitamin E May Reduce Diabetic Complications .....	3
Vitamin C May Help Prevent Lead Toxicity .....	4
Elevated Homocysteine and the Risk of Stroke .....	5
Vitamin E and Diabetes .....	6
Supplemental Vitamin C and Heart Disease .....	6

intake, increased consumption of carotenoids was associated with more than a 40% reduction in breast cancer risk among women who consumed at least 15 g/day of alcohol but had little protective effect among those with lower alcohol intakes. These findings suggest that antioxidant nutrients may help to attenuate the elevated risk of breast cancer observed in women who routinely consume alcohol and those with a positive family history of the disease but that they have only minor protective effects among postmenopausal women and those without these other risk factors.

*Continued on page 7*

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## Plasma Lycopene Levels and Prostate Cancer

**P**ROSTATE cancer is a common form of cancer in men, with more than 2.6 million cases and 34 thousand deaths reported in the U.S. each year. Because population studies have found that the occurrence of prostate cancer varies widely by both geographic region and ethnicity, researchers have speculated that dietary factors, such as vitamins, may play a role in its development. We have previously reported that supplemental vitamin E reduces prostate cancer incidence and deaths among smokers (see *VitaminNews*, Vol. V, No. 3). Moreover, a recent large prospective study found an inverse relation between prostate cancer risk—particularly aggressive cancer—and dietary intake of lycopene, a plant component similar to beta-carotene that occurs in highest concentrations in tomato products. Lycopene is a powerful antioxidant and scavenger of free radicals, and, unlike beta-carotene, it is not converted to vitamin A. The mechanisms through which lycopene confers protection against prostate cancer are not known with certainty, although both its antioxidant properties and its ability to influence cell-cell communication have been implicated.

To further explore the relation between lycopene and prostate cancer risk, researchers at Northwestern University Medical School, in Chicago, and Harvard University, in Boston, conducted a nested case-control study using data from the Physicians' Health Study. This randomized, double-blind, placebo-controlled trial of aspirin and beta-carotene was begun in 1982 and includes data on over 22 thousand male physicians in the U.S.. For the present analysis, cases were the 578 men who reported a diagnosis of prostate cancer over the years of follow-up, and controls were 1,294 men, matched to cases by age and smoking status, without a history of prostate cancer. Because previous studies have

shown that aggressive prostate cancer may have different risk factors than those associated with less aggressive disease, a subset of 259 cases with more aggressive disease was identified for additional comparisons. Plasma concentrations of vitamins A and E, lycopene, and other carotenoids were determined in blood samples obtained several years earlier, at the time of enrollment, and were divided into five equal groupings, or quintiles, ranging from the lowest to the highest concentrations.

Plasma lycopene levels were significantly lower in case subjects than in controls (369 vs. 388 ng/mL) and were even lower in men with aggressive disease (356 ng/mL). The odds of developing prostate cancer were 25% lower among men in the highest quintile of plasma lycopene compared to those in the lowest quintile, and this protective effect was even more marked among men with aggressive disease, for whom high plasma lycopene was associated with a significant 45% reduction in the odds of cancer. Although a 35% reduction in the odds of aggressive prostate cancer was observed for men in the highest quintile of plasma vitamin E, this effect was not statistically significant. No other significant protective effects were observed for retinol (vitamin A) or for the other carotenoids.

In this observational study, high plasma levels of lycopene were associated with reduced risk of prostate cancer, particularly aggressive cancer. Long-term clinical trials are needed to confirm that lycopene, and not some other compound associated with it, is responsible for this protective effect. Until then, these results provide further evidence in support of diets rich in fruits and vegetables.

### Reference

Gunn PH, Ma J, Giovannucci E, et al. Lower prostate cancer risk in men with elevated plasma lycopene levels: results of a prospective analysis. *Cancer Res* 1999;59:1225-30.

## Vitamins E and C Help Preserve Lung Function Following Ozone Exposure

**O**ZONE is a high-energy form of oxygen that is produced when sunlight reacts with volatile organic compounds and nitrogen oxides in the atmosphere. Because of its chemical structure, ozone is a powerful oxidizing agent, capable of damaging body tissues directly and generating free radicals, which can, in turn, lead to further tissue damage. Acute exposure to environmental ozone reduces lung function and can trigger ear, nose, and throat irritation, coughing, shortness of breath, headache, chest tightness, and asthma attacks. Because ozone levels are highest in the late afternoon, persons who exercise outdoors at this time of day, breathing air deeply into their lungs, are especially vulnerable to the respiratory effects of ozone exposure. The results of several studies have suggested that antioxidant vitamins, such as vitamins E and C, may help protect against the effects of ozone exposure. The findings from these studies have been difficult to compare, however, since the subjects in the various trials were exposed to different levels of ozone, all of which were generally much higher than ozone concentrations typically found in ambient air.

To determine the effect of supplemental antioxidants on lung function in persons exposed to low levels of ozone, researchers at Wageningen Agricultural University, in The Netherlands, conducted a double-blind, placebo-controlled trial among 38 nonsmoking men and women cyclists, aged 16 to 59 years. Twenty persons were randomly assigned to receive a daily dose of 500 mg vitamin C and 100 mg vitamin E, and 18 persons received an identical-looking placebo. Plasma concentrations of vitamins E and C were determined at baseline and at the end of the 15-week supplementation trial. For each subject, lung function was assessed on several occasions both

before and immediately after outdoor cycling by measuring the forced expiratory volume in one second (FEV<sub>1</sub>) and the forced vital capacity (FVC). Throughout the study period, daily concentrations of ozone in the cycling region were obtained from a nearby environmental monitoring station.

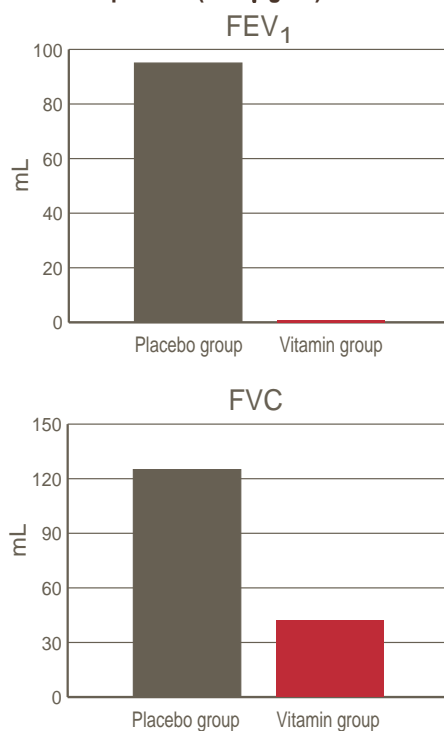
Exposure to relatively low concentrations of ozone was associated with reduced postexercise FEV<sub>1</sub> and FVC in all cyclists, confirming earlier reports that acute ozone exposure negatively affects lung function. Supplementation with vitamins E and C, however, significantly reduced the degree to which lung function was affected by ozone exposure. For

These findings indicate that supplementation with vitamins C and E at levels about ten times the RDA helps to prevent mild reductions in lung function in healthy exercising persons exposed to relatively low levels of ozone. Persons who routinely exercise outdoors may benefit from supplementation with these vitamins. Additional studies are needed to determine whether these vitamins can also preserve lung function following exposure to higher levels of ozone or among persons with chronic respiratory diseases, such as asthma.

### Reference

Grievink L, Zijlstra AG, Ke X, Brunekreef B. Double-blind intervention trial on modulation of ozone effects on pulmonary function by antioxidant supplements. *Am J Epidemiol* 1999;149:306-14.

**Fig. 1. Decrease in Lung Function Associated with Ozone Exposure (100 µg/m<sup>3</sup>)**



instance, exposure to ozone at a concentration of 100 µg/m<sup>3</sup> reduced FEV<sub>1</sub> by 95 mL (about 2%) in the placebo group compared to only 1 mL in the supplemented group. Similarly, FVC following ozone exposure was reduced by 125 mL (about 1.5%) in the placebo group compared to just 42 mL in those receiving antioxidant supplements (Figure 1).

## Supplemental Vitamin E May Reduce Diabetic Complications

**I**NSULIN-dependent diabetes mellitus (IDDM), also known as juvenile or type I diabetes, is an endocrine disorder that occurs when the body's immune system attacks special cells in the pancreas, destroying their ability to produce the hormone insulin. Without adequate insulin, glucose (blood sugar) cannot enter the cells, resulting in elevated blood glucose levels (hyperglycemia). According to recent estimates, this form of diabetes, which occurs most commonly in lean persons, usually under age 30, affects as many as one million persons in the U.S. In addition to the immediate risks associated with IDDM, such as diabetic coma, persons with the disease also are at greater risk for vascular complications, including blindness and kidney disease. Recent studies have linked these conditions to hyperglycemia, which is thought to increase oxidative stress in blood vessels and diminish their ability to dilate, thereby robbing these tissues of the oxygen and nutrients they require and leading, ultimately, to permanent tissue damage.

*Continued on page 6*

## Vitamin C May Help Prevent Lead Toxicity

**L**EAD toxicity is a serious public health problem in the U.S. and throughout the world. Based on national health surveys and data provided by the Environmental Protection Agency, in 1988 as many as 40 million U.S. children under age seven were exposed to potentially toxic levels of lead from various environmental sources. Up to 85% of lead exposure is related to ingestion of lead-containing

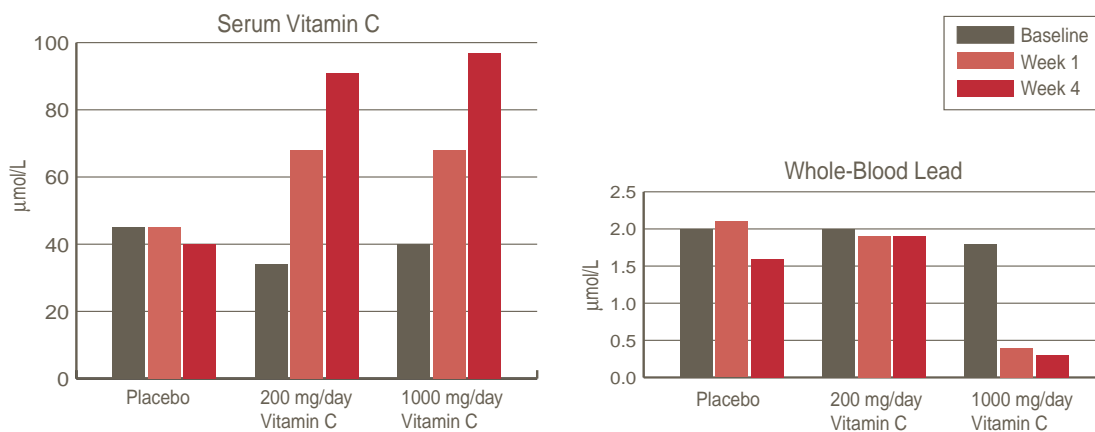
1991–1995 among 747 men aged 49 to 93 years, blood lead levels were 1.7 mg/dL higher among men in the lowest quintile (fifth) of dietary vitamin C intake (<109 mg/day) compared to those in the highest quintile (339 mg/day or more). The second study utilized data collected during the Third National Health and Nutrition Examination Survey (NHANES III), a cross-sectional sample of over 4,000 youths aged 6 to 16 years and over 15 thousand adults over age 16, conducted in 1988–1994. In an analysis by researchers at the University

of California at San Francisco,<sup>2</sup> the odds of elevated blood lead levels were nine times greater among youths with low serum levels of vitamin C compared to those with the highest vitamin C levels. In adults, the prevalence of elevated blood lead levels was about 65% lower among those in the two highest tertiles (thirds) of serum vitamin C compared to those in the lowest tertile.

one of three treatment groups: placebo, 200 mg/day vitamin C, or 1000 mg/day vitamin C. Vitamin C and lead concentrations were determined in blood and urine samples obtained at baseline and weekly throughout the four-week supplementation period.

Although serum vitamin C levels were similar among the three groups at baseline and did not change over the course of the study in the placebo group, by week 1 they had increased significantly in both supplemented groups and had more than doubled in these groups by the end of the trial. Interestingly, serum vitamin C levels at week 4 were similar in both supplemented groups, suggesting that tissues were essentially “saturated” with vitamin C at the 200 mg/day dose (Figure 2). Although urinary excretion of vitamin C increased significantly in the supplemented groups over the study period, urinary lead concentrations remained similar to baseline levels in all three experimental groups.

**Fig. 2. Serum Vitamin C and Whole-Blood Lead Concentration after Vitamin C Supplementation**



materials, such as lead paint and contaminated drinking water, dust and soil, with the remainder resulting from inhalation of lead-containing particles and fumes. Although children are more likely to be exposed to lead and are more vulnerable to the effects of lead toxicity, adults also are at risk. Numerous studies have shown that cigarette smoking or exposure to second-hand smoke is an important route of lead exposure among adults, resulting in elevated blood lead concentrations. Left untreated, chronic lead toxicity can produce serious irreversible effects, such as cognitive deficits in children and progressive renal disease in adults.

Evidence from two recent population studies suggests that vitamin C may help to protect against lead toxicity. In the Normative Aging Study,<sup>1</sup> conducted in

of California at San Francisco,<sup>2</sup> the odds of elevated blood lead levels were nine times greater among youths with low serum levels of vitamin C compared to those with the highest vitamin C levels. In adults, the prevalence of elevated blood lead levels was about 65% lower among those in the two highest tertiles (thirds) of serum vitamin C compared to those in the lowest tertile.

These epidemiologic studies provide evidence of an association between blood lead levels and dietary intake or serum levels of vitamin C. However, intervention studies are necessary to show that vitamin C actually causes reduced blood concentrations of lead. Researchers at the University of Texas Medical Branch at Galveston<sup>3</sup> conducted a vitamin C supplementation trial among 75 male smokers, aged 20 to 30 years. The subjects were randomly assigned to

Blood lead levels were unchanged from baseline in both the placebo group and those receiving 200 mg/day of vitamin C. However, in the group receiving 1000 mg/day of vitamin C, blood lead levels were significantly lower than baseline by week 1, and they remained extremely low in this group throughout the supplementation period (Figure 2).

In this study, daily supplementation with high doses of vitamin C (more than 16 times the RDA) rapidly reduced blood lead to nearly undetectable levels in young men who smoked. These findings are important for several reasons. First, they support data provided by epidemiologic studies and suggest that high intakes of vitamin C actually cause reductions in blood lead. Second, they suggest that among persons who smoke cigarettes, intakes of vitamin C in excess of 200 mg/day are necessary to

significantly influence blood lead levels. Finally, because urinary lead concentrations did not change in response to supplemental vitamin C, these findings suggest that vitamin C influences blood lead levels by reducing intestinal absorption of lead rather than by increasing urinary losses of the metal. Additional intervention trials are needed to determine the lowest effective dose of vitamin C and to determine the efficacy of supplemental vitamin C among children and persons suffering from greater lead exposures.

#### References

1. Cheng Y, Willett WC, Schwartz J, Sparrow D, Weiss S, Hu H. Relation of nutrition to bone lead and blood lead levels in middle-aged to elderly men. The Normative Aging Study. *Am J Epidemiol* 1998;147:1162-74.
2. Simon JA, Hudes ES. Relationship of ascorbic acid to blood lead levels. *JAMA* 1999;281:2289-93.
3. Dawson EB, Evans DR, Harris WA, Teter MC, McGanity WJ. The effect of ascorbic acid supplementation on the blood lead levels of smokers. *J Am Coll Nutr* 1999;18:166-70.

## Elevated Homocysteine and the Risk of Stroke

**O**VER three million strokes occur among persons in the U.S. each year. Although more common in older persons, strokes can occur at any age. The most common cause of stroke in the U.S. is atherosclerosis, the accumulation of fatty plaques along arterial walls. When arteries within the brain become narrowed by atherosclerosis, small clots can become lodged, blocking blood flow to the brain and resulting in neurologic damage. Although some strokes are very mild and many persons recover full function, strokes remain a major cause of death and disability.

Recent studies have linked elevated blood levels of the amino acid homocysteine to increased risk of vascular diseases, including heart disease and stroke. Homocysteine is a by-product of protein metabolism that accumulates in the blood as a result of genetic

abnormalities or inadequate dietary intakes of folic acid and/or vitamins B<sub>12</sub> and B<sub>6</sub>. Homocysteine is thought to increase the risk of stroke by contributing to the development of atherosclerosis and high blood pressure as well as by altering blood clotting mechanisms (see article on supplemental vitamin C and heart disease, this issue).

Although elevated homocysteine appears to be an independent risk factor for stroke among older white men, relatively little information has been available on its potential role in more diverse populations. However, in a recent epidemiologic study,<sup>1</sup> researchers at the Centers for Disease Control and Prevention, in Atlanta, analyzed data from the Third National Health and Nutrition Examination Survey (NHANES III). This study, conducted between 1988 and 1994, was designed to estimate the prevalence of various chronic conditions among a nationally representative sample of the U.S. population. The study sample for the current analysis included 4,534 persons over age 35 for whom serum homocysteine measurements were available. Among these, a total of 185 non-fatal strokes were reported.

When serum homocysteine concentrations were divided into four groupings, or quartiles, ranging from the lowest to the highest levels, the odds of suffering a stroke were 250% greater for white persons in the highest quartile of homocysteine compared to those in the lowest quartile. Among African-Americans, the odds of stroke were 40% greater among persons in the highest versus the lowest homocysteine quartile.

A second population-based investigation,<sup>2</sup> conducted by researchers at the University of Maryland at Baltimore, examined the association between elevated homocysteine and the risk of stroke in young women. The study cases were 167 women, aged 15 to 44 years, who were diagnosed with a cerebral infarction (stroke) at one of 59 hospitals within the study area. Control subjects were 328 women without a history of stroke, matched to cases by age and area of residence. Plasma homocysteine

concentrations were determined in nonfasting blood samples, and information regarding health and lifestyle factors known to influence the risk of stroke was collected through interviews.

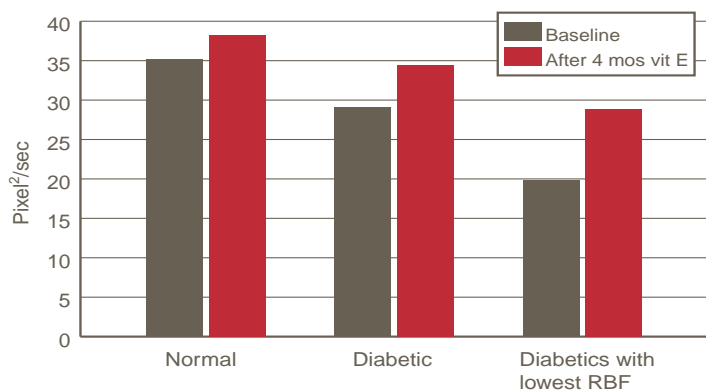
In general, stroke cases were significantly more likely than control subjects to be black, to live below the poverty line, to smoke cigarettes, and not to use vitamin supplements. When the risk of suffering a stroke was compared across levels of plasma homocysteine, the odds of a stroke were twice as great among those whose homocysteine levels were in the upper two-fifths of the distribution compared to those in the lowest fifth, regardless of race. Even after adjusting for poverty status, vitamin use, and cigarette use, elevated homocysteine levels remained associated with a 60% increase in the risk of stroke.

A third study,<sup>3</sup> by researchers at the University Hospital of Umeå, Sweden, examined the association between homocysteine and stroke in young adults. Study cases were 50 men and 30 women, aged 18 to 44 years, and control subjects were 41 men and women of similar age. Plasma levels of homocysteine were determined in fasting blood samples. In addition, homocysteine levels also were assessed four hours following a single dose of the amino acid methionine (100 mg/kg body weight), the metabolic precursor of homocysteine. This technique, known as a methionine load test, is used to identify persons with abnormal homocysteine metabolism with greater sensitivity.

Unlike the previous two studies, in this study fasting homocysteine levels were similar in case and control subjects. However, the increase in plasma homocysteine following the methionine load was significantly greater among cases than controls. After adjusting for potentially confounding factors, including age and gender, this difference in the postload increase in homocysteine was associated with nearly a fivefold increase in the risk of stroke.

Taken together, the results of these three studies suggest that elevated

*Continued on page 8*

**Fig. 3. Improved Retinal Blood Flow Following Vitamin E Treatment**

### Vitamin E and Diabetes

*Continued from page 3*

In the last issue of *VitaminNews* (Vol. VI, No. 3), we reported the results of a Finnish population study which suggested that poor vitamin E status increases the risk of IDDM. Now a double-blind, placebo-controlled study by researchers at Harvard Medical School has shown that high doses of vitamin E may help to prevent the risk of visual and renal complications in persons with IDDM. For the current study, 36 persons who had IDDM for less than 10 years and 9 nondiabetic subjects were enrolled. All participants were 18 to 44 years of age. At baseline, blood flow in the retina of the eye was determined by injecting a dye into an arm vein and monitoring passage of the dye through the retina. Kidney function was assessed by measuring renal excretion of creatinine (a by-product of muscle protein metabolism) in overnight urine samples. Subjects were then randomly assigned to receive either a placebo or an oral supplement containing 1800 IU vitamin E/day. After four months, kidney function and retinal blood flow were reassessed, and subjects were crossed over to the alternative treatment for another four months. Retinal blood flow and kidney function were assessed a final time at the end of the study.

At baseline, retinal blood flow was significantly lower in diabetic subjects

than in controls. Although retinal blood flow was unchanged in diabetic persons following placebo treatment, it improved by nearly 20% following treatment with vitamin E, reaching levels similar to those in nondiabetic persons. Improvement in retinal blood flow

was most pronounced among those diabetic persons with the lowest baseline values. Retinal blood flow in control subjects was virtually unchanged by vitamin E supplementation (Figure 3). Creatinine clearance at baseline was significantly greater among diabetic subjects than controls, indicating renal hyperfiltration. Following vitamin E treatment, however, creatinine clearance was 10% lower than baseline levels among diabetics and, again, was similar to baseline levels in nondiabetics. Vitamin E treatment had no effect on creatinine clearance among nondiabetic control subjects.

These findings suggest that long-term supplementation with high doses of vitamin E help to normalize kidney function and retinal blood flow in persons with IDDM. The authors caution, however, that "the results of the current study should not be misconstrued as an indication for the widespread use of vitamin E for the treatment of diabetic retinopathy." Additional clinical trials are needed to determine whether this extremely high dose of vitamin E is necessary to produce these beneficial effects and whether use of vitamin E in a medical context translates into reduced risk of diabetic complications.

#### Reference

Bursell S-E, Clermont AC, Aiello LP, et al. High-dose vitamin E supplementation normalizes retinal blood flow and creatinine clearance in patients with type I diabetes. *Diabetes Care* 1999; 22:1245-51.

### Supplemental Vitamin C and Heart Disease

**C**ORONARY artery disease (CAD) occurs when fatty plaques accumulate in the walls of the large and medium-sized arteries of the heart, restricting the flow of nutrient-rich blood to the heart muscle. The major consequences of CAD include angina (chest pain), myocardial infarction (MI or heart attack), and sudden death. In the U.S., CAD and other cardiovascular diseases remain the leading cause of death among both men and women, accounting for nearly one million deaths each year.

In addition to the build-up of fatty plaques, CAD also is characterized by impaired activity of endothelium-derived nitric oxide (NO). This powerful compound is produced in the cells of blood vessels in response to other chemical signals. Recent research indicates that NO helps to regulate arterial contraction and dilation as well as the activity of platelets, the cell-like structures involved in clot formation. Although the cause of impaired NO activity in persons with CAD is not known with certainty, some studies have suggested that increased vascular production of prooxidants, such as superoxide anion, may play a role. The link between oxidative stress and impaired NO activity is supported by numerous studies showing that short-term administration of high doses of vitamin C, an antioxidant nutrient, improves vasodilation in the arteries of the heart and forearm.

Other evidence has implicated high blood levels of the amino acid homocysteine in the development of atherosclerosis (fatty plaques). Elevated homocysteine occurs in response to inadequate dietary intake of folic acid and/or vitamins B<sub>12</sub> and B<sub>6</sub> or as a result of genetic mutations. Numerous population studies have shown that high homocysteine levels are an independent risk factor for vascular diseases, including CAD and stroke (see article on homocysteine and

stroke in this issue of *VitaminNews*). Researchers speculate that homocysteine contributes to the development of fatty plaques through several mechanisms, including directly damaging vessel walls, increasing oxidation of LDL (i.e. "bad") cholesterol, and promoting clot formation. Moreover, recent evidence suggests that elevated homocysteine also may influence NO activity, possibly by increasing oxidative stress, which would further increase the risk of CAD by interfering with vasodilation.

Two recent clinical trials have addressed the role of oxidative stress in the blood vessel dilation abnormalities observed in CAD. The first study, by researchers at Boston University School of Medicine,<sup>1</sup> determined the effects of both short- and long-term treatment with vitamin C on blood flow in the brachial (forearm) artery. A total of 46 men and

*Continued on page 8*

## Vitamins & Breast Cancer

*Continued from page 1*

### Folic Acid and Vitamin B<sub>12</sub>

Evidence from laboratory and animal studies suggests that folic acid and vitamin B<sub>12</sub> may play a role in the development of cancer, including breast cancer. Both B vitamins are involved in the synthesis of nucleotides, the building blocks of DNA. Dietary deficiencies can lead to impaired synthesis and repair of DNA, which could increase the risk of genetic mutations. In addition, both vitamins also are necessary for a process known as DNA methylation, an important step in converting gene-encoded messages into body proteins. Low intakes of folic acid have been linked to colon cancer, but until very recently there was little evidence that either vitamin influenced the risk of breast cancer.

In a second analysis of data from the Nurses' Health Study,<sup>7</sup> Harvard researchers found no association between folate intake and overall risk of breast cancer. However, when the analysis was separated according to alcohol intake (less

than 15 g/day versus 15 g/day or more), increased consumption of folic acid was associated with a 45% lower risk of breast cancer among women with higher alcohol intake but had no effect on risk among women with lower alcohol consumption. As was true for antioxidant vitamins, these findings suggest that high intakes of folic acid may help to reduce the excess risk of breast cancer associated with alcohol intake.

Other evidence<sup>8</sup> suggests that vitamin B<sub>12</sub> may help protect against breast cancer. In a case-control study by researchers at the Johns Hopkins University School of Hygiene and Public Health, vitamin B<sub>12</sub> levels were significantly lower among cases than controls. Moreover, the odds of developing breast cancer were two-and-a-half times greater among women in the lowest vitamin B<sub>12</sub> quintile (fifth) compared to those in the highest. When the analysis was restricted to women who were postmenopausal both at the time of blood donation and breast cancer diagnosis, those in the lowest vitamin B<sub>12</sub> quintile were four times more likely to develop breast cancer than those in the highest quintile.

### Vitamin D

Although vitamin D is commonly associated with bone health, researchers now know that it also plays an important role in cell differentiation—the process through which cells develop their specialized functions. Unlike normal cells, cancerous cells grow without differentiating. Previous studies have shown that death rates from breast cancer are higher in northern latitudes and are inversely related to sun exposure. Because vitamin D is synthesized in the skin upon exposure to ultraviolet radiation, researchers have speculated that vitamin D status may influence breast cancer risk. In an analysis of data from the first National Health and Nutrition Examination Survey, a large population-based study, John et al.<sup>9</sup> found that the risk of breast cancer was 64% lower among women with high sun exposure and vitamin D intakes of at least 200 IU/

day compared to those with little sun exposure and lower vitamin D intakes.

### Conclusions

Data from epidemiologic studies suggest that vitamin status may influence a woman's risk of developing breast cancer, particularly among premenopausal women and those who consume alcohol. Because most risk factors associated with breast cancer, such as age and family history, cannot be altered, efforts to reduce breast cancer risk should focus on lifestyle modifications, including increased intake of vitamins.

### References

1. Willett WC. Dietary fat and breast cancer. In: *Nutritional Epidemiology*, 2<sup>nd</sup> ed. New York: Oxford University Press, 1998, 377–413.
2. Zhang S, Tang G, Russell RM, et al. Measurement of retinoids and carotenoids in breast adipose tissue and comparison of concentrations in breast cancer cases and control subjects. *Am J Clin Nutr* 1997;66:626–32.
3. Potischman N, McCulloch CE, Byers T, et al. Breast cancer and dietary and plasma concentrations of carotenoids and vitamin A. *Am J Clin Nutr* 1990;52:909–15.
4. Dorgan JF, Sowell A, Swanson CA, et al. Relationships of serum carotenoids, retinol, alpha-tocopherol, and selenium with breast cancer risk: results from a prospective study in Columbia, Missouri. *Cancer Causes Control* 1998; 9:89–97.
5. Bohlke K, Spiegelman D, Trichopoulou A, Katsouyanni K, Trichopoulos D. Vitamins A, C and E and the risk of breast cancer: results from a case-control study in Greece. *Br J Cancer* 1999;79:23–9.
6. Zhang S, Hunter DJ, Forman MR, et al. Dietary carotenoids and vitamins A, C, and E and risk of breast cancer. *J Natl Canc Inst* 1999;91:547–56.
7. Zhang S, Hunter DJ, Hankinson SE, et al. A prospective study of folate intake and the risk of breast cancer. *JAMA* 1999;281:1632–7.
8. Wu K, Helzlsouer KJ, Comstock GW, et al. A prospective study on folate, B<sub>12</sub>, and pyridoxal 5'-phosphate (B<sub>6</sub>) and breast cancer. *Cancer Epidemiol Biomark Prev* 1999;8:209–17.
9. John EM, Schwartz GG, Dreon DM, Koo J. Vitamin D and breast cancer risk: The NHANES I Epidemiologic Follow-up Study, 1971–1975 to 1992. *Cancer Epidemiol Biomark Prev* 1999;8:399–406.

### Supplemental Vitamin C and Heart Disease

*Continued from page 7*

women, mostly in their mid-50s, were randomly assigned to receive either placebo or vitamin C. All participants had documented CAD, but persons who reported recent use of antioxidant vitamins and those whose cardiac status was considered unstable were excluded from the study. Baseline measurements of flow-mediated dilation of the brachial artery were determined using ultrasound imaging. Subjects then received placebo or an oral supplement containing 2000 mg of vitamin C, and two hours later the short-term effects of vitamin C were determined by reassessing arterial dilation. Subjects assigned to vitamin C treatment were then provided with daily supplements containing 500 mg vitamin C, and the long-term effects of supplementation were assessed 30 days later.

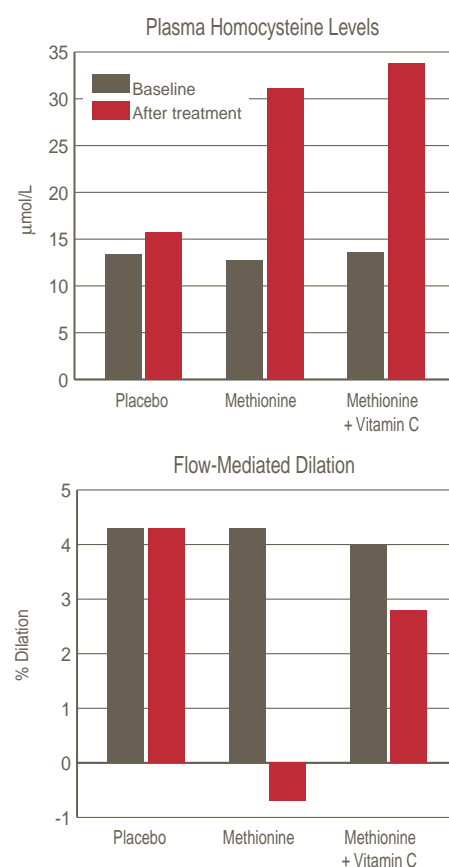
Flow-mediated brachial artery dilation was unchanged following both short- and long-term treatment with placebo. However, dilation increased from an average baseline level of 6.6% up to 10.1% after short-term treatment with 2000 mg vitamin C. After 30 days of vitamin C supplementation, dilation remained significantly improved from baseline at 9.0%. The beneficial effects of vitamin C were particularly evident in a subset of participants whose baseline dilation was less than 10%. These findings indicate that short-term treatment with supplemental vitamin C improves flow-mediated vasodilation in persons with CAD and that this effect is sustained following long-term vitamin C supplementation.

The second study,<sup>2</sup> conducted by researchers at the Imperial College School of Medicine in London, assessed the effects of elevated homocysteine and vitamin C supplementation on vasodilation in 17 healthy men and women, aged 21 to 59 years. Elevated homocysteine was induced in study subjects by oral administration of the amino acid methionine, which is the metabolic precursor of homocysteine. Flow-mediated brachial artery dilation and plasma homocysteine concentrations were determined at baseline (fasting) and at two

and four hours after treatment with either 1) oral methionine only (100 mg/kg body weight), 2) oral methionine preceded by vitamin C (1000 mg/day for 1 week), or 3) placebo. The three treatments were administered in random order on separate days, at least two weeks apart, and included all 17 subjects.

As expected, plasma homocysteine levels increased significantly from baseline

**Fig. 4. Supplemental Vitamin C and Heart Disease**



levels following oral administration of methionine alone or methionine and vitamin C but were unaffected by placebo treatment. Following treatment with methionine only, flow-mediated dilation was significantly lower than baseline levels at both two and four hours, indicating that elevated levels of homocysteine do contribute to reduced vessel function. However, this reduction in flow-mediated dilation was prevented when vitamin C was provided in addition to methionine

(Figure 4). These findings suggest that, even though vitamin C supplements do not directly influence plasma levels of homocysteine, they may prevent some of the detrimental vascular effects associated with elevated homocysteine.

Although both of these studies used relatively few subjects, their results are important because they provide further evidence that oxidative stress interferes with normal blood vessel function and that normal function can be at least partly restored by provision of supplemental vitamin C. Larger clinical trials are needed to establish the optimal dose of vitamin C needed to produce these beneficial effects.

#### References

1. Gokce N, Keaney JF Jr., Frei B, et al. Long-term ascorbic acid administration reverses endothelial vasomotor dysfunction in patients with coronary artery disease. *Circulation* 1999;99:3234-40.
2. Chambers JC, McGregor A, Jean-Marie J, Obeid OA, Kooner JS. Demonstration of rapid onset vascular endothelial dysfunction after hyperhomocysteinemia. An effect reversible with vitamin C therapy. *Circulation* 1999;99:1156-60.

### Elevated Homocysteine and Stroke

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homocysteine is an independent risk factor for stroke among blacks as well as whites, among women as well as men, and among young persons as well as old. Additional studies are needed to determine whether long-term supplementation with folic acid and other B vitamins, which has been shown to reduce plasma homocysteine levels, can reduce the risk of stroke in these populations.

#### References

1. Giles WH, Croft JB, Greenlund KJ, et al. Total homocyst(e)ine concentration and the likelihood of nonfatal stroke: results from the Third National Health and Nutrition Examination Survey, 1988-1994. *Stroke* 1998;29:2473-7.
2. Kittner SJ, Giles WH, Macko RF, et al. Homocyst(e)ine and risk of cerebral infarction in a biracial population. The Stroke Prevention in Young Women Study. *Stroke* 1999;30:1554-60.
3. Kristensen B, Malm J, Nilsson TK, et al. Hyperhomocysteinemia and hypofibrinolysis in young adults with ischemic stroke. *Stroke* 1999;30:974-80.