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BREAST CANCER IN DEVELOPING POPULATION: A NUTRITION CAVEAT

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ABSTRACT

From January 1992- January 1998, 1404 patients attended the "Breast Clinic" of R.N.T. Medical College M.B. Hospital, Udaipur. Out of these, 11% and 81% patients had breast cancer (B.C.) and benign breast cancer (B.B.D.) respectively. The oxidative load in B.C. was 2.32 times higher than controls, but comparable to B.B.D. β-Carotene deficiency was uncommon in patients, whereas vitamin A deficiency was almost equally common in both B.C. and controls. Most of the patients had almost depleted levels of α-tocopherol and ascorbic acid but their TBAR levels were in normal range. The data in the present study when compared with B.B.D. and other local normal subjects point out: a) oxidative burden in B.C. is a consequence and not the cause of the disease, (b) oxidative stress could be one of the etiological factors in tumor expression, which need not to be malignant and c) α-tocopherol and ascorbic acid are not importantly responsible for higher oxidative burden in B.C.

KEY WORDS : Breast Cancer, Oxidative Stress, Antioxidants, α-Tocopherol, Ascorbic acid.

INTRODUCTION

Cancer remains an enigmatic disease even today as we are still gropping inconclusively about the molecular basis of the loss of regulation of cell growth and cell differentiation in some cancers. The knowledge about cell differentiation is still meagre. Therefore, it continues to be a menacingly challenging global health problem with alarming rate of mortality. (1). Sex wise segregation of cancer incidence shows that in females breast cancer is first rank cause of morbidity and mortality in developed populations, second rank cause in underdeveloped population after cervix cancer and almost equal cause in developing populations, showing its direct increase with social awareness and economic affluence .For example, a survey in 1996 indicated that in developed populations breast cancer and cervix cancer ratio was 494000 and 102000 whereas in developing world it was 416000 and 421000 (1).

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A host of factors have been implicated with the etiology of breast cancer and lately the importance of nutrition in both etiology and management is under increasing scrutiny (2,3), because man, depends inevitably on food for energy requirements, growth, defence, repair and sustenance. A vast spectrum of diseases are now known where the imbalanced nutrition, either deficient or excess, is major cause of the disease and there is now compelling evidence that nutrition plays a significant role in both the prevention and management of several types of cancers too (1,4). Therefore functions of dietary components especially oxidants and antioxidants in modulating cancer tend to be vigorously investigated.

In breast cancer, the important factors related to diet are obesity (usually a consequence of over nutrition), quantity and quality of fat though not proven till date (5), food preservations, inadequate consumption of fruits and vegetables, contaminants like aflatoxin and nitrosamines and alcohol. Ambrosone et al (6) have reported important role of dietary oxidants and antioxidants in breast cancer. However, the precise commitment of nutrition in breast

cancer is still a moot issue. Further, such types of studies in Indian population where the food is at premium, are inadequate. This study initiates efforts in this direction and this paper addresses the oxidative burden and nutrient antioxidant provitamin β-carotene vitamin A, α-tocopherol and ascorbic acid status in breast cancer.

MATERIALS AND METHODS

A Breast Clinic is run in R.N.T. Medical College, Maharana Bhopal Hospital, Udaipur. Systematic records are maintained in this clinic about their investigations, clinical profile and type of management given. In the present study, the patients attending this clinic from January 1992 to January 1998 are included. They belong to southern part of Rajasthan and western part of Madhya Pradesh. The patients were divided into urban and rural groups depending upon their residential status. Controls matched in respect to their age, weight, socio-economic and residential status were selected.

Diagnosis was confirmed by Fine Needle Aspiration Cytology (FNAC). The aspirated material was smeared on the slides and processed for May Grunwald Geimsa Staining. TNM Classification was followed for clinical staging of carcinoma .For biochemical analysis blood sample was collected in EDTA vials. Standard procedures were used for the analysis of TBAR(7), β-carotene, vitamin A, ascorbic acid(8) and α-tocopherol (9). The categorization of patients on the basis of oxidative stress and deficiency of antioxidants is given in table 1.

RESULTS

During the above said period 1404 patients attended the Breast Clinic. Out of these 11%(n=154) had breast cancer, 81%(n=1140) suffered from benign breast disease and 8%(n=110) attended the clinic for routine check up. The details of their clinical status are given in table 2. Among the breast cancer patients, 62 were urban and 92 were rural. Their weight wise distribution is given in figure 1. As per recommendations of Indian Council of Medical Research (ICMR), the average weight of Indian women should be 50 kgs. The data impresses the fact that obesity was not an important risk factor in the breast cancer. Further 47% rural and 10% urban women were under weight (<50 kg.) and apparently looked under nourished. Family history (14.3% patients) was also not a major factor.

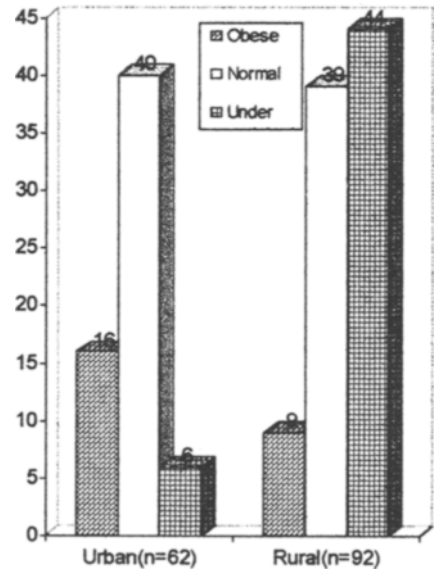

Fig. 1. Weight wise distribution among patients with breast cancer

The TBAR levels in breast cancer patients was 2.3 times (5.32±3.17nmol/ml) compared to that of controls (2.30±0.86). Ascorbic acid and α-tocopherol levels were significantly lower in breast cancer patients. β-carotene levels did not show any difference (Table 3). A better picture emerged when the data of individual patients was classified on the basis of mean+SD or mean-SD(Table 4). 51.8% patients showed severe oxidative burden and nutrient antioxidant defence was moderate to severely depleted in majority of patients (Table 5).

DISCUSSION

The rationale for implicating nutrition in the etiology of breast cancer arises for two reasons, first there is a tacit evidence for the involvement of nutrition in cancer initiation, promotion and progression and also in prevention or retardation (1,3) and second, cancer is an age related disease and that longivity is

Table 1. Nutrient antioxidant and plasma TBAR levels.

Parameters (normal values with units)	Range of depletion	Accepted Range	Suggested range (present stud
TBAR 1.05-3.2nmol/ml plasma	Mild oxidative stress		> (M+ 2SD) - (M+3SD)
	Moderate oxidative stress		4.01+4.87
	Severe oxidative stress		> +4.87
Retinol 20-65 μg/dl	Mild deficiency	10-20	< (M-2SD) 18.89-14.59
	Moderate deficiency		< (M-2SD) - (M-3SD)
	Severe deficiency	< 10	< (M-3SD) < -14.59
β-carotene 60-200 mg/dl	Mild deficiency	40-80	< (M-2SD)
	Moderate deficiency		< (M-2SD) - (M-3SD)
	Severage deficiency	< 40	< (M-3SD) < -14.44
Ascorbic acid 0.8-1.5 mg/dl	Mild deficiency	0.2-5.0	< (M-2SD) 0.8-1.5
	Moderate deficiency		< (M-2SD) - (M-3SD)
	Severe deficiency	< 0.2	< (M-3SD) < -0.25
α-tocopherol 0.8-1.2 mg/dl	Mild deficiency	0.2-5.0	< (M-2SD) 0.80-1.20
	Moderate deficiency	< 0.2	< (M-3SD)
	Severe deficiency		< -0.43

Table 2. Total cases examined in breast clinic from Jan. 1992 to Jan. 1998 disease wise distribution.

S. No.	Disease	No. of cases	% of total
1.	Total Cases	1404	100%
2.	Breast Cancer cases	154	11%
3.	Routine examination	110	8%
4.	B.B.D. Total	1140	81%
(a)	Mastalgia with glandular breast	478	42%
(b)	Fibroadenoma	178	16%
(c)	Cystic disease/Hormonal/Adenosis	197	17%
(d)	Tuberculosis	20	2%
(e)	Inflammation	95	8%
(f)	Nipple discharge	139	12%
(g)	Miscellaneous	33	3%

largely, if not entirely dependent on nutrition (10,11) and under some settings dependent on each other. Our observations also subscribe to this opinion. Though some foods have directly been related to specific type of cancers but far more important is the total composition of diet in which oxidant/antioxidant balance plays a central role in all cancers including breast cancer; and antioxidants, in which nutrients β-carotene and vitamin A, E and C are important coalition partners and try to pre-empt the peremptory function of free radicals.

Since breast tissue mainly consists of fat, and unsaturated fatty acids are preferentially prone to peroxidation, dietary fat has been incriminated with breast cancer, we therefore thought it germane to

Table 3. Level of plasma and nutrients antioxidant in breast cancer cases and controls.

S.No.	Parameters	Control Group		Breast Cance		
		Urban (n=60)	Rural (n=30)	Urban (n=46)	Rural (n=27)	Total (n=73)
1.	TBAR (n mol /ml)	2.30±0.86	2.42±0.87	5.04±3.11	5.10±3.32	5.32±3.17
2.	Retinol (μg/dl)	23.19±4.30	22.25±4.90	23.22±14.69	22,72±18.61	23.19±16.17
3.	β–carotene (μg/dl)	90.10±23.64	96.54±29.23	82.38±39.42	87.05±41.29	82.48±39.02
4.	Ascorbic acid (mg/dl)	0.86±0.61	0.80±0.25	0.53±0.42	0.46±0.33	0.49±0.38
5.	α-tocopherol (mg/dl)	0.96±0.53	1.02±0.50	0.58±0.38	0.44±0.28	0.53±0.35

Table 4. Percentage of rural patients on different ranges of nutrients antioxidant according to Mean±SD of respective controls.

Different Ranges	TBAR (n mol/ml) (2.47±0.87)	Retinol (μg/dl) (22.25±4.9)	β-carotene (μg/dl) (96.54±29.2)	Ascorbic acid (mg/dl) (.80±0.25)	α-tocopherol (mg/dl) (1.02±0.50)
≤ M	11.1	-	-	-	-
> M - M+1SD	7.4	31.8	-	-	4.5
> M+1SD - M+2SD	18.5	9.0	-	-	-
> M+2SD - M+3SD	11.1	-	-	-	-
> M+3SD	51.8	-	-	-	-
> M	-	-	40.9	22.7	-
< M - M-1SD	-	13.6	18.2	22.7	31.8
< M-1SD - M-2SD	-	31.8	27.2	18.2	63.6
< M-2SD - M-3SD	-	9.0	13.6	27.3	-
< M-3SD	-	4.5	-	9.0	-

Table 5. Percentage of urban patients on different ranges of TBAR and nutrients antioxidant according to mean±SD of respective controls.

Different Ranges	TBAR (n mol/ml) (1.94±0.73)	Retinol (μg/dl) (23.96±3.7)	β-carotene (μg/dl) (83.18±12.8)	Ascorbic acid (mg/dl) (.92±0.83)	α-tocopherol (mg/dl) (1.07±0.63)
≤ M	8.0	-	-	-	-
> M - M+1SD	6.0	6.0	28.0	20.0	-
> M+1SD - M+2SD	12.0	22.0	16.0	2.0	-
> M+2SD - M+3SD	12.0	-	-	-	-
> M+3SD	62.0	-	-	-	-
> M	-	-	-	-	10
< M - M-1SD	-	20.0	4.0	68.0	54.0
< M-1SD - M-2SD	-	22.0	28.0	10.0	36.0
< M-2SD - M-3SD	-	26.0	-	-	-
< M-3SD	-	4.0	-	-	-

measure "Thiobarbituric Acid Reactive Substances" (TBAR) of which malondialdehyde (MDA), an adduct of fatty acid oxidation, is a major constituent. The observed levels of TBAR in breast cancer (BC) were 2.32 times to that of controls, suggesting an increased oxidative burden in BC which corroborates with the observation of other workers. What we have noticed, and others have not, is that this increased oxidative burden in BC is primarily a consequence and not the cause because the magnitude of rise in TBAR levels

was same in benign breast disease.

Notably 51.8% patients suffered from severe oxidative stress raising the doubt that in some patients this persistent and perpetual oxidative stress spliced with its toxic products, some of which have carcinogenic attributes too, maybe playing a causative role too because it is known that some of the benign breast tumors under clinical provocative environment may turn malignant. For example Suy et. al. (12) concluded that oxidants could initiate signal transduction by demonstrating that free radical nitroxides induce divergent signal transduction pathways in MDA-MB 231 breast cancer cells and that antioxidants can combat this assault to a significant degree. Further, the important effects of tamoxifen, which is now most widely used drug in the management of cancers including BC, are through its inhibition of lipid peroxidation. It is here the quality and quantity of dietary liquids come into reckoning and so is obesity.

In a recent prospective study on 88795 women followed for 14 years, Holmes et. al. (5) did not find the association of either quality or quantity of fat which is contrary to the claim of others (13,14). This indirectly suggests that low body fat confer some protection against cancer. Further the caloric restriction in animals has been shown to have protective effect on development of cancer due to decreased oxidative damage (15) and that fat increases the risk of cancer which can be prevented by simultaneous moderate exercise (16). In contrast to these observations, the results of our present study show that the percentage of prevalence of under weight patients was double than that of obese patients; and that both the groups of patients in this study were engaged in moderate to severe physical activity before the detection of the disease.

The explant studies sufficiently indicate that β-carotene, vitamin A, E and C exhibit anticancer property (17), though the debate continues about the magnitude of participation and amplitude of their effectiveness (18). The role of β-carotene in humans as antioxidant continues to be a moot issue but our observations clearly indicate that β-carotene deficiency is not a discernible issue in breast cancer in this population.

The important functions of vitamin A and its products in humans besides vision are cell differentiation and growth and as an antioxidant and these are attributed to be related to carcinogenesis though precise mechanism of involvement remains elusive. Meysken (19) has sufficiently stressed its general role in cancer. Though Cassidy et. al. (20) and Modiano et. al. (21) were unable to find any therapeutic value of vitamin A in a small number of breast cancer patients the animal studies, on the contrary, have shown distinct beneficial effects of retinoids, related to structure to retinol and retinoic acid, on several cancers including breast cancer (22, 23). Hill et. al. (22) suggested that retinoid esters accumulate in mammary tissue and remain there for prolonged periods and get released as free acids slowly which behave as anticancer agents. Unfortunately vitamin A deficiency is very common in this region (24, 25). In this series almost half the control subjects showed low/deficient status. Among breast cancer patients 52% urban and 45.3% rural had levels <17.3 mg%. This is certainly a bemoaning feature but whether this chronic deficiency has any relevant connection with breast cancer needs further examination.

It is persuasively believed that α-tocopherol intercalates into the lipid bilayers of cell membranes and acts there directly to scavenge free radicals or terminates free radical generated oxidative chain in polyunsaturated fatty acids thereby shielding the membranes from oxidative damage in several diseases including cancer. Wald et. al. (26) concluded from their studies that its anti cancerous therapeutic behaviour in breast cancer was due to its ability to restore the process of apoptosis in rebellious malignant cells through glutathione associated pathway. In this study the mean antioxidant (α-tocopherol) level was much below (0.53 ± 0.35 mg %) the normal level. Notably 36% patients had level <0.44 mg %. Since our unpublished data indicate that its level in the benign breast disease is even lower than BC, and there by suggesting that α-tocopherol is decidedly not a primary

risk factor in this disease.

In view of its enormous nutritional value presently much higher intake of ascorbic acid is argued than presently recommended levels. Its level was significantly low in BC. Surprisingly 54.5% patients had levels <0.13 mg %, representing a distressingly depleted status but then picture was again similar to benign breast disease. Though Prasad et. al. (17) demonstrated in his in vitro studies that ascorbic acid inhibited the growth of melanoma cells in a concentration dependent manner and summarized that this nutrient has anti carcinogenic property but proven answer had yet to come.

As a corollary considering all the data together, we are inclined to conclude that oxidative burden in breast cancer is a consequence but the possibility does exist that in some cases due to persistent oxidant load along with the higher concentration of toxic oxidative adducts, oxidative stress may behave as abetting congregate with other risk factors and that feeble antioxidant defence was not the sole cause of this oxidative stress. We hypothesize that in the firmament of disdainful multi factorial complex etiology of breast cancer, wherein environmental factors in connivance with propitious genetic and hormonal disposition play dominating role, low caloric diet with low fat may be providing a protective shield against breast cancer in developing populations.

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