
Tocotrienol Levels in Adipose Tissue of Benign and Malignant Breast Lumps in Patients in Malaysia

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INTRODUCTION

Breast cancer worldwide affects nearly one million women per year and although current treatments do help many patients, more than 350 000 die from the disease. In the United States, 215 990 women were diagnosed with breast cancer in 2004 and 40 110 died from the disease (American Cancer Society, 2004). In Malaysia, breast cancer is the most frequent cancer amongst women. In 2002, the National Cancer Registry recorded 4337 new cases of breast cancer in Malaysia, which constituted 30.4% of all cancers in women (National Cancer Registry, 2003). The established risk factors for breast cancer include a family history of breast cancer, early menarche, late age at first childbirth, late age at menopause and history of benign breast disease. With the exception of the genetic predisposition to the disease, the rest of the risk factors point to the life time exposure of women to estrogen. Estrogen does not cause the disease, but is involved in the progression and development of breast cancer. Anti-estrogens are therefore used as therapy in the control of breast cancer progression.

International variation in breast cancer incidence rates and changes in incidence amongst migrant populations have indicated that breast cancer risk is also influenced by environmental factors, in particular diet, and therefore preventable (Ingram *et al.*, 1991).

A lot of scientific investigations have been performed to discover possible functional properties, antioxidant or otherwise in the diet, which could be efficient in preventing diseases like cancer. One such antioxidant is vitamin E. Previously eight dietary components α -, β -, γ -, δ - tocopherols (T) and α -, β -, γ -, δ - tocotrienols (T3) (Papas, 1993; Kajima, 1993) were all considered forms of vitamin E. The α -T is thought to be the most biologically important form of vitamin E (Institute of Medicine, 2000; Kajima, 1993). Recent

guidelines have equated α -T with vitamin E, discounting other tocopherols and the tocotrienols (Institute of Medicine, 2000). Tocopherols and tocotrienols are present in the oil fraction of cereal grains, seeds and nuts. In most food sources, tocopherols are more prevalent than tocotrienols. Palm oil is a particularly rich source of α -, γ -, δ -tocotrienol (Ingram *et al.*, 1991; Ong, 1993). Palm oil is today the second largest vegetable oil in terms of world production and makes up about 50% of the world's traded oils. Malaysia and Indonesia are the two biggest producers and exporters of the oil (Mielke, 2004).

Observational studies that have assessed exposure to vitamin E by plasma or adipose tissue concentrations of α -T have failed to provide consistent support for the idea that α -T provides any protection against breast cancer (Ishii *et al.*, 1989; Ip, 1982).

In contrast, studies in human breast cancer cells indicate that of α -, γ -, δ -T3 have potent anti-proliferative and pro-apoptotic effects that would be expected to reduce the risk of breast cancer (Nesaretnam *et al.*, 1995; 1998; 2000; Guthrie *et al.*, 1997; Yu,

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1999) whilst α -T had no effect. Galli *et al.* (2004) recently demonstrated that γ -T when compared with α -T showed a much stronger inhibitory effect on prostate cancer cell growth. However, when tested further with the T3 homologues (Conte *et al.*, 2004) found that γ -T3 had greater anti-proliferative effects than γ -T. Thus, it seems plausible that the modest protection from breast cancer associated with dietary vitamin E may be due to the effects of the other T and T3 in the diet.

Information regarding the prognosis of women with breast cancer in relation to breast adipose tissue concentrations of tocopherols and tocotrienols would provide insight into the roles that tocopherols and tocotrienols might play in preventing or reducing the risk of breast cancer. In the current study, we investigated vitamin E levels in Malaysian women where palm oil and a particularly rich source of tocotrienols is the main fat consumed in the diet. Among all biological markers of qualitative composition of dietary intake of fatty acids, adipose tissue fatty acid composition is particularly advantageous because it reflects qualitative dietary intake of fatty acids on a long-term basis (Riboli *et al.*, 1987; Kaaks *et al.*, 1996; Katan *et al.*, 1991) thereby avoiding the potential bias derived from the disease on the measured biochemical parameters. Additionally, because the ability of tocopherol and tocotrienols to reduce risk of breast cancer is likely to be determined by their delivery to the breast, it will be important to determine concentrations of these dietary constituents in the breast adipose tissue, and to relate these concentrations to dietary intake

TABLE 1. FATTY ACID COMPOSITION OF BREAST ADIPOSE TISSUE IN BENIGN AND MALIGNANT BREAST LUMPS

Fatty acids		Benign mean value % (\pm SD) n = 35	Malignant mean value % (\pm SD) n = 40
Saturates	12:0	1.23 (0.35)	0.91 (0.44)
	14:0	2.25 (0.46)	2.21 (0.55)
	16:0	29.93 (0.95)	28.43 (1.97)
	18:0	2.98 (1.29)	4.83 (0.97)
	20:0	0.19 (0.09)	0.51 (0.30)
	Total	36.58 (0.63)	36.89 (0.84)
Monounsaturates	16:1 n-7c	5.52 (2.11)	3.43 (1.19)
	18:1 n-9c	46.30 (0.93)	45.65 (2.34)
	20:1 n-9	0.51 (0.04)	0.49 (0.18)
	Total	52.33 (1.02)	49.57 (1.24)
n-6 PUFA	18:2 n-6	10.82 (0.89)	12.45 (1.05)
	18:3 n-6	0.26 (0.06)	0.28 (0.11)
	Total	11.08 (0.48)	12.73 (0.58)

TABLE 2. TOCOPHEROL AND TOCOTRIENOL CONTENT IN BREAST ADIPOSE TISSUE OF MALIGNANT AND BENIGN BREAST LUMPS

Parameters measured		Benign mean value ($\mu\text{g g}^{-1}$) (\pm SD) n=35	Malignant mean value ($\mu\text{g g}^{-1}$) (\pm SD) n=40
Tocopherols	α	147.04 (61.90)	126.17 (80.94)
	β	2.75 (1.57)	2.81 (1.53)
	γ	7.51 (3.79)	6.18 (4.17)
	δ	1.26 (0.85)	0.65 (0.31)
	Total	158.56 (65.41)	135.81 (85.12)
Tocotrienols	α	11.35 (3.31)	7.21 (4.28)
	γ	7.90 (2.61)	6.03 (2.47)
	δ	0.82 (0.29)	0.49 (0.31)
	Total	20.07 (6.02)	13.73 (6.09)

Fatty Acid Composition in Breast Adipose Tissue

Table 1 shows the fatty acid composition of breast fat in benign and malignant lumps. The major fatty acids in breast adipose tissue were oleic acid (18:1 n-9c),

palmitic acid (16:0), linoleic acid (18:2 n-6) and stearic acid (18:0). These fatty acids accounted for about 90% of total area under the chromatographic curve. There was no significant difference in the FAC of breast adipose tissue from benign and malignant lumps.

Vitamin E Composition in Breast Adipose Tissue

Table 2 shows the T and T3 measured in the lipid extract of breast adipose tissue obtained from 40 patients with malignant and 35 with benign breast lumps. The content of T and T3 was expressed in $\mu\text{g g}^{-1}$ adipose tissue. In malignant lumps, the mean content of α -T in breast adipose tissue was $126.2 \mu\text{g g}^{-1}$ adipose tissue whilst in the benign lumps it was $147.0 \mu\text{g g}^{-1}$. There was a large variability between patients especially for α -T. This could be due to different dietary intake patterns as tocopherols are prevalent in many food items. The mean of α -T value in adipose tissue was however not significantly different in malignant cancer patients than in benign subjects ($p=0.435$). The mean γ -T (7.51 vs. 6.18) and δ -T (1.26 vs. 0.65) levels were also reduced in malignant patients as compared to benign. Whilst it was not significant for γ -T ($p=0.363$), the reduced level of δ -T was significant ($p=0.033$).

In breast cancer patients, the mean content of α -, γ -, and δ -T3 in breast adipose tissue was $13.73 \mu\text{g g}^{-1}$ adipose tissue. In patients with benign lumps, it was $20.0 \mu\text{g g}^{-1}$ adipose tissue. Mean T3 value was significantly ($p=0.006$) lower in breast cancer patients than in subjects with benign lumps. There was a decrease in α -T3 ($p=0.006$), γ -T3 ($p=0.047$), and δ -T3 ($p=0.018$) in malignant tissue compared to benign. The distribution of tocotrienols with α and γ -T3 being higher also reflects closely the composition of tocotrienols in palm oil.

DISCUSSION

The evaluation of long-term nutritional vitamin E status in breast cancer patients using adipose tissue concentrations has definite advantages over measurement of plasma levels. Plasma levels of tocopherols and tocotrienols change very rapidly in humans following modifications in the dietary intake, reaching new steady state levels within a few days (Baker *et al.*, 1986). The content of α -T in adipose tissue has been evaluated in humans in relation to dietary intake of vitamin E and it has been shown that α -T content reflects a long-term dietary intake of vitamin E (EA, 1986).

Several studies that carefully collected adipose tissue have investigated the relationship between adipose tissue tocopherols and breast cancer risk (Traber *et al.*, 1987; Chajes *et al.*, 1996). Overall, studies of the association of vitamin E with breast cancer risk suggest the possibility that increased dietary exposure to vitamin E may slightly reduce breast cancer risk (Ohrvall *et al.*, 2002). However, there is no evidence that supplemental vitamin E, most, if not all of which is in the form of α -T, confers any protection at all (Ohrvall *et al.*, 2002). Furthermore, cell culture data has showed that α -T combined with tamoxifen increased the IC50 for tamoxifen in MCF-7 cells more than 1000-fold (Schwenke, 2002) and in a further study α -T completely blocked the potent growth inhibitory effects of tamoxifen on MDA-MB-231 cells (Gundimeda *et al.*, 1996). In contrast, we have shown that

α -, γ -, and δ -T3 and the tocotrienol rich-fraction of palm oil inhibited proliferation of MCF-7 and in ZR-75-1 cells, both in the absence and the presence of estradiol and tamoxifen (Nesaretnam, 2000). The inhibitory effect on cell growth was more pronounced with γ - and δ -T3. The mechanism of action is unknown, with previous data suggesting action does not reside in antagonism of estrogen action or in alterations to growth inhibitory insulin-like growth factor binding proteins in MCF-7 human breast cancer cells (Nesaretnam, 1998). Tocotrienols are also reported to have a pro-apoptotic effect on several tumour cell lines (Guthrie *et al.*, 1997; Gundimeda, 1996; McIntyre *et al.*, 2000). However, McIntyre *et al.* (2000) have also shown that highly malignant cells are more sensitive to the anti-proliferative and apoptotic effects of tocotrienols in comparison with pre-neoplastic cells.

The FAC data reflects closely the intake of a palm oil diet in Malaysia. This is not surprising as it is the cheapest and most readily available oil in the country and is reported to constitute the major fat in the diet of the majority of Malaysians (Mo and Elson, 1999). While most vegetable oils provide mainly α - or γ -T, palm oil is unique in the sense that it contains relatively large concentrations of T3. The distribution of the various T and T3 fractions in palm oil are as follows: α -T 32%, α -T3 25%, γ -T3 29% and δ -T3 14%. In the United States, analyses of balanced diets ranging from 2000 to 3000 kcal per day indicated that the average daily intakes of vitamin E

range from 7 to 11 mg (Ng, 1989). Malaysian data on vitamin E intakes are presently limited. However, it is envisaged that for a 2000 to 3000 kcal per day diet one would be consuming between 10 to 15 mg of tocotrienols per day (National Research Council, 1989).

The most significant finding of the present study was the higher, 65% more tocotrienol (α -T3, γ -T3 and δ -T3) concentrations in the adipose tissue of the benign lumps in comparison to the women with malignant breast lumps. There was no difference in the α -T and γ -T content. However, δ -T showed a significant reduction in malignant vs. benign adipose tissue. The depletion in tocotrienols in patients with malignant breast lumps compared to patients with benign lumps could be due to its role as an antioxidant in quenching free radicals and regulating peroxidation reactions.

Tocotrienols possess powerful antioxidant, anti-cancer and cholesterol-lowering properties. Some studies have confirmed that tocotrienol activity as an antioxidant, anti-cancer and cholesterol-reducing substance is stronger than tocopherols (Ng *et al.*, 1991). Tocotrienols are thought to have more potent antioxidant properties than α -T (Sen *et al.*, 2004; Serbinova, 1991). The unsaturated side-chain of tocotrienol allows far more efficient penetration into tissues, such as the adipose, brain and liver, that have saturated fatty layers (Serbinova and Packer, 1994). Experimental research examining the antioxidant, free radical scavenging effects of tocopherols and tocotrienols

revealed that tocotrienols appear superior because of their better distribution in the fatty layers of the cell membrane (Serbinova and Packer, 1994).

Oxidative stress has also been implicated in breast cancer (Suzuki, 1993; Boyd and McGuire, 1991; Lee *et al.*, 1998) and may influence breast cancer by altering gene expression (Li *et al.*, 1999) or by promoting oxidative DNA damage. We however did not measure the hydroperoxide levels in the breast adipose tissue. Other authors (Traber *et al.*, 1987) demonstrated higher conjugated dienes and hydroperoxides in breast adipose tissue of breast cancer patients than in control patients.

In Malaysia, we are fortunate that palm oil contains high amounts of tocotrienols and we have previously demonstrated *in vitro* (Nesaretnam *et al.*, 1995; 1998; 2000) and *in vivo* (Matsui *et al.*, 2000) that tocotrienols protect against breast cancer. Thus, it seems plausible that the modest protection from breast cancer associated with dietary vitamin E maybe due to the effects of tocotrienols in the diet.

The low tocotrienols in the adipose tissue of malignant breast lumps needs to be further investigated as to whether their intake of tocotrienols was low or whether it was used up because they had cancer. Studies have shown that tocotrienol supplementation up to 240 mg for 16-month duration does not have any apparent adverse effect (Nesaretnam *et al.*, 2004). Furthermore, it is likely that breast adipose tissue concentrations will be five- to 10-fold of those in plasma.

This indicates that lower levels of tocotrienol supplementation might be adequate to reach breast adipose tissue tocotrienol concentrations similar to those that inhibit proliferation and promote apoptosis in breast cancer cells. Further studies will be needed to determine whether individuals that achieve such plasma and tissue tocotrienol concentrations are protected from development of breast cancer. A further extension to this project would also look at the tocotrienol levels in the adipose tissue of normal subjects, since in this article, we determined levels in subjects with benign and malignant breast lumps only. It could well be that benign and control subjects may reflect the same amounts. The potentially protective effect of tocotrienols against breast cancer and the mechanism by which these dietary constituents protect women needs to be further investigated.

REFERENCES

- AMERICAN CANCER SOCIETY (2004). Cancer facts and figures. Atlanta.
- BAKER, H; HANDELMAN, G J; SHORT, S; MACHLIN, L J; BHAGAVAN, H N; DRATZ, E A and FRANK, O (1986). Comparison of plasma alpha and gamma tocopherol levels following chronic oral administration of either all-*rac*-alpha tocopherol acetate or RRR-alpha-tocopherol acetate in normal adult male subjects. *Am J Clin Nutr.*, 43: 382-387.

- BOYD, N F and MCGUIRE, V (1991). The possible role of lipid peroxidation in breast cancer risk. *Free Radic. Biol. Med.*, 10: 185-190.
- CHAJES, V; LHUILLERY, C; SATTLER, G M; KOSTNER, G M and BOUGNOUX, T (1996). Alpha-tocopherol and hydroperoxide content in breast adipose tissue from patients with breast tumours. *Int J Cancer*, 67: 170-175.
- CONTE, C; FLORIDI, A; AISA, C; PIRODDI, M and FLORIDI A, GALLI (2004). γ -Tocotrienol metabolism and antiproliferative effect in prostate cancer cells. *Annals NY Acad Sci.*, 1031: 391-394.
- EA, FRANK (1986). Comparison of plasma alpha and gamma tocopherol levels following chronic oral administration of either all-rac-alpha tocopheryl acetate or RRR-alpha-tocopheryl acetate in normal adult male subjects. *Am J Clin Nutr.*, 43: 382-387.
- GALLI, F; STABILE, A M and BETTI, M (2004). The effect of alpha- and gamma-tocopherol and their carboxyl hydroxychroman metabolites on prostate cancer cell proliferation. *Arch Biochem Biophys.*, 423: 97-102.
- GUNDIMEDA, U; CHEN, Z H and GOPALAKRISHNA, R (1996). Tamoxifen modulates protein kinase C via oxidative stress in estrogen receptor-negative breast cancer cells. *J Biol Chem.*, 271: 13504-13514.
- GUTHRIE, N; GAPOR, A; CHAMBERS, A F and CAROLL, K K (1997a). Inhibition of proliferation of estrogen receptor-negative MDA-MB-435 and positive MCF-7 human breast cancer cells by palm oil tocotrienols and tamoxifen, alone and in combination. *J Nutr.*, 127: 544S-548S.
- GUTHRIE, N; GAPOR, A; CHAMBERS, A F and CAROLL, K K (1997b). Inhibition of proliferation of estrogen receptor negative MDA-MB-435 and positive MCF-7 human breast cancer cells by palm tocotrienols and tamoxifen, alone or in combination. *J Nutr.*, 127: S544-S548.
- INGRAM, D M; NOTTAGER, E and ROBERTS, T (1991). The role of diet in the development of breast cancer: a case control study of patients with breast cancer, benign epithelial hyperplasia and fibrocystic disease of the breast. *Br J Cancer*, 64: 187-191.
- INSTITUTE OF MEDICINE (2000). Subcommittee on Upper Reference Levels of Nutrients and Interpretation and Uses of Dietary Reference Intakes, and the Standing Committee on the Scientific Evaluation of Dietary Reference Intakes, Food and Nutrition Board, Vitamin E. *Dietary Reference Intakes for Vitamin C, Vitamin E, Selenium, and Carotenoids, Panel on Dietary Antioxidants and Related Compounds*. National Academy Press 2000, Washington, DC. p. 186-283.
- IP, C (1982). Dietary vitamin E intake and mammary carcinogenesis in rats. *Carcinogenesis*, 30: 53-56.
- ISHII, K; ZHEN, DH; WANG, Y; FUNAMORI, K; OGAWA, K and TAKETA, K (1987). Prevention of mammary tumorigenesis in acatalesmic mice by vitamin E supplementation. *Jpn J Cancer Res.*, 87: 680-684.
- KAACKS, R; RIBOLI, E and SINHA, R (1996). Biological markers of dietary intake. Applications of biomarkers of dietary intake. *Applications of Biomarkers in Cancer Epidemiology*, 142: 103-109.
- KATAN, M; VAN, BIRGELEBA; DESLYPERE, J P; PENDERS, M and VAN STAVERON, W A (1991). Biological markers of dietary intake with emphasis on fatty acids. *Ann Nutr Metab.*, 35: 249-252.
- KAJIMA, S (1993). Chemistry of vitamin E. *Vitamin E - Its Usefulness in Health and in Curing Diseases* (Mino M ed.). Japan Science Society. p. 3-7.
- LEE, J Y; GALOFORO, S S; BERNIS, C M; CHEN, J C; DAVIS, B H; SIM, J E; CORRY, P M and SPITZ, D R (1998). Glucose deprivation induced cytotoxicity and alterations in mitogen-activated protein kinase activation are mediated by oxidative stress in multi drug-resistant human breast carcinoma cells. *J Biol Chem.*, 273: 5294-5299.
- LI, D; ZHANG, W; SAHIN, A A and HITTELMAN, W N (1999). DNA adducts in normal tissue adjacent to breast cancer: a review. *Cancer Detect Prev.*, 30: 54-62.
- MATSUI, A; IKEDA, T; ENOMOTO, K; HOSODA, H; NAKASHIMA, K; OMAE, K; WATANABE, M; HIBI, T and KITAJIMA, M (2000). Increased formation of oxidative DNA damage, 8-hydroxyl-2'-deoxyguanosine, in human breast cancer tissue and its relationship to GSTP1 and COMT genotypes. *Cancer Lett.*, 151: 87-95.

- MCINTYRE, B S; BRISKI, K P; GAPOR, A and SYLVESTER, P W (2000). Antiproliferative and apoptotic effects of tocopherols and tocotrienols on preneoplastic and neoplastic mouse mammary epithelial cells. *Proc. of the Soc Exp Biol Med.*, 224. p. 292-301.
- MIELKE, T (2004). Global analysis. All major oilseeds, oils and oilmeals. Supply, demand and price outlook. *Oil World Annual 2004*. ISTA Mielke GmbH, Hamburg, Germany.
- MO, H and ELSON, C E (1999). Apoptosis and cell-cycle arrest in human and murine tumour cells are initiated by isoprenoids. *J Nutr.*, 129: 804-813.
- NATIONAL CANCER REGISTRY (2003). Ministry of Health, Malaysia.
- NATIONAL RESEARCH COUNCIL (1989). Food and Nutrition Board. Recommended dietary allowances, 10th ed. National Academy Press, Washington, DC.
- NESARETNAM, K; AMBRA, R; SELAVDURAY, K R; RADHAKRISHNAN, A; RAZAK, G and VIRGILI, F (2004). Tocotrienol-rich fraction from palm oil affects gene expression in tumours resulting from MCF-7 cell inoculation in athymic mice. *Lipids*, 39: 459-467.
- NESARETNAM, K; DORASAMY, S and DARBRE, P D (2000). Tocotrienols inhibit growth of ZR-75-1 mammary cancer cells. *Int J Food Sc Nutrition*, 51: 97-105.
- NESARETNAM, K; GUTHRIE, N; CHAMBERS, A F and CARROLL, K K (1995). Effect of tocotrienols on the growth of a human breast cancer cell line in culture. *Lipids*, 30: 1139-1143.
- NESARETNAM, K; STEPHEN, R; DILS, R and DARBRE, P (1998). Tocotrienols inhibit the growth of human breast cancer cells irrespective of estrogen receptor status. *Lipids*, 35: 461-465.
- NG, T K W (1989). Palm olein as the predominant fat in the diet of Malaysians - some major nutritional considerations. *Fam Physician*, 1: 43-46.
- NG, T K W; HASSAN, K; LIM, J B; LYE, M S and ISHAK, R (1991). Non hypercholesterolemic effects of a palm oil diet in Malaysian volunteers. *Am J Clin Nutr.*, 53: 1015S-1020S.
- OHRVALL, M; TENGBLAD, B and VESSBY, B (2002). Tocopherol concentrations in adipose tissue. Relationships of tocopherol concentrations and fatty acid composition in serum in a reference population of Swedish men and women. *Eur J Clin Nutr.*, 48: 212-218.
- ONG, A S H (1993). Natural sources of tocotrienols. *Vitamin E in Health and Disease* (Packer, L and Fuchs, J eds.). Marcel Decker, New York, USA. p. 3-8.
- PAPAS, A M (1993). Oil soluble antioxidant in foods. *Toxicol Ind Health*, 9: 123-50.
- RIBOLI, E; RONNHOLM, H and SARACCI, R (1987). Biological markers of diet. *Cancer Surv.*, 6: 85-88.
- SCHWENKE, D C (2002). Does lack of tocopherols and tocotrienols put women at risk of breast cancer. *J Nutr Biochemistry*, 13: 3-20.
- SEN, C K; KHANNA, S and ROY, S (2004). The natural vitamin E to defend the nervous system? *Ann NY Acad Sci.*, 1031: 127-142.
- SERBINOVA, E (1991). Free radical recycling and intramembrane mobility in the antioxidant properties of alpha-tocopherol and alpha-tocotrienol. *Free Radic Biol Med.*, 10: 263-275.
- SERBINOVA, E A and PACKER, L (1994). Antioxidant properties of alpha-tocopherol and alpha-tocotrienol. *Methods Enzymol.*, 234: 354-366.
- SUZUKI, Y J (1993). Structural and dynamic membrane properties of alpha-tocopherol and alpha-tocotrienol: implication to the molecular mechanism of their antioxidant potency. *Biochemistry*, 32: 10692-10699.
- TRABER, M G and KAYDEN, H J (1987). Tocopherol distribution and intracellular localization in human adipose tissue. *Am J Clin Nutr.*, 46: 488-495.
- WAHLQVIST, M L; BOGETIC, M; KROKOVUCA, Z; HAGE, H; SMITH, R and LUKITO, W (1992). Differential serum responses of tocopherols and tocotrienols during vitamin supplementation in hypercholesterolemic individuals without changes in coronary risk factors. *Nutr Res.*, 12: S181-S201.
- YU, W; SIMMONS-MENCHACHA, M; GAPOR, A; SANDERS, G and KLINE, K (1999). Induction of apoptosis in human breast cancer cells by tocopherols and tocotrienols. *Nutr Cancer*, 33: 26-32.