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Antioxidant Vitamins and Breast Cancer

By Nicola McKeown, PhD

IN THE UNITED STATES, BREAST CANCER IS SECOND ONLY TO LUNG cancer as the most common cause of cancer mortality in women. In 2000, it is predicted that 182,800 new cases of breast cancer will be diagnosed and that an estimated 40,800 U.S. women will die of this disease.[1]

The cause of breast cancer is unknown but presumably represents a complex interplay of genetic and environmental factors, including dietary patterns. Migration studies have found that people who migrate from low-risk to high-risk areas acquire the breast cancer rates of the host country within two generations.[2] Furthermore, breast cancer rates have been increasing steadily in countries formerly associated with low incidence rates.[3,4] Since genetic susceptibility is believed to account for 10-15% of all breast cancer cases,[5] non-inherited factors therefore must play a role in breast cancer etiology. Diet has been identified as a potential modifiable risk factor.[6]

Epidemiological studies have provided evidence that diets rich in fruits and vegetables are associated with decreased risk of breast cancer.[7,8] However, few specific dietary factors have been linked definitively to breast cancer predisposition. Some fruits and vegetables are high in antioxidants, such as beta-carotene, vitamin C, and vitamin E. (*See Table 1.*) It has been hypothesized that these antioxidants protect DNA from damage by scavenging free radicals and inhibiting lipid peroxidation.[9] To date, most studies of breast cancer risk and dietary antioxidants have been observational, including both case-control and cohort studies. While case-control studies require fewer people and are less expensive than prospective cohort studies, dietary intake is subject to recall bias among cases; also, the disease may have influenced dietary habits among cases. Prospective cohort studies overcome this limitation by measuring current diet without the presence of the disease; however, individuals need to be followed up for longer periods of time and repeat measures of diet are required to monitor changes in diet.[10] This article will review the observational data linking antioxidant intake and breast cancer risk.

Beta-Carotene Intake

Total vitamin A is comprised of retinol (preformed vitamin A)

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and some carotenoids (provitamin A) that can be converted to vitamin A in the body. More than 600 naturally occurring carotenoids have been identified; of these, beta-carotene is the best known.[11] The effect of reported vitamins A, C, E, and beta-carotene intake on breast cancer risk recently was examined among 83,234 women, aged 30-55, participating in the Nurses' Health Study.[12] After 14 years of follow-up, 2,697 incident cases of invasive breast cancer were identified among women (784 premenopausal and 1,913 postmenopausal) not previously diagnosed with breast cancer. Women with the highest intake of dietary beta-carotene had a lower risk of breast cancer compared to those who ate lower amounts of beta carotene, even after adjustment for age, parity, family history of breast cancer, age at menarche, body mass index, alcohol consumption, or energy intake. This protective association between beta-carotene intake and breast cancer risk also has been observed in case-control studies among women with diagnosed breast cancer.[13,14] In both studies, women who consumed approximately > 8.0 mg/d of beta-carotene had a lower risk of dying from their breast cancer than women who had a lower daily beta-carotene intake (< 3.5 mg/d); however, a significant reduction in breast cancer risk was observed in only one study (hazard ratio 0.48; 95% CI 0.23-0.99).[14]

However, there appear to be inconsistencies among published studies regarding whether there is a relationship between beta-carotene intake and breast cancer risk. Although several case-control and cohort studies on diet and breast cancer support a protective effect of beta-carotene,[13,15-19] others have found no association.[20-23] Similarly, studies investigating serum/plasma beta-carotene and subsequent risk of breast cancer have not been consistent.[20,24,25] Meta-analysis often is used to determine potentially important associations in epidemiological studies that can be missed because of insufficient statistical power.[26] A recent meta-analysis of 11 epidemiological studies found that high consumption of beta-carotene (≥ 7.0 mg/d) compared to low consumption (≤ 1.0 mg/d) was associated with a lower risk (RR = 0.82; 95% CI 0.76-0.91) of breast cancer.[8] Inconsistencies in these studies may be in part because of the inherent problems associated with the accurate recording of dietary intake by study participants, the differences in study design, and the different lengths of follow-up in cohort studies. An international panel has concluded that while dietary carotenoids (particularly beta-carotene) may have a weak protective effect against breast cancer risk, uncertainty remained as to whether the protective component was a specific carotenoid or another constituent found in carotenoid-rich foods.[7]

The Women's Health Study, a randomized, double-blind, placebo-controlled trial, was designed to examine the health benefits of low-dose aspirin, vitamin E, and beta-carotene on cardiovascular disease and cancer risk among 40,000 female health professionals. The beta-carotene (50 mg on alternative days) component of the trial was terminated after two intervention studies demonstrated that supplementation increased the risk of lung cancer among smokers.[27,28] At the time of termination (after a median of 2.1 years), there was no statistical difference in risk of breast cancer between women assigned to beta-carotene and women assigned to placebo.[29]

Vitamin C

In the United States, several observational studies have examined the association between dietary vitamin C intake and breast cancer risk. In Western New York, a case-control study was conducted among 439 postmenopausal women diagnosed with breast cancer. These women were compared to a random sample of age-matched controls. Researchers found that a daily vitamin C intake (≥ 229 mg) was associated with reduced risk of breast cancer.[18] Conflicting results have emerged in other case-control studies examining the association between vitamin C intake and breast cancer risk.[15,21]

In the Nurses' Health Study, the relationship between vitamin C and breast cancer risk was examined after eight years of follow up in 1,439 women diagnosed with breast

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Table 1

Typical antioxidant content of selected foods

Antioxidant	Food Type	Food items	Serving Size	Nutrient Content of Serving
Beta-carotene	Vegetable[1]	Pumpkin	1/2 cup	17.0 mg
		Sweet potato	1 medium	14.3 mg
		Spinach	1 cup	9.4 mg
		Collards	1 cup, chopped	8.4 mg
		Carrots	1/2 cup sliced	6.3 mg
		Broccoli	1 medium stalk	1.9 mg
		Tomatoes	1 cup, chopped	0.7 mg
	Fruit	Mangoes	1 medium	0.9 mg
		Apricots	1 medium	0.9 mg
Vitamin C	Vegetable	Broccoli	1 medium stalk	134 mg
(ascorbic acid)		Peppers, green, raw	1 cup, sliced	82 mg
		Collards	1 cup	35 mg
		Tomatoes	1 cup, chopped	34 mg
		Cabbage	1 cup	25 mg
		Spinach	1 cup	18 mg
	Fruit	Strawberries	1 cup, sliced	94 mg
		Kiwi	1 medium	75 mg
		Oranges	1 small	51 mg
		Grapefruit	1/2 medium	44 mg
		Raspberries	1 cup	31 mg
Vitamin E	Vegetable	Asparagus	1/2 cup	0.34 mg
(alpha-tocopherol equivalents)		Spinach	1 cup	1.7 mg
		Broccoli	1 medium stalk	3.0 mg
		Collards	1 cup	1.7 mg
	Other Sources	Wheat germ	1/4 cup	5.1 mg
		Sunflower seeds	1/4 cup	18 mg
		Vegetable oil[2]	1 tablespoon	2.9 mg
		Margarine, vegetable[3]	1 tablespoon	1.1 mg

[1]All vegetables are cooked (boiled and without skin). [2]Vegetable oil, canola. [3]Margarine-butter blend, 60% corn oil and 40% butter

Adapted from: US Department of Agriculture. USDA Nutrient Database for Standard Reference. Washington, DC: US Dept of Agriculture; 1998. Release 12.

cancer, and then again in 2,697 women after 14 years of follow-up.[12,30] After adjustment for known and suspected risk factors, vitamin C intake was not associated with decreased breast cancer risk at either follow-up period. This apparent lack of a protective association with high intakes of vitamin C has been confirmed in other prospective studies.[23,31,32,33] However, a combined analysis of nine case-control studies found that a high vitamin C intake was associated with a 31% reduction (RR = 0.69; $P < 0.001$) in breast cancer risk.[34] This association remained after the adjustment for beta-carotene and fiber, two nutrients that independently may decrease breast cancer risk. These data were confirmed in a recent meta-analysis of nine observational studies, which compared a high vitamin C intake (≥ 400 mg/d) with low vitamin C intake (≤ 50 mg/d) and found that a high vitamin C intake was associated with a reduction (RR = 0.80, 95% CI 0.68-0.95) in breast cancer risk. While there is some evidence to suggest that a high vitamin C intake may decrease breast cancer risk, conclusive evidence is not available.[7,21]

Vitamin E

The association between vitamin E intake and breast cancer arises primarily from epidemiological studies. Several case control studies have found that high vitamin E intakes were associated with a lower risk of breast cancer.[15,17-19,22] However, most cohort studies do not confirm a protective role of vitamin E.[12,23,30-32,35] Based on current evidence, it is unlikely that vitamin E plays a considerable role in prevention of breast cancer.[7]

Dietary Supplements and Breast Cancer Risk

A recent study reported that approximately 81% of women with diagnosed breast cancer reportedly were taking dietary supplements. The most common dietary supplements reported were vitamin E, followed by vitamin C, and multivitamin and mineral supplements.[36] However, there is limited information on the effect of

dietary supplementation on the recurrence of breast cancer. The majority of observational studies have not found an overall reduced risk of breast cancer among those women who take vitamin C or E supplements.[12,18,22,30,32,33] Currently there is no evidence to support the use of vitamin or mineral supplementation in the treatment or prevention of breast cancer.[37]

Two intervention trials currently are underway to examine whether dietary change or dietary supplements will lead to a decrease in breast cancer risk among U.S. women. The first is the Women's Health Study. The second study, the Women's Health Initiative is a large multicenter study involving an observational study and several randomized clinical trials, one of which is a dietary modification intervention. More than 48,000 postmenopausal women between ages 50 and 79 are involved in this intervention that aims to study the effect of a low-fat, high fruit, vegetable, and grain diet on breast cancer risk.[38] The planned completion date for this trial is 2007. Both intervention trials will provide important and relevant information on the benefits or risks of supplementation and dietary change in the prevention of breast cancer in women.

Conclusion

Although diets high in fruits and vegetables are associated with lower breast cancer risk, uncertainty remains over which specific dietary constituents are the protective agents. It is unlikely that the observed beneficial effect associated with diets high in fruits and vegetables is due to increased intake of a single nutrient; the interaction of several nutrients is more likely. Women who eat large amounts of fruits and vegetables may have an overall healthier lifestyle and dietary pattern. For example, dietary intakes of fruits, vegetables, and carotenoids reportedly are lower among smokers compared to nonsmokers.[39,40] Consequently, the health benefits associated with fruit and vegetable intakes may be confounded by other characteristics or unmeasured confounding factors. Diets high in fruits and vegetables have a protective effect against the risk of several diseases, including breast cancer.[41] Therefore, from a public health point of view, the current recommendation to increase fruit and vegetable intake should be practiced as part of an overall healthful lifestyle. ❖

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Morinda citrifolia (Noni)

By Jerry Cott, PhD

HAWKED AS A PANACEA, NONI FRUIT JUICE HAS BEEN marketed heavily in the United States since the early 1990s. Promotion of this product primarily has been through network marketing companies that distribute exaggerated claims and testimonials for noni's purported benefits as a general tonic and for a variety of diseases, including cancer, heart disease, diabetes, hypertension, arthritis, stroke, gastrointestinal disorders, malaria, depression, and drug addiction.[1]

Traditional Use

Morinda citrifolia (family Rubiaceae), also known as noni, or Indian mulberry, is a small evergreen shrub or tree that grows up to 10 feet high. Native to the Pacific islands, Polynesia, Asia, and Australia, noni has large, dark green, deeply veined, shiny leaves; small white flowers; and warty, pitted, three- to four-inch long fruits that start out green and turn yellow and then white with ripening. The ripe fruit has a foul odor due to short-chain carboxylic acids.

On its native soil, noni fruit generally is not considered edible, although the unripe fruit (less noxious than the ripe fruit) may be eaten. Traditional Hawaiian healers apparently have used the fruit medicinally as a purgative, cleanser, blood purifier, and more recently for intestinal worms and for tuberculosis.[1] However, it is

said that only sick and desperate people will consume noni fruit because of its unpleasant odor and bitter taste. The indigenous medicinal use of this plant, however, utilizes not the fruit but the leaves, primarily as a topical treatment for wound healing. In Chinese medicine, *M. officinalis* root is a standard medication (known as *bai ji tian* or *pa chi tien*) used for the digestive system, kidneys, heart, and liver. In addition, a red dye is made from the bark and a yellow dye from the root.

Contemporary Claims

Noni fruit juice or extract has been marketed as a treatment for a variety of diseases. Noni marketers claim that the key medicinal component of noni is an alkaloid called "xeronine."[2] However, a thorough review of the chemical literature does not substantiate the existence of such a compound, and the person credited with discovering xeronine, Dr. Heinicke, did not publish any of his findings. Xeronine appears to exist only in promotional materials for noni.

Commercial products usually contain noni juice or a juice concentrate. The carboxylic acids that give noni its foul smell are not present to any great extent in the marketed products, which also often incorporate other fruit juices or flavorings to make preparations more palatable. The usual dose for juice products is the equivalent of four ounces noni juice 30 minutes before breakfast.

Tablets and capsules containing the fruit and the whole plant also are available. For liquid concentrates the typical recommendation is two tablespoons daily, and for powdered extracts the recommended dose is 500-1,000 mg/d. It is suggested that noni be taken on an empty stomach (to maximize absorption and "activation" of xeronine).

Pharmacology

The leaves of *M. citrifolia* and other *Morinda* species contain high levels of vitamins and minerals, including vitamin C, beta-carotene, calcium, iron, phosphorus, niacin, riboflavin, and thiamin.

According to the USDA Phytochemical Database, *M. citrifolia* root constituents include morindin, rubichloric acid, rubiadin-1-methyl ether, soranjidiol, asperuloside, nordamnacanthal, and trihydroxyanthraquinones (responsible for the mild laxative effect). The ripe fruit is characterized by a large amount of carboxylic acids (which account for its odor), primarily hexanoic and octanoic acids. In addition, Levand and Larson reported caproic and caprylic acids and asperuloside in the fruit.[3]

Ripe fruit contains hexanoic and octanoic acids;[4] the toxicity of these acids makes microbial contamination of fruits less likely than with other plant products.[5] However, these toxic acids apparently don't bother one species of fruit fly, which chooses to lay its eggs in the fruit.[6]

Evidence

No human clinical trials have been conducted, and no animal studies have been performed that would approximate human usage of the plant. Intraperitoneal doses (300-750 mg/kg) of a polysaccharide-rich substance extracted from the fruit juice may have anticancer activity in the Lewis lung carcinoma model in mice.[7-9] However, since both the noni extract and the tumor cells were administered by intraperitoneal injection, the effects reported may not apply to noni given orally. When applied to tumor cells in vitro, a more purified formulation than the one that was injected into the mice showed direct cytotoxicity only at high concentrations.[9] However, this lack of direct toxicity does not apply to the mouse carcinoma study since it was a different formulation.

An in vitro study from Japan found that high concentrations (5-20 mcg/mL) of damnacanthal, a purified anthraquinone compound from a chloroform extract of the root, may have immune-enhancing activities.[10] Other studies show that damnacanthal inhibits tyrosine kinase and stimulates UV-induced apoptosis.[11] Whether these effects are related to the activity of the fruit extract in the lung carcinoma model is unknown, but seems doubtful.

The lyophilized aqueous extract of *M. citrifolia* root was evaluated in another study that examined analgesic and behavioral effects in mice.[12] Intraperitoneal doses of 800 and 1,600 mg/kg had analgesic activity in standard writhing and hot plate tests that was reversed by the narcotic antagonist naloxone. Administration of 500-1,600 mg/kg of the extract decreased all behavioral parameters suggesting general sedative properties. However, any relevance of these huge intraperitoneal doses of root extracts to therapeutic oral ingestion of the fruit material seems very doubtful.

Extracts from other *Morinda* species have been reported to possess anti-diabetic,[13] anti-malarial,[14] and anti-parasitic[15] activities in in vitro and animal studies. Whether any of these properties can also be attributed to *M. citrifolia* fruit has not been established.

Risks and Side Effects

Although adverse effects have not been reported with noni, no safety studies have been performed. The potassium content is similar to that in orange juice, and noni juice consumption was linked to hyperkalemia in a patient with chronic renal insufficiency.[16] Because of the lack of data, use of noni by pregnant or nursing women, or those with liver or kidney disease, is not recommended.

In summary, although noni fruit products appear benign, they have not yet been proven effective for any condition in humans. In addition, the fruit is not an important part of traditional medicine in its native lands. The scant animal and in vitro data that exist are primarily

on other parts of *M. citrifolia* or other species of *Morinda* and cannot be extrapolated to noni fruit products. ❖

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Caffeine and Detrusor Instability

By Jean L. Fourcroy, MD, PhD, MPH

Source: Arya LA, et al. Dietary caffeine intake and the risk for detrusor instability: A case-control study. *Obstet Gynecol* 2000;96:85-89.

A RECENT ARTICLE BY BROWN UNIVERSITY SCHOOL OF Medicine authors examines the association between high caffeine intake and detrusor instability in 259 consecutive women referred for evaluation of urinary incontinence to the urodynamic center. Participants all had symptoms of urinary incontinence, completed a 48-hour voiding diary detailing caffeine and fluid intake, and had undergone a standardized multichannel urodynamic study. The final study population included 131 women with detrusor instability (defined by provocative cystometry and a maximum urethral closure pressure greater than 20 cm of water) and 128 controls, who did not have detrusor instability but had stress incontinence. Women with diabetes, neurologic disorders, on anticholinergic or alpha-adrenergic agonists, or on antagonist medications were excluded from the study. Caffeine intake of < 100 mg/d was defined as minimal, 100-400 mg/d as moderate, and > 400 mg/d as high. Table 1 indicates how the investigators made the calculation of caffeine.

The two groups were similar in parity, weight, estrogen status, and number of prior surgical procedures. The mean age of those with detrusor instability was older (55.6 ± 2.3) than those without detrusor instability (45.2 ± 1.2).

Risk factors identified in this study for detrusor instability were age, current smoking, and high caffeine intake. Smoking may be a confounding factor because of its relationship with dietary caffeine intake. Women older than 55 years of age had an increased risk for detrusor instability than women younger than 55 (odds ratio [OR] 1.7, 95% CI 1.03-2.9, P = 0.028). Women with high caffeine intake had significantly higher odds for detrusor instability than women with low caffeine intake (OR 2.7, 95% CI 1.2-5.8, P = 0.006). Controlling for both age and smoking, the adjusted risk was 2.4 (95% CI 1.1-6.5, P = 0.018) for women with high caffeine intake compared with women with minimal caffeine intake. Moderate caffeine intake was not a significant risk.

Although this is an excellent study several things should be noted. Urinary incontinence can be divided intro three major types—urge or detrusor instability (also termed overactive bladder), stress, and mixed. About one

Table 1

Caffeine content calculation

Beverage	Caffeine content
Brewed coffee, 5 oz	128 mg
Coffee, instant	66 mg
Iced tea, 8 oz	47 mg
Tea, hot nonherbal, 5 oz	38 mg
Cola soft drinks, 8 oz	24 mg
Cocoa, 5 oz	4 mg
Coffee, decaf, 5 oz	3 mg

third of women will have mixed incontinence symptoms and signs that include elements of both urge and stress incontinence. The incidence of urge incontinence increases with age. The most important risk factors for stress incontinence are vaginal delivery and hysterectomy. It is highly unusual that consecutive patients would not include any patients with mixed incontinence. However, if a decrease in caffeine intake decreases urge symptoms in women with detrusor instability, one can assume that incontinence of mixed category also will respond. The next important study to do would be to test whether a decrease in caffeine intake decreases urinary symptoms. Also, total fluid intake could have an effect on detrusor instability. Future studies should also take into account the total fluid intake; rapid bladder filling has been posited as a detrusor irritant. A woman who is ingesting 400 mg caffeine from 17 cans of cola is filling her bladder more rapidly than someone whose caffeine comes from four cups of coffee. If the effect of caffeine were purely pharmacologic, there would be a significant association between urge incontinence and moderate caffeine intake.

Caffeine is an interesting drug. A little caffeine makes you vigilant and alert while too much causes shaking. High caffeine levels are prohibited in Olympic sports. Symptoms of too much caffeine (usually more than 500 mg/d) include anxiety, agitation, restlessness, insomnia, and a general feeling of being wired. Both caffeine overdose and withdrawal may be associated with headaches. Caffeine withdrawal (which may be precipitated by an intake of less than 250 mg/d) is associated with irritability, lethargy, and occasional nausea.

Caffeine, along with nicotine and alcohol, are the most commonly used drugs worldwide. About 10 billion pounds of coffee are consumed yearly throughout the world and in the last decade there has been an increase in the number of coffeehouses as well as the consumption of coffee. Caffeine long has been blamed for urinary and other symptoms without scientific proof. Gastroesophageal reflux responds to a decrease or avoidance of caffeine, probably by a gastric acid secretion mechanism.[1] The effect of caffeine on fibrocystic changes of the breast is controversial.[2]

Patients with increased urinary frequency, particularly of any inflammatory origin (including interstitial cystitis), have been counseled to decrease intake of caffeine as well as alcohol and spicy foods. Food diaries long have been important in evaluating patients to identify possible food intolerance that could contribute to symptoms.

Why would caffeine have an effect on urinary incontinence? Caffeine may have an excitatory effect on smooth muscle and is thought to cause an increased effect during bladder filling. It has also been shown to induce transient contraction of smooth muscle through the release of intracellular calcium from intracellular storage sites.

The authors are to be congratulated in studying the risks of caffeine and detrusor instability. However, the key follow-up clinical study should be designed to identify whether or not removal of caffeine from the diet improves urge symptoms. Perhaps we should consider decreasing caffeine in the diet of women with urge incontinence prior to considering medication or surgery. ❖

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References

1. Boekema PJ, et al. Coffee and gastrointestinal function: Facts and fiction. A review. *Scand J Gastroenteral Suppl* 1999;230:35-39.
2. Heyden S, Fodor JG. Coffee consumption and fibrocystic breasts: An unlikely association. *Can J Surg* 1986;29:208-211.

CME Questions

1. **Which of the following has been convincingly linked to lower breast cancer rates?**
   a. A diet high in fruits and vegetables
   b. Vitamin E supplementation
   c. Beta-carotene
2. **Limitations of case-control dietary intake studies include:**
   a. recall bias.
   b. dietary habits may be affected by disease or disease diagnosis.
   c. both of the above.
3. **Anticancer effects of orally administered noni have been demonstrated in:**
   a. humans.
   b. primates.
   c. mice.
   d. None of the above
4. **A recent study found a connection between detrusor instability and:**
   a. high doses of caffeine (> 400 mg/d).
   b. moderate doses of caffeine (100-400 mg/d).
   c. all doses of caffeine.