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## COVER STORY

Does Vitamin E  
Prevent Breast Cancer?

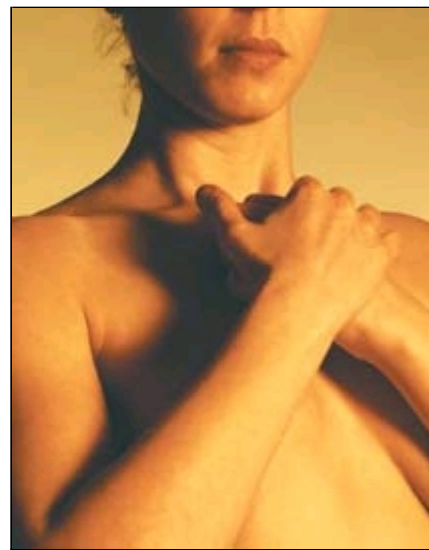
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Since one out of every eight women is destined to develop breast cancer,[1] a tremendous amount of research has been undertaken to discover ways of preventing this common killer. One compound that has been extensively studied for its role in preventing breast cancer is vitamin E.

Up until now, however, no one has compiled and analyzed the large volume of published data about vitamin E and breast cancer. A researcher at Wake Forest University School of Medicine took on this enormous task and her comprehensive work was just published in the *Journal of Nutritional Biochemistry*. [2]

If you take vitamin E supplements, this eye-opening report reveals startling findings about what forms of vitamin E may be effective, which women are most likely to benefit, and a form of vitamin E that certain women should avoid.

As a prelude to this article, readers should know that emerging evidence is calling into question previously held concepts about how vitamins function in the body. While this new information corroborates what has been earlier cited in this publication, it is nonetheless critical to remind readers of the need to keep up with current findings. For women concerned about breast cancer, there now appear to be validated methods of reducing the risk if the proper forms of vitamin E are consumed.



by Dr. Michele Morrow, Board Certified Family Physician

Some people believe that vitamin E reduces breast cancer risk because of reports showing that severely deficient women suffer far higher rates of breast cancer.

Several studies, for instance, show that premenopausal women with very low intakes of vitamin E are twice as likely to contract breast cancer compared to women who come close to meeting the minimum requirements. This statistic is relatively useless, however, since it was women who consumed less than 7 mg a day who were at a 50% greater risk of contracting breast cancer.[3-7] Other studies show no risk reduction in women obtaining greater than 8 mg a day of vitamin E.[8,9]

Since supplement users take 400 mg or more a day of vitamin E, everyone wants to know how much reduction in breast cancer incidence can be expected when potencies of 400 mg (400 IU) and higher are consumed.



Studies on total vitamin E intake show that women with a family history of breast cancer may derive an 80% risk reduction, whereas women who don't have a family history obtain a 60% risk reduction.[5] The risk reduction, however, is not consistent amongst different groups of women. When subsequent analyses of this data was conducted, more definitive information was obtained.[5] The chart on the upper right shows different categories of women and the specific risk reduction effect from foods that are high in vitamin E.

Controlled studies on alpha tocopherol

The Nurses Health Study studied 83,234 women at baseline and sought to assess incidences of breast cancer during a 14 year follow-up. This study showed that premenopausal women with a family history who consumed the highest quantity of vitamin E enjoyed a 43% reduction in breast cancer incidence compared to only a 16% risk reduction for women without a family history of

breast cancer.[11] Based on this study, vitamin E appears to protect against genetic- predisposed breast cancer better than environmental-induced breast cancer. (Note that nutrients like indole-3-carbinol may specifically protect against environmental breast carcinogens.)

Several studies reviewed the effects of standard vitamin E products (alpha tocopherol acetate) taken by themselves. The results fail to show a protective benefit, even when high doses of these alpha tocopherol supplements are consumed.[7,11-15] This indicates that other forms of vitamin E found in food (such as gamma tocopherol and tocotrienols) may be responsible for providing the dramatic protective effect against breast cancer shown in surveys that evaluate total vitamin E intake.

Patient Category	Breast cancer incidence based on comparing the highest to lowest levels of vitamin E intake
Premenopausal women with family history of breast cancer	90% risk reduction
Premenopausal women without family history of breast cancer	50% risk reduction
Postmenopausal women with a family history of breast cancer	30% risk reduction
Postmenopausal women without a family history of breast cancer	50% risk reduction
Please note that the statistics above are based on total vitamin E intake. Food-derived vitamin E contains primarily gamma tocopherol and to a lesser extent, the tocotrienols.[10]	

Another method that scientists have used to ascertain vitamin E's potential benefit is to measure frozen blood levels of vitamin E and then follow up to see how many women subsequently develop breast cancer. One study of postmenopausal women showed a modest 20% reduction in breast cancer risk in the highest quartile of serum vitamin E (alpha tocopherol) compared to the lowest. [16] Other studies based on measuring alpha tocopherol from stored blood serum do not show a protective effect.[17,18]

Some doctors believe the best way of determining vitamin E status is to test breast adipose (fat) tissue for vitamin E concentration in healthy controls as opposed to newly diagnosed breast cancer patients. One compelling study showed that newly diagnosed breast cancer patients had six times less vitamin E in their breast tissue compared to women without breast cancer.[19] The major flaw to this study was that the control group was nine years younger on average than the breast cancer patients and other confounding factors were not accounted for. Other studies seeking to assess adipose concentrations of vitamin E in breast cancer patients are inconclusive. [20,21]

Taken together, the results of the studies presented indicate that certain vitamin E fractions found in food confer a significant protective effect, but that commercial alpha tocopherol acetate supplements fail to reduce breast cancer incidence for most women. The data indicate that some other vitamin E component in food may account for the dramatic reductions in breast cancer incidence (as much as 90%) when dietary intake levels of vitamin E are measured.

(Note: 400 mg of vitamin E succinate provides 400 IU of vitamin E activity whereas 400 mg of vitamin E acetate typically provides 200 IU of vitamin E activity.)

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### Tocotrienols and breast cancer cell growth

We now know that the form of vitamin E used in most commercial preparations (alpha tocopherol acetate) has not been shown to protect against breast cancer in humans. A natural form of vitamin E called alpha tocopheryl succinate, found in more expensive supplements, may provide some protection. In test tube studies, the alpha tocopheryl succinate form of vitamin E has been shown to inhibit breast cancer cell growth. [22-35]

It is the tocotrienols, however, that have demonstrated the most significant potential to not only reduce the incidence of breast cancer, but also to inhibit existing breast cancer cell propagation.

Tocotrienols have been shown to inhibit growth of estrogen receptor positive breast cancer cells by as much as 50% in culture.[36-39] In contrast, many studies have found that alpha tocopherol does not influence proliferation.[36,38-40] Even in studies where alpha tocopherol was shown effective against some breast cancer cell lines, the amount required for 50% growth inhibition was more than 20 times higher than the growth inhibitory concentrations of the tocotrienols.[37]

Comparison of multiple studies indicates that the growth inhibitory effects of alpha tocopherol wears off,[41] whereas limited data suggest that the growth inhibitory effects of the tocotrienols on breast cancer cells is maintained or increases with duration of exposure (in culture).[39,42]

Tamoxifen interferes with breast cancer cell proliferation via several mechanisms, most notably by blocking estrogen receptor sites on the cell membrane surface so that estrogen cannot fuel hyper-proliferation. Tamoxifen is known to induce side effects, but the documented effectiveness of the drug causes many breast cancer patients to use it for two to five years (or longer).

In cell culture, tamoxifen can reduce estrogen receptor positive breast cancer cell proliferation by 50%. When palm-oil derived tocotrienols are added with tamoxifen, the dose of tamoxifen required to induce 50% cell arrest was lowered by 75%.[37]

In estrogen receptor negative cancer cell lines, tamoxifen can inhibit proliferation by 50%, but at much higher concentrations. When tocotrienols are added, the dose of tamoxifen required to inhibit cancer cell proliferation is reduced by as much as 95%![37] When alpha tocopherol is added to these breast cancer cell cultures, it increases the amounts of tamoxifen required to inhibit growth.[37]

These cell culture studies, showing that tocotrienols dramatically potentiate the effects of tamoxifen, indicate the desire to test a combination of tocotrienols and tamoxifen in both estrogen receptor positive and estrogen receptor negative breast cancer patients.

The study showing that alpha tocopherol increases the amount of tamoxifen required to induce cell arrest implies that breast cancer patients using tamoxifen may want to avoid consuming high potencies of alpha tocopherol.

(Note: Life Extension magazine has previously reported that vitamin D3 and melatonin work synergistically with tamoxifen to inhibit breast cancer cell propagation.)

### Tocotrienols induce breast cancer cell death

The objective of any cancer therapy is to induce the cancer cells to differentiate in a way that promotes programmed cell death (apoptosis). Several studies indicate that tocotrienols induce breast cancer cell apoptosis.[41-43]

When different kinds of live breast cancer cells were injected into the mammary tissue of female mice, tocotrienols were found to be growth inhibitory on each breast cancer cell line tested. Although apoptosis could be achieved, the dose of tocotrienol needed to induce 50% apoptosis was 2-4 times higher than the dose of tocotrienol required to induce 50% growth inhibition.[42]



In cell culture, tamoxifen can reduce estrogen receptor positive breast cancer cell proliferation by 50%. When palm-oil derived tocotrienols are added with tamoxifen, the dose of tamoxifen required to induce 50% cell arrest was lowered by 75%.

It is interesting to note that the growth inhibition and promotion of apoptosis occur preferentially in the cancerous part of the breast so that healthy cells remain largely unaffected.[42]

Can women obtain enough tocotrienols to reduce breast cancer risk?

For those seeking to use tocotrienols to reduce breast cancer risk, it is essential to quantify the optimal daily dose. In humans not consuming tocotrienol supplements, the average plasma concentration is less than 1 microgram per liter of blood.[45-47] After supplementation with a palm-oil concentrate containing about 78 milligrams of tocotrienols for four weeks, plasma tocotrienol levels increased to 8.14 micrograms per liter of blood (an eight-fold increase).[47]

This plasma concentration of 8.14ug/l of tocotrienol is similar to the amount used to achieve an inhibitory effect on the proliferation of estrogen receptor positive breast cancer cells in vitro by 50%. The amount of tocotrienol to promote apoptosis in vitro by 50% would be approximately 24ug/liter according to this study.[2]

It is interesting to note that the body naturally concentrates tocotrienols into breast adipose tissue. Based on studies done to date, it is likely that breast adipose tissue levels of tocotrienols will be 5 to 10 times greater than plasma.[48-50] This indicates that even lower tocotrienol supplementation might be adequate to saturate breast adipose tissue with the amount of tocotrienols that have inhibited breast cancer cell proliferation and induced apoptosis in culture.

It is encouraging to know that the in vitro tests that document the anti-cancer effects of tamoxifen also show tocotrienols to have similar cell inhibitory properties. Compared to tamoxifen, however, tocotrienols are safe. Human studies have shown that daily doses of up to 240 mg of tocotrienols for 16 months produce no adverse effects.[47,51,52] Further studies will determine whether humans who saturate their breast adipose tissue with tocotrienol from supplements will achieve a reduced incidence of breast cancer. (Please note that it is the palm-oil tocotrienols, and not rice-bran tocotrienols, that have primarily demonstrated these anti-cancer effects.)

#### Summary of findings

When reviewing all the published evidence, it does not appear that alpha tocopherol vitamin E confers a protective effect against breast cancer. Yet studies show that women who consume foods high in other forms of vitamin E substantially reduce their risk of contracting breast cancer (by as much as 90%).

A cardinal feature of breast tumors are rapidly proliferating cells. Estrogen drugs promote hyper-proliferation and this is one reason why these drugs may quadruple the incidence of breast cancer. [53]

Studies of breast cancer cells in culture indicate that tocotrienols have potent effects in inhibiting proliferation and inducing apoptosis (cancer cell death). These studies show that alpha tocopherol does not have this same benefit.

Alpha tocopherol acetate is the most common supplement form of vitamin E, yet the evidence points to other forms of vitamin E as being responsible for the dramatic reduction in breast cancer incidence observed in large human studies.

We now know that the individual tocopherols and tocotrienols have different biological activities as they relate to their effects on cellular function. Gamma tocopherol, for instance, has demonstrated significant cancer prevention effects compared to alpha tocopherol.

The potential anti-cancer effects of gamma tocopherol and the tocotrienols merits aggressive human clinical research to determine if women who supplement with these unique forms of vitamin E can reduce their risk of contracting breast cancer. Further research should be conducted on breast cancer patients to see if the addition of tocotrienols to tamoxifen improves long-term survival rates.

Based on a review of all the published data, we cannot find compelling evidence to indicate that standard (alpha tocopherol) vitamin E supplements reduce breast cancer incidence. While alpha tocopherol has been shown to protect against a wide range of other

Tocotrienols should be taken with food

For oil-soluble vitamin E to be absorbed, it should be taken with some kind of food. When people take oil-based vitamin E preparations on an empty stomach, very little makes its way into the bloodstream.

It is especially important to take the tocotrienols with some form of oil or fat-containing food. One study showed that when tocotrienols are taken on an empty stomach, absorption was reduced by an average of 64%.44

When taking gamma tocopherol and/or tocotrienol vitamin E supplements, try to take them with a meal or with fatty acid capsules like fish oil (EPA-DHA), GLA, CLA etc.



diseases,[54-70] it would appear that the tocotrienols are the ideal form of vitamin E to specifically reduce breast cancer risk.

For additional information about novel adjuvant ways of preventing and treating breast cancer, refer to the Breast Cancer Treatment Protocol.

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