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INSIDE

*Foods high in
antioxidants
page 60*

*Table:
Best sources
of food
antioxidants
page 60*

*Got stones?
Get milk
page 62*

*Poor urban
populations
frequently use
some form of
CAM, study
shows
page 64*

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Cervical Cancer and Antioxidants

*By Lynn Keegan, RN, PhD, HNC, FAAN
and Gerald T. Keegan, MD, FACS*

CERVICAL CANCER IS THE SECOND MOST COMMON CANCER WORLD-wide and is a leading cause of cancer-related deaths in women in underdeveloped countries. Worldwide, approximately 500,000 cases of cervical cancer are diagnosed yearly.^{1,2} Invasive cervical cancer is more common in middle-aged and older women of poor socioeconomic status. There is a higher rate of incidence in African-American, Hispanic, and Native American women. Specific genotypes have been associated with the development of the malady.³

Etiology of Cervical Cancer

Although the cause of cervical cancer is unknown, there has been association of the disease with two types of human papilloma virus (HPV), both of which are transmitted sexually. Evidence of HPV is found in nearly 80% of cervical carcinomas. Human immunodeficiency virus (HIV) infection reduces the immune system's ability to combat infection, including HPV, and thus increases the likelihood of the disease.⁴⁻⁶ It also has been established that women who smoke are twice as likely to develop cervical cancer.⁷ The authors of this paper have suggested that cigarette byproducts may affect the early evolution of HPV-related lesions, possibly by increasing the rate of cell turnover. It is likely that the actual cause of the disease is multifactorial and that the presence of the HPV induces the development of premalignant cells, which under the influence of oxidative stress and perhaps genetic⁶ and nutritional⁸ factors will further evolve into malignant and eventually invasive lesions. Some of these enabling factors may be reversible by the use of appropriate antioxidants.⁸

Mechanisms of Action

Although there are a number of studies on the mechanistic role of antioxidants in the prevention of the evolution of precancerous cervical cells into frank malignancy, the entire relationship has yet to be elucidated. Epidemiologic nutritional studies suggest that higher dietary consumption and circulating levels of certain micronutrients may be protective against cervical cancer. Low levels of essential

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antioxidants in the circulation have been found to be associated with an increased risk of cancer.¹ It is possible that the infection with HPV induces an oxidative stress in cervical cells which then in association with other factors proceeds to the development of premalignant cells including cervical intraepithelial neoplasia (CIN) and thence to frankly malignant dedifferentiation. Antioxidants are theorized to reverse this process by a variety of mechanisms.

Clinical Studies

A study was undertaken in Japan to investigate the effect of the major tea polyphenol, (-)-epigallocatechin gallate (EGCG) in cervical carcinogenesis. This study suggested that EGCG prevents the carcinogenesis of cervical cancer, induces apoptosis, and inhibits telomerase activity. The effect by EGCG treatment may be associated with the induction of apoptosis and telomerase inhibition in early cervical lesions.⁹ A related study assessed the effect of EGCG on epidermal growth factor receptor (EGFR). EGFR signaling activation is absolutely required for cervical cell proliferation and is a promoter of the disease. Thus, EGFR-inhibitory agents

may be of therapeutic value. The authors demonstrated that EGCG treatment caused apoptosis of the abnormal cervical cells. In addition, they found EGCG acts simultaneously at multiple levels to inhibit epidermal growth factor (EGF)-dependent signaling. These results suggest that EGCG acts to selectively inhibit multiple EGF-dependent kinases to inhibit cell proliferation.¹⁰ A study from South Korea reinforced the anti-proliferative effects of EGCG. This study of HPV-associated cervical cancer cells in tissue culture demonstrated both a gene-regulatory role for EGCG as well as inhibition of cervical cancer cell growth through the induction of apoptosis and cell cycle arrest.¹¹ Another study from South Korea that investigated clinical efficacy of green tea extracts EGCG in patients with HPV-infected cervical lesions demonstrated that the extract in a form of ointment or a capsule was effective in treating cervical lesions. These findings suggest that green tea extracts can be a potential therapy regimen for patients with HPV-infected cervical lesions.¹²

Cofactors, such as nutritional factors, may be necessary for viral (HPV) progression to neoplasia. Many studies have suggested that higher dietary consumption and circulating levels of certain micronutrients might be protective against cervical neoplasia. A study was undertaken to evaluate the role of vitamin A and carotenoids on HPV persistence by comparing women with intermittent and persistent infections. The results showed a 56% reduction in HPV persistence risk observed in women with the highest plasma cis-lycopene concentrations compared with women with the lowest plasma cis-lycopene concentrations. These data suggest that vegetable consumption and circulating cis-lycopene may be protective against HPV persistence.¹³ A very interesting finding, possibly applicable to the treatment of invasive carcinoma of the cervix, was the effect of d-alpha-tocopheryl succinate (alpha-TS) in modifying radiation-induced chromosomal damage in human normal cells and cancer cells in culture. The use of this vitamin E-like substance during radiation therapy possibly could improve the efficacy of radiation therapy in cervical cancer by enhancing tumor response and decreasing some of the toxicities on normal cells.¹⁴

Another antioxidant, resveratrol, is a polyphenol isolated from the skins of grapes. This substance has been shown to significantly alter the cellular physiology of tumor cells, as well as block the process of initiation and progression. One mechanism for the intracellular actions of resveratrol involves the suppression of prostaglandin (PG) biosynthesis. The involvement of PGs and other eicosanoids in the development of human cancer is well-established. A study using two human

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cervical tumor cell lines demonstrated that resveratrol alters both cell cycle progression and the cytotoxic response to ionizing radiation.¹⁵

A cross-sectional study was undertaken to investigate the comparative plasma concentrations of three potent antioxidants—coenzyme Q₁₀ (CoQ₁₀), alpha-tocopherol, and gamma-tocopherol—in women with normal Pap smears and patients with a biopsy-confirmed histopathological lesion diagnosed as CIN or overt cervical cancer. After controlling for age and smoking, an inverse association between histological grades of epithelial lesions and both plasma CoQ₁₀ and alpha-tocopherol concentrations was observed. The low plasma concentration of CoQ₁₀ in the women with cervical lesions was believed to be secondary either to deficient dietary intake or a decrease in endogenous CoQ₁₀ biosynthesis. The decreased CoQ₁₀ biosynthesis possibly reflected increased utilization of this enzyme as a result of free radical reactive oxygen species-induced oxidative stress.¹⁶ The extent of free radical-induced oxidative stress can be exacerbated by the decreased efficiency of antioxidant defense mechanisms.

To assess the extent of oxidative stress, Manju et al measured the levels of antioxidants superoxide dismutase (SOD), catalase (CAT), and ceruloplasmin, and evaluated tumor markers, such as aspartate transaminase, alanine transaminase, alkaline phosphatase, and total sialic acid levels, in circulation of women with cervical carcinoma. These data were compared with levels in age-matched controls. Low levels of SOD and CAT were observed in the circulation of cervical cancer patients.¹⁷

This effect was believed to be secondary to the increased utilization of these enzymes to scavenge lipid peroxides as well as their sequestration by tumor cells.¹ This conclusion was verified by a case-control study that was conducted to investigate the status of circulating lipid peroxidation and the enzymic and nonenzymic antioxidants of cervical cancer patients. Plasma thiobarbituric acid reactive substances (TBARS), conjugated dienes (CD), and the levels of antioxidants such as reduced glutathione (GSH), glutathione peroxidase (GPx), glutathione-S-transferase (GST), SOD, vitamin C, and vitamin E, were estimated in circulation of 30 patients and an equal number of age-matched normal subjects as control. The authors observed significantly elevated levels of plasma TBARS and CD and significantly lowered levels of GSH, GPx, GST, SOD, vitamin C, and vitamin E in cervical cancer patients as compared to controls. The study confirmed increased lipid peroxidation and possible breakdown of antioxidant status in patients with cervical carcinoma and suggested that the

low levels of antioxidants may be due to their increased utilization to scavenge lipid peroxides as well as their sequestration by tumor cells.¹⁷

With the theory that oxidative stress is implicated in the etiology of many diseases, the antioxidants are thought to diminish oxidative stress. To this effect, researchers in Hong Kong evaluated the effects of ingested vitamins C (500 mg) and E (400 IU), alone and in combination, on biomarkers of plasma antioxidant status, lipid peroxidation, and lymphocyte DNA damage in 12 volunteers. The data showed no evidence of either a protective or deleterious effect on DNA damage, resistance of DNA to oxidant challenge, or lipid peroxidation. No evidence of a synergistic or cooperative interaction between vitamins C and E was seen, but further study is needed to determine possible interactive effects in a staggered supplementation cycle. Study of subjects under increased oxidative stress or with marginal antioxidant status would be useful. It would be of interest also to study the effects of these vitamins ingested with, or in, whole food to determine if they are directly protective at doses above the minimum required to prevent deficiency; if combinations with other food components are needed for effective protection; or if vitamins C and E are largely surrogate biomarkers of a “healthy” diet, but are not the key protective agents.¹⁸

An Austrian study monitored the dietary habits of 59 healthy, middle-aged men and women to assess the effect of supplementation with a natural phytonutrient preparation from fruits and vegetables on plasma levels of various antioxidant micronutrients and oxidative stress. Results found significant increases in blood nutrient levels after active supplementation for beta-carotene, vitamin C, vitamin E, selenium, and folate. Ranges measured after supplementation often fell into those associated with a reduced risk for disease. The researchers concluded that supplementation with mixed fruit and vegetable juice concentrates increased plasma levels of important antioxidant nutrients.¹⁹

Food Sources and Patterns of Usage for Antioxidants

A Spanish study of 41,446 healthy volunteers assessed the principal food sources of vitamin C, vitamin E, alpha-carotene, beta-carotene, lycopene, lutein, beta-cryptoxanthin, and zeaxanthin in an adult Spanish population. Foods that provided at least two-thirds of the studied nutrients were: fruits (mainly oranges) (51%) and fruiting vegetables (mainly tomato and sweet pepper) (20%) for vitamin C; vegetable oils (sunflower and olive) (40%), non-citrus fruits (10%), and nuts and seeds (8%) for vitamin E; root vegetables (car-

Foods High in Antioxidants

By Lynn Keegan, RN, PhD, HNC, FAAN,
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Most high antioxidant foods are vegetable matter (i.e., tomatoes, broccoli, cauliflower, and peppers). Fruits and vegetables that have rich hues of color contain phytonutrients, which are nutrients concentrated in the skins of many vegetables and fruits and are responsible for not just their color, but scent, and flavor as well. Phytonutrients are the best antioxidant foods that exist in nature.

For example red onions, rather than white ones contain the antioxidants. If you like grapes, eat the red ones. Instead of green peppers, try yellow, orange, purple, or red. Remember, the deeper and richer the color of the fruit or vegetable, the more phytonutrients that are present in it. Blueberries and bilberries are two of the best antioxidant foods and are very rich in phytonutrients.

Table 1 depicts 20 food sources of antioxidant foods. ❖

rots) (82%) for alpha-carotene; green leafy (28%), root (24%) and fruiting vegetables (22%) for beta-carotene; fruiting vegetables (fresh tomato) (72%) for lycopene; green leafy vegetables (64%) for lutein; citrus fruits (68%) for beta-cryptoxanthin; citrus fruits (43%) and green leafy vegetables (20%) for zeaxanthin.²⁰

In the United States, the percentage of adults using any vitamin and mineral supplement daily increased from 23.2% in 1987 to 23.7% in 1992 to 33.9% in 2000. This pattern was consistent for both sexes, all race/ethnic groups, and adults age 25 and older. The increase in the percentage of daily users of multivitamins, vitamin A, and vitamin E was 10.5%, 1.2%, and 7.3%, respectively, from 1987 to 2000. Increases in daily use of vitamin C (3.3%) and calcium (6.1%) occurred between 1992 and 2000. All trend analyses were significant at $P < 0.001$. In the 2000 National Health Interview Survey, personnel queried the use of nonvitamin/nonmineral supplements for the first time. At that time, 6.0% of respondents reported using them daily.²¹

Adverse Effects

There are no specific contraindications of intake of antioxidants; however, excessive dosages of any one thing could be detrimental. For example, increased levels of vitamin C are linked to the formation of kidney stones and vitamin A is toxic in extremely high doses.

Socioeconomic Status

For some time we have suspected that socioeconomic status relates to quality and type of food intake. Lack of education and motivation often results in poor food choices and the resultant health consequences. British researchers did a randomized trial comparing behavioral counseling with nutritional education counseling to increase fruit and vegetable consumption and associated biomarkers in 271 adults from a low-income neighborhood. The objective was to assess the impact of interventions on quality of life and health status, and associations between changes in fruit and vegetable consumption, plasma levels of vitamins C and E, and quality of life. The findings were that with reported increase in fruit and vegetable consumption, plasma vitamin C, E, and beta-carotene increased along with reported increased health. The researchers concluded that increases in fruit

Table 1

Best sources of food antioxidants: Top 20 fruits, vegetables and nuts (as measured by total antioxidant capacity per serving size)

Rank	Food item	Serving size	Total antioxidant capacity per serving size
1	Small red bean (dried)	½ cup	13727
2	Wild blueberry	1 cup	13427
3	Red kidney bean (dried)	½ cup	13259
4	Pinto bean	½ cup	11864
5	Blueberry (cultivated)	1 cup	9019
6	Cranberry	1 cup (whole)	8983
7	Artichoke (cooked)	1 cup (hearts)	7904
8	Blackberry	1 cup	7701
9	Prune	½ cup	7291
10	Raspberry	1 cup	6058
11	Strawberry	1 cup	5938
12	Red Delicious apple	1	5900
13	Granny Smith apple	1	5381
14	Pecan	1 ounce	5095
15	Sweet cherry	1 cup	4873
16	Black plum	1	4844
17	Russet potato (cooked)	1	4649
18	Black bean (dried)	½ cup	4181
19	Plum	1	4118
20	Gala apple	1	3903

Source: American Chemical Society. Largest USDA study of food antioxidants reveals best sources. Available at: www.eurekalert.org/pub_releases/2004-06/aas-lus061504.php. Accessed July 11, 2004.

and vegetable intake and plasma vitamin levels may stimulate beneficial changes in physical health status in socioeconomically deprived adults.²²

Conclusion

The literature clearly establishes both a protective and a therapeutic advantage in selected antioxidants including vitamins A, C, and E, CoQ₁₀, EGCG, resveratrol, and vegetable lycopenes. Similarly, it may be contended that the higher incidence of disease in lower socioeconomic groups may be related to dietary deficiency of those same substances. There are a number of things women can do to deter the risk of cervical cancer, such as avoid smoking and second hand smoke; practice safe sex (the use of condoms prevents most sexually transmitted diseases including HPV, a common precursor of cervical cancer); and increase intake of antioxidants through foods and supplements. ❖

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Got Stones? Get Milk

Synopsis: Dietary calcium, phytate, and fluid intake are associated with a decreased risk of symptomatic nephrolithiasis in younger women.

Source: Curhan GC, et al. Dietary factors and the risk of incident kidney stones in younger women: Nurses' Health Study II. *Arch Intern Med* 2004;164:885-891.

THE NURSES' HEALTH STUDY II ENROLLED 116,671 female registered nurses in 1989 and continues to follow them. After completing an initial questionnaire, each participant receives follow-up mailings every two years. Curhan and colleagues began asking questions about diet in 1991. This prospective, longitudinal cohort study already has yielded intriguing information about the protective effect of vitamin D on multiple sclerosis¹ and the relationship between dietary animal fat and breast cancer.² Using data from the original Nurses' Health Study I, this same group of investigators demonstrated that a high intake of dietary calcium in older women appeared to decrease the risk of symptomatic kidney stones. On the other hand, supplemental calcium seemed to increase the risk.³ The current study asked the question, "Is there a relationship between diet and kidney stones in younger women?"

A semiquantitative food inventory assessed average food and beverage intake. Information was obtained about supplemental calcium intake (separately and as part of a multivitamin). After excluding women with a history of kidney stones and those in whom the date of diagnosis could not be confirmed, 96,245 women remained. At the beginning of the study these women ranged in age from 25 to 42. If a subject reported a kidney stone in any of the biennial questionnaires, a follow-up questionnaire was mailed that gathered information about the date of occurrence, symptoms, relevant medical circumstances (for example, inflammatory bowel disease, hyperparathyroidism, hyperthyroidism, or urinary tract infection), and stone composition.

During 685,973 person-years of follow up, 1,223 symptomatic kidney stones were reported. Only 5.1% of women reported a chronic illness that could conceivably be related to stone creation. However, 17.5% had a UTI. A family history of kidney stones was present in 36.4%, and gout in 21.1%. Stone composition was known in 439 cases; 87.5% contained calcium, 10.0% were urate. In 95.2%, pain was the presenting symptom.

The subjects were divided into five groups based on dietary calcium intake. Dietary calcium intake was directly related to intake of animal protein, sodium,

potassium, magnesium, phosphorus, vitamin B₆, vitamin C, vitamin D, and fluid. It was inversely related to the intake of sucrose and alcohol. The average consumption of calcium supplements and phytate did not vary across the five calcium groups. The age-adjusted relative risk (RR) of kidney stones fell dramatically as dietary calcium increased. The lowest quintile was the reference (RR = 1.00). At the upper quintile the RR = 0.54 (95% confidence interval [CI], 0.45-0.63). The RR rose to 0.73 (95% CI, 0.59-0.90) after adjusting for body mass index and multiple dietary constituents (including supplemental calcium and phytate). Supplemental calcium was not associated with risk of kidney stones.

Other dietary factors were studied, again by dividing the group into quintiles and using the lowest as the reference. In multivariate analysis, two were associated with a reduced RR of kidney stones: phytate (RR = 0.63; CI, 0.51-0.78) and fluid (RR = 0.68; CI, 0.56-0.83). Animal protein showed a trend toward protection (RR = 0.84; CI, 0.68-1.04). Sucrose intake was associated stone formation at the highest quintile (RR = 1.31; CI, 1.07-1.60).

Comment by Allan J. Wilke, MD

In the United States, the annual incidence of kidney stones is 7-21 per 10,000 population.⁴ What does this study add to our understanding of this disease (remembering that cohort studies such as this cannot prove causation, only show associations)?

1. An increased intake of fluid reduces the risk of kidney stones makes sense intuitively and forms the basis of advice to patients who have just completed their first episode of passing a stone. A previous study showed that coffee, tea, and wine, but not grapefruit juice,⁵ reduced risk.

2. Current teaching is that practitioners should instruct patients to limit intake of animal protein to reduce urate excretion,⁶ although a randomized controlled study showed no more benefit to a low animal protein, high-fiber, high fluid volume diet than just increased fluid alone.⁷ The current study showed a trend favoring animal protein as a protective factor. This did not reach statistical significance.

3. Increased dietary calcium, but not calcium supplements, is associated with protection against stone formation. This is somewhat counterintuitive, since most stones contain calcium, but consistent with a previous study in men.⁸ Why dietary calcium, but not calcium supplements? Curhan et al speculate that dietary calcium binds oxalate in the gut. (Calcium oxalate comprises 70% of kidney stones.) They previously reported that most people take calcium supplements without food or only with breakfast.³ If so, there would be fewer opportu-

nities for calcium to bind oxalate. Another theory is that dairy products contain some other constituent that mitigates the risk.

4. Sucrose intake is associated with a higher risk of kidney stones. One might assume that is the result of the subjects substituting soft drinks for milk, but sucrose intake remained a risk in multivariate analysis. Curhan et al note that sucrose promotes urinary calcium excretion.

5. Phytate intake is associated with a reduced risk of stone formation. Phytate (phytic acid or inositol hexaphosphate) is a source of phosphorus from plants. It forms insoluble complexes with calcium in the gut. That would reduce urinary calcium excretion and, presumably, the formation of calcium-containing stones. Another theoretical mechanism relies on phytate's ability to inhibit nucleation of calcium oxalate crystals. Phytate is an antioxidant and is present in high concentration in cereal grains, nuts, legumes, and seeds.

While remembering the caveats that this study's design can only show associations and that the study population was relatively young females, this study supports dietary recommendations that promote consumption of dairy products, fluid in increased volume, cereal grains, nuts, legumes, and seeds, and limits consumption of sucrose. ❖

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CE Objectives

After reading *Alternative Therapies in Women's Health*, the health care professional will be able to:

1. evaluate alternative medicine and complementary therapies for women's health concerns;
2. identify risks and interactions associated with alternative therapies;
3. discuss alternative medicine options with patients; and
4. offer guidance to patients based on the latest science and clinical studies regarding alternative and complementary therapies.

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After completing this activity, you must complete the evaluation form provided and return it in the reply envelope provided at the end of the semester to receive a certificate of completion. When your evaluation is received, a certificate will be mailed to you.

CE / CME Questions

32. According to a recent study, what percent of U.S. adults were taking a vitamin and mineral supplement daily in 2000?
 - a. 23.2%
 - b. 23.7%
 - c. 33.9%
 - d. 45.6%
33. A South Korean study that investigated clinical efficacy of green tea extract in patients with HPV-infected cervical lesions demonstrated that the extract in the form of ointment or a capsule was effective in treating cervical lesions.
 - a. True
 - b. False
34. In a study of nurses, consumption of which of the following was not associated with a decreased risk of kidney stones?
 - a. Dietary calcium
 - b. Increased fluids
 - c. Sucrose
 - d. Dietary phytate

Answers: 32. c, 33. b, 34. c.

Poor Urban Populations Frequently Use Some Form of CAM, Study Shows

Poor urban populations use complementary and alternative medicine (CAM) modalities as commonly as the general population, according to a recent study.

The researchers from the Division of General Internal Medicine in the Department of Medicine at State University of New York at Buffalo looked at all patients with valid appointments for internal medicine resident teaching clinics at two publicly supported centers. Patients were surveyed about current medications and a variety of CAM modalities. Medical records were reviewed for demographic information and to confirm diagnoses, allergies, medications, and any documented adverse effects.

The researchers found that use of CAM was common by 85.4% of patients, including those using some form of diet, exercise, and prayer. A smaller number (32.3%) were currently using alternate health care providers and products; about 5% of the population used six products or more. Use by this primarily poor urban population appeared similar to that in previous reports, with some exceptions, the researchers say. Expensive modalities were less frequently used, whereas use of prayer appears more prevalent.

The results of this study were published in the May 10 issue of the *Archives of Internal Medicine*.

Cranberry Juice May Reduce Risk of Female Urinary Tract Infections

Drinking cranberry juice on a regular basis may help prevent urinary tract infections (UTIs) in some women, according to a review article in the May 15 issue of *Clinical Infectious Diseases*.

Cranberries contain two compounds that prevent infection-causing bacteria from adhering to the lining of the urinary tract. Whether provided in juice or tablet form, the contents of the berries have been the subject

of clinical study since 1966 in association with urinary tract infections and bacteriuria. The review noted, however, that limitations in many of the studies conducted, such as small size, short duration, or use of a wide variety of cranberry products and dosing levels, make the results difficult to assess and compare.

The group most likely to reap benefits from regular doses of cranberry juice or tablets is sexually active adult women with recurring UTIs, who may experience a 50% drop in infection rates, according to some findings. Cranberry juice's value in treating already established cases of UTI is unknown, as most studies have focused on its ability to prevent infection.

One-Third of Patients Pray for Health Concerns

A recently published study found that one-third of adults used prayer for health concerns in 1998.

The researchers wanted to determine the prevalence and patterns of use of prayer for health concerns. They conducted a national survey in 1998 of 2,055 patients on the use of prayer. Data also were collected on sociodemographics, use of conventional medicine, and use of complementary and alternative medical therapies. Factors associated with the use of prayer were analyzed using multivariable logistic regression.

The researchers found that 35% of respondents used prayer for health concerns; 75% of these prayed for wellness, and 22% prayed for specific medical conditions. Of those praying for specific medical conditions, 69% found prayer very helpful.

Factors independently associated with increased use of prayer included age older than 33 years; female sex; education beyond high school; and having depression, chronic headaches, back and/or neck pain, digestive problems, or allergies. Only 11% of respondents using prayer discussed it with their physicians.

The results of this study were published in the April 26 issue of the *Archives of Internal Medicine*. ❖

In Future Issues:

St. John's Wort for Depression

Feverfew for Migraine

**NSAIDs and Calcium with Vitamin D
for Prevention of Colon Cancer**

Alternative Approaches to Treatment of Leiomyomas