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Alterations in Serum Lipid Profile & Lipid Peroxidation Status in Female Breast Tumour Patients

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Abstracts
Breast Carcinoma is the most common cause of death in middle aged women in western countries. In India it is the second most common carcinoma in female next to cervical carcinoma. Our aim was to evaluate the relationship of lipid profile and Lipid peroxidation status with breast tumour. These findings suggest that obesity is not an important risk factor in development breast tumour. Early menarche, late menopause and low parity are definite risk factors. Dyslipidemia is definitely associated with breast tumour whether it is a cause or effect of tumour it is not exactly known. There is definite increase in ROS production oxidative stress is more in case of breast tumour patients both in benign and malignant group.
Keywords: *Lipid profile, Malondialdehyde & breast tumour.*

Introduction

A tumour or neoplasm is an abnormal mass or tissue, the growth of which exceeds and is uncoordinated with that of normal and persists in the same excessive manner after cessation of the stimuli which evoked the change. It may be benign or malignant. A tumor is said to be benign when its microscopic and gross characteristics are considered relatively innocent, implying that it will remain localized. Malignant tumor referred to as cancer is a neoplasm that invades and destroys adjacent structures and spread to distant sites to cause death. Anaplasia or lack of differentiation is considered to be the hall mark of malignant transformation. In contrast to malignant tumors, benign tumors are well differentiated[1].

Breast Carcinoma is the most common cause of death in middle aged women in western countries[2]. In India it is the second most common carcinoma in female next to cervical carcinoma[3].

Only 10% of breast mass in women under 40 are malignant as compared to 60% of masses in women over age 50[1].

Significant risk factors include age, late age of first pregnancy, oral contraceptives, diet, family

history, null parity, hormone replacement therapy, early age of menarche, late age of menopause non lactation etc[4]. There is a strong correlation between obesity and breast carcinoma. As these are estrogen dependent tumors, the major source of estrogen in postmenopausal women is from the conversion of androstenedione to estradiol in adipose tissue.[5] Long term consumption of high fat diet contributes to an increased risk of breast cancer by increasing serum estrogen level[3,6].

The relationship between lipid and breast tumor is obscure. Until now conflicting results have been reported on association between lipids and breast tumors in females. Recently reports have documented altered levels of serum lipids i.e. increased levels of total cholesterol and TG (Triacylglycerol) in different breast tumor patients but the result of HDL is contradictory.[7]

Obese women are at higher risk of development of breast cancer as hyperlipidemia is common in obese person. Body mass index (BMI) is inversely related to serum levels of SHBG (Sex hormone binding globulin) low level of SHBG indicates high level of serum estradiol and high risk of breast cancer.[4]

Oxygen derived free radical (OFR) or Reactive oxygen species (ROS) are highly reactive and toxic, but biological system has evolved an array of enzymatic and non-enzymatic antioxidant defense mechanism to combat the deleterious effect of OFR [8].

Oxidative stress arises when there is an imbalance between OFR formation and scavenging antioxidants. Excess generation of OFR can cause oxidative damage to biomolecules resulting in lipid peroxidation, mutagenesis and carcinogenesis. OFR induced lipid peroxidation has been implicated in neoplastic transformation.[9]

OFR can cause direct DNA damage which includes modification of all bases, as well as production of base free sites, deletions, strand breaks, frame shift mutation etc. All these lead to inactivation of tumor suppressor gene or activation of proto-oncogenes which initiate carcinogenesis.[10]

The present study is to evaluate the relationship of lipid profile and Lipid peroxidation status with breast tumour.

Materials & Methods

The present study was undertaken in the department of Biochemistry, V.S.S. Medical college and Hospital, Burla on diagnosed patients attending outpatient department and admitted in the department of Surgery and Radiotherapy between Sept 2009 to Sept 2011. The study included 44 breast tumour patients (20 benign & 24 malignant tumour cases) between 25 to 55 years of age. 30 number of age and sex matched healthy individuals were taken as control.

Patients were cases of essential hypertension if they have with following criteria's:

i. Systolic blood pressure more than or equal to 140 mm Hg and diastolic blood pressure more than or equal to 90 mm Hg.
ii. Patients not taking antihypertensive drugs.
iii. Patients not having :
   - Drug induced or drug related hypertension
   - Chronic kidney disease
   - Primary hyperaldosteronism
   - Reno vascular disease
   - Chronic steroid therapy and Cushing's syndrome
   - Pheochromocytoma
   - Coarctation of aorta
   - Thyroid and parathyroid disease
   - Sleep apnea

Following biochemical investigations were carried out in both the study groups by standard methods.

Routine blood test

- Fasting blood sugar: Nelson-Somogyii method (1952)
- Serum urea: Diacetyl monoxime method (Natelson, 1952)
- Serum creatinine: Modified Folin-Wu tungstic acid method
- Serum lipid profile
  - Total cholesterol- Modified Zak's method (1957)
  - Triglyceride- Fletcher et al (1953)

- High density lipoprotein cholesterol- Zlatkis et al (1953)
- Very low density lipoprotein cholesterol- Calculated by using Friedwald's formula
- Low density lipoprotein cholesterol- Calculated by using Friedwald's formula
- Serum sodium, potassium and calcium: Ion selective electrodes (ECOLYTE of ESCHWEILER)

Special test

- Plasma Nitric oxide (NO) estimation by Griess reaction according to the modified method of Ding et al (1998)

Following statistical tests are done:

- Chi- square test
- 'p' test
- 't' test

RESULTS

The present study was undertaken in the department of Biochemistry, V. S. S. Medical College and Hospital, Burla. This present study included 44 breast tumour patients (20 benign & 24 malignant tumour cases) between 25 to 55 years of age. 30 number of age and sex matched healthy individuals were taken as control.

Table -1: Distribution of Controls and Cases According to Age

Age	No of controls	%	No of Benign cases	%	No of Malignant cases	%
25-35	6	19.98%	12	60%	3	12.98%
35-45	11	36.63%	6	30%	9	37.44%
45-55	13	43.29%	2	10%	12	49.42%

TABLE-1. Shows the number of healthy controls, benign and malignant cases found in different age groups with their percentages. All the cases are within 25-55 yrs. In the age group of 25-35 yrs highest number of benign cases (60%) and lowest number of malignant cases (12.98%) are found. Around 50% malignant cases and only 12% benign cases are seen in the age group of 45-55 yrs. Age matched healthy controls are included in the study.

Table-II: Distribution of Cases According to Type of Tumour

Group	No. Of Cases	Percentage
Benign	20	45.50%
Malignant	24	54.50%
Total	44	100%

Table –II Shows the percentage of benign and malignant cases included in the study. Approximately the same percentages of benign and malignant tumour cases are included in the study.

Table-III: Distribution of Benign Cases According to Type

GROUP	No. of cases	Percentage
ACD	10	50%
FA	8	40%
CP	2	10%
TOTAL	20	100%

Table-III Shows the percentage of type of benign tumours found in the study. Maximum numbers of cases are of Adenoid cystic diseases followed by fibroadenoma and then cystosarcoma phylloides.

Table-IV: Distribution of Malignant Cases According to Stages

Stages	No of cases	Percentage
I	1	4.20%
II	2	8.30%
III	9	37.50%
IV	12	50%
Total	24	100%

Table-IV. Shows distribution of percentage of cases according to stages of tumour. Major percentage of cases i.e. 12 cases out of 24 cases are in advanced stage or stage-IV.

Table-V: Average age, Menstrual age Distribution and Obstetrics History of Control and Cases

Group	Age		BMI		Age of menarche		Age of menopause		PARITY	
	Range	Mean ±SD	Range	Mean ±SD	Range	Mean ±SD	Range	Mean ±SD	Range	Mean ±SD
Control	25-55	43.60 ±11.75	19.4-23	20.82 ±1.39	13-15	13.43 ±0.67	45-48	47.16 ±1.19	0-6	2.83 ±1.07
Benign	25-55	39.05 ±8.03	20-24.45	23.42 ±2.88	11-14	12.45 ±0.6	47-55	50 ±1.41	0-3	1.35 ±1.35
Malignant	35-55	49.33 ±7.28	16.9-26	21.74 ±2.86	11-13	12.21 ±0.83	48-55	51 ±1.13	0-3	1.31 ±1.04

Table-V shows average age, age of menarchae, age of menopause and parity of healthy controls, benign and malignant cases. Average age is highest among malignant groups where as it is lowest among benign groups. Age matched controls have been taken for study. There is early menarchae, late menopause and low parity in malignant as well as benign groups in contrast to controls. Mean BMI of benign group is more than malignant and control group .Though BMI of benign group shows a higher value i.e the range of 20-25 all the benign cases are within normal range in contrast to the malignant group ,where some women have a higher BMI in obese range.

Table-VI: Comparison of Age, Age of Menarchae, Age of Enopause, Parity and BMI Among Control, Benign, and Malignant Breast Tumour Patients.

Table-VI.(A): Comparison Between Control And Benign Groups

Parameters	Control (Mean±SD)	Benign (Mean ± SD)	"t" Value	"p" Value
Age	43.60±11.75	39.05±8.03	2.36	.0.05
Age of menarchae	13.430 ±0.67	12.45 ±0.6	5.23	<0.01
Age of manopause	47.16±1.19	50±1.41	4.13	<0.01
Parity	2.83±1.07	1.35±1.35	4.04	<0.05
BMI	20.82±1.39	23.42±2.88	6.9	<0.001

Table VI (A) shows the comparison between different clinical parameters of benign and control group. There is no stastically significant difference in age in between both the study groups ,thus age matched control group has been taken for study. Statistically significant early menarchae, late menopause and low parity are found in benign group in comparison to healthy controls. BMI in case of benign group is significantly higher in comparison to control group

Table-VI.(B): Comparison Between Control and Malignant Group

Parameters	Control (Mean±SD)	Malignant (Mean±SD)	"t" Value	"p" Value
Age	43.60±11.75	49.33±7.28	3.40	>0.05
Age of menarchae	13.430±0.67	12.21±0.83	3.95	<0.01
Age of menopause	47.16±1.19	51±1.13	4.33	<0.01
parity	2.83±1.07	1.31±1.04	4.95	<0.05
BMI	20.82±1.39	21.74±2.86	1.75	<0.05

Table-VI.(B) Shows the comparison between the different clinical parameters of control and malignant group. Statistically significant age difference is not found in between both the groups as age matched control group is included in the study. Early menarchae , late menopause and low parity are found in malignant breast tumour patients and when compared to control healthy individuals it is found to be statistically significant. BMI is higher in malignant group than control group which is statistically significant.

Table-VI.(C): Comparison Between Benign and Malignant Group

Parameters	Benign	Malignant	"t" Value	"p" Value
Age	39.05±8.03	49.33±7.18	3.97	<0.001
Age of menarchae	12.45 ±0.6	12.21±0.83	1.08	>0.05
Age of menopause	50±1.41	51±1.13	4.13	>0.05
Parity	1.35±1.35	1.31±1.04	0.326	>0.05
BMI	23.42±2.88	21.74±2.86	2.3	<0.05

Table –VI(C) Shows the comparison between different clinical parameters between benign and malignant group. Malignant tumour cases are found in older age and benign tumours occur in younger age group women .Mean age of these two groups when compared, it was found to be statistically significant. Early age of menarchae, Late age of menopause and low parity are found in both benign and malignant groups and the difference is not statistically significant.

Table-VII: Biochemical Parameters in Control, Benign and Malignant Breast Tumour Patients.

Bio-chemical parameters	Control		Benign		malignant	
	Range	Mean ±SD	Range	Mean ±SD	Range	Mean ±SD
Tch (mg/dl)	150-210	176.74 ±12.52	170-210	184.36 ± 9.45	180-210	204.24 ±8.87
TG (mg/dl)	80-150	125.5 ±16.45	110-129	130.15 ±12.83	150-170	160.80 ± 4.81
HDLc (mg/dl)	30-55	45.04 ±6.64	30-45	35.53 ±6.42	26-39	31.39 ± 4.54
LDLc (mg/dl)	79-150	106.54 ±12.40	108-152	126.71 ±10.13	120-160	130.69 ±11.23
VLDL (mg/dl)	16-30	25.1 ± 2.64	22-30	26.30 ± 1.50	30-34	32.16 ±1.50
MDA (µmol/L)	0.8-2.5	1.77 ± 0.33	1.29-3.5	3.23 ± 0.40	2.72-4.9	4.43 ± 0.32

Table –VII shows the mean ± SD and range of control, benign and malignant groups studied. It is observed that serum Tch, TG and LDLc is highest among malignant tumour cases followed by benign tumour cases followed by controls. In contrast HDLc is highest among healthy controls followed by benign cases followed by malignant tumour cases.

Serum MDA level is highest among malignant tumour cases followed by benign cases and it is lowest in healthy controls.

Table-VIII: Comparison of Biochemical Parameters of Control and Benign Tumour Cases:

Table-VIII (A): Comparison Between Control and Benign Group

Biochemical parameters	Control Mean±SD	Benign Mean±SD	"t"value	"p"value
TCh(mg/dl)	176.74 ±12.52	184.36 ± 9.45	3.05	>0.05
TG(mg/dl)	125.5 ±16.45	130.15 ±12.83	1.13	>0.05
HDL(mg/dl)	45.04	35.53	4.9	<0.001

	±6.64	±6.42		
LDL(mg/dl)	106.54 ±12.40	126.71 ±10.13	3.9	<0.001
VLDL(mg/dl)	25.1 ± 2.64	26.30 ±1.50	1.9	>0.05
MDA(µmol/L)	1.77 ± 0.33	± 0.40	16.8	<0.001

TABLE-VIII (A) Shows comparison of biochemical parameters between control and benign groups. The levels of TCh, TG, and VLDL of benign group show no statistical significance as compared to control group , while the level of HDLc is significantly lower & LDLc level is significantly higher in respect to control group. Serum MDA level is significantly higher in benign group in comparison to control group.

Table-VIII (B): Comparison between Control and Malignant Group.

Biochemical parameters	Control Mean±SD	Malignant Mean±SD	"t" value	"p" value
TCh(mg/dl)	176.74 ±12.52	204.24 ±8.87	7.79	<0.001
TG(mg/dl)	125.5 ±16.45	160.80 ±4.81	9.38	<0.01
HDL(mg/dl)	45.04 ±6.64	31.39 ± 4.54	10.58	<0.001
LDL(mg/dl)	106.54 ±12.40	130.69 ±11.23	8.4	<0.001
VLDL(mg/dl)	25.1 ± 2.64	32.16 ±1.50	9.32	<0.01
MDA(µmol/L)	1.77 ± 0.33	4.43 ±0.32	34.98	<0.001

Table VIII (B) shows the comparison of serum biochemical parameters between malignant group with control group. Statistically significant higher value of TCh, TG, LDL VLDL and lower value of HDLc are found in malignant tumour cases in comparison to control group. Serum MDA level is significantly increased in malignant group in comparison to control group.

Table-VIII (C): Comparison Between Benign and Malignant Group

Biochemical parameters	Benign Mean±SD	Malignant Mean±SD	"t" value	"p" value
TCh(mg/dl)	184.36 ± 9.45	204.24 ±8.87	3.4	<0.01
TG(mg/dl)	130.15 ±12.83	160.80 ±4.81	9.42	<0.01
HDL(mg/dl)	35.53 ±6.42	31.39 ± 4.54	4.4	<0.001
LDL(mg/dl)	126.71 ±10.13	130.69 ±11.23	5.02	<0.001
VLDL(mg/dl)	26.30 ± 1.50	32.16 ± 1.50	9.87	<0.01
MDA(µmol/L)	± 0.40	4.43 ± 0.32	14.95	<0.001

TABLE-VIII(C) Shows the comparison of serum biochemical parameters between benign and malignant cases. There is significantly higher value of TCh ,TG and VLDL in malignant tumour cases in comparison to benign group. The decreased level of HDLc and increased level of LDLc which are highly significant found in malignant tumour cases in comparison to benign tumour group. Serum MDA level is significantly higher in malignant group in comparison to benign group.

Table –IX: Correlation of MDA with Lipid Profile in Control Group

Parameters (mg/dl)	TCh	TG	HDL	LDL	VLDL
r value	+0.13	+0..44	-0..28	+0.36	+0.42
p value	<0.001	<0.001	<0.001	<0.001	<0.001

Table-IX- shows correlation between MDA and lipid profile in controls. MDA has positive correlation with TCh,TG LDL and VLDL which is statistically significant and has negative correlation with HDL which is also statistically significant .

Table –X: Correlation of MDA With Lipid Profile in Benign Groups.

Parameters(mg/dl)	TCh	TG	HDL	LDL	VLDL
r value	+0.35	+0.69	-0.50	+0.63	+0.69
p value	<0.001	<0.001	<0.001	<0.001	<0.001

Table-X shows correlation between MDA and lipid profile in benign group. MDA has positive correlation with TCh, TG, LDL and VLDL which is statistically significant and has negative correlation with HDL which is also statistically significant .

Table XI: Correlation of MDA with Lipid Profile in Malignant Groups

Parameters(mg/dl)	TCh	TG	HDL	LDL	VLDL
r value	+0.64	+0.48	-0.41	+0.49	+0.97
P value	<0.001	<0.001	<0.001	<0.001	<0.001

Table XI shows correlation between MDA and lipid profile in malignant group. MDA has positive correlation with TCh,TG ,LDL and VLDL which is statistically significant and has negative correlation with HDL which is also statistically significant .

DISCUSSION

Present study was undertaken to evaluate the alteration in serum lipid level and the lipid peroxidation status by estimating serum lipid and serum MDA level in benign and malignant breast tumour cases and compared with healthy controls. Due to increased conversion of steroid hormone to estradiol in body fat there is increased incidence of breast tumour in obese women in post menopausal age group[2] . Oxidative stress is a common pathway which links diverse mechanism for pathogenesis of breast tumour[8].Taking in to consideration all the above facts this study has been taken up which may help to explain the role of oxidative stress and the affect of body lipid content in development of breast tumour.

Breast cancer is the second most common cancer among Indian women and in developed countries it is the commonest cancer[4]. It is also reported that breast cancer is proportionately on the increase in few metropolitan areas of India. This appears to be related to late marriage, birth of first child at later age, fewer children and shorter period of breast feeding which are increasingly a common practice among the educated urban women[3].

Although a specific cause for breast cancer has not been identified, there are risk factors that increase the likelihood that a women will develop breast cancer. The risk factors are longer reproductive span, null parity, elderly primi, maternal relative with breast cancer, obesity, increased dietary fat intake, association of BRCA 1 and BRCA 2 genes, atypical epithelial hyperplasia etc[11].Though breast tumour is very common and the incidence has been increasing steadily studies regarding the association of these risk factors are scarce and contradictory.

In this study it was tried to evaluate the degree of alteration in serum lipids, lipid peroxidation status (in form of thiobarbituric acid reacting substances i.e TBARS) association of obesity, affect of early menarchae, late menopause and

parity in different benign and malignant breast tumour patients.

A total 44 breast tumour patients were studied out of which 24 (54.5%) had malignant tumour& 20 (45.5%) patients had benign diseases(Table-I). 30 number of age matched controls were studied for comparision. All subjects were within the range of 25-55 years. Major number of benign cases i.e. 60 % were within 25-35 yrs while only 13 % malignant cases belong to this group. 50% malignant cases were within 45-55 yrs age group where as least number (10%) of benign cases belong to this group(Table- I). Thus in our study the incidence of malignancy was common around the age of menopause & benign breast tumour at an younger age usually before the age of 35.

Our finding corroborates with the findings of Ray et al [12] in their study on incidence of breast tumour (2005).*They have concluded that breast cancer is very rare before the age of 20 and is very rarely diagnosed in women before the age of 25 .Above this age the incidence rises steadily to reach a peak around the age of menopause. The rate of increase is lessened after menopause but older women are still at increasing risk. Majority of benign cases i.e. 50% had adenoid cystic diseases least no of cases(10%) cystoarcomaphylloides (Table - III). Major percentage of malignant cases i.e 50% were in advanced stage or in stage-IV (Table-IV). From this it can be opined that malignant breast tumour cases are diagonosed in an advanced stage probably due to ignorance and negligence to the disease among women in the study group. The mean±SD age of control, benign & malignant cases were 42.60±10.65,39.05 ± 9.03 and 46.33 ± 6.18 respectively (Table- VI). There was no statistically significant difference ($p>0.05$) of age among these groups (Table-VII). In all the three groups age had a positive correlation with serum MDA .So with advanced age the oxidative stress and ROS production increases in our body.

In this study the BMI of control, benign and malignant cases ranged from 18.4-23.2, 20.8-25.4, 16.9-26.7 with a mean±SD of 20.59 ±1.38,23.2±1.18&21.64±2.86 respectively (Table-VII. The BMI of benign breast tumour patients were significantly higher($p<0.001$) when compared to healthy control group and malignant group but it was not in obese range in any of the groups as per the guidelines established by National Institutes of Health (NIH). Thus in present study obesity was not observed in malignant cases.

Our finding corroborates with the earlier reports of Mehta et al [13](mean ± SD of BMI in benign group are 24.12 ± 1.2, in malignant group it is 22.32± 2.13 & in control group it is21.35±2.32). Gonenc et al[14] reported a statistically no significant lower level of BMI in malignant group (25.45±1.10) as compared to healthy control group and benign group (25.71±1.32). However some research authors (Suga et al[15,] Tessitore et al [16])have reported a statistically significant higher level of BMI in malignant group as compared to healthy control and benign group. Though obesity is associated with many cancers there are controversies connecting obesity as a risk factor in breast in breast cancer[6].Obesity may also influence premenop-ausal women differently than it does post menopausal women. In post menopausal women breast cancer is more common in obese ,may be due to an increased conversion of steroid hormone to estradiol in body fat[7.]

According to Suga et al[15] high BMI may increase breast cancer risk by increasing serum estrogens thus modulating cell cycle and inhibiting apoptosis. BMI also alters the level of other hormones and growth factors like leptin, adiponectin, insulin and IGFs[17]. Leptin has been linked to increased breast cancer risk as reported by Tessitore et al (2000)[18]&Hu et al [19] (2002)

In our study Mean ± SD of serum cholesterol level in mg/dl were 174.6 ±15.6,186.65±8.57 and 203.2±9.94 in control, benign and malignant

cases respectively (Table- VII). The serum cholesterol in all the cases studied were within normal range but it was highest in malignant group. The higher serum cholesterol level found in benign tumour cases was not statistically significant (p>0.05) when compared to control group (Table-VIII). However the higher serum cholesterol level found in malignant tumour patients was significant statistically(p<0.001) when compared to control and benign groups (Table-VIII).

Kiran Hansija et al found significantly higher(p<0.001) Tch level in malignant group (190.74±7.76) in comparison to healthy control group(168.7±13.4). Diets rich in PUFA (poly unsaturated fatty acid) have been shown to be more potent in enhancing tumour growth rate. PUFAs generate free oxygen radicals and lipid peroxides and may stimulate cell proliferation by an effect on cell membrane fluidity, enzymes or receptors[20.] This is particularly evident in cells derived from proliferating mammary tumours which have a higher linoleic acid content than normal mammary cells[20].

It is evident that evident that n-6 PUFAs have a strong promoting effect on growth of human mammary cancer cells in vitro while n-3 PUFA s inhibit the growth of human mammary cells in vitro (Supplementary fish oil inhibits growth and metastasis in human mammary cells in explants.)[21] However some research authors (Dhaval Shah et al[22,]Gonenc et al[14]) have found significantly lower Tch level in malignant group as compared to benign and healthy control group.

In our study the mean ± SD serum Trigyceride level in mg/dl in control ,benign & malignant cases were 119.2 ±17.9,129.2 ±12.8, &158.19±5.7 respectively(Table-VII). The higher serum TG value found in benign group was not statistically significant (p>0.05) when compared to control group. In contrast the higher serum TG value in malignant group was statistically significant (p<0.001) when compared to healthy control and benign group(Table-VII).

Our finding corroborates with the earlier reports of Franky Dhaval Shah et al[23].They have found plasma TG(p=0.05) was significantly higher (p=0.05) in malignant group as compared to healthy control and patients with benign breast diseases (p=0.014).

Some research authors (AmelekGonec et al)[24] reported significantly lower level of serum TG in malignant breast tumour cases as compared to healthy control group and benign group.

The mean ±SD serum HDLc level in mg /dl of control, benign and malignant cases ranged from 30-55,30-45&25-39 with a mean ± SD of 45.03±5.4, 37.4±5.3 & 31.45±3.51(Table-VII).The lower HDLc level in benign and malignant cases when compared to healthy control subject was found to be statistically significant (p<0.001). There was a statistically significant negative correlation between serum MDA and HDLc in all the three groups . (Table –XII). Our finding was supported by the finding of Franky Dhaval Shah et al(p=0.001)who reported significantly lower HDLc (p=0.001) level in malignant group as compared to healthy control. Amylek Gonec et al [25] in their study also found significantlly lower HDLc level (50.60±2.51) in malignant group as compared to benign group (59.80±3.87) and healthy control group. Hansija et al have reported that the ratio of HDL: LDL and Tch:HDL values were increased significantly in breast cancer patients. It has been postulated that changes in the concentration of serum lipids could result in increase production of tumour necrosis factor and inhibit adipose lipoprotein lipase activity of insulin[26,27].These changes impair the catabolism of VLDL , leading to an increase in HDLc[28]. HDLc level has been shown to be higher in subjects with mammography dysplasia and family history of breast cancer.[22]

In this study, serum LDLc and VLDLc level ranged from 80-150, 110-155, 120-160 & 16-30, 22-30, 30-32 with mean ±SD of 105.52 ± 17.5, 123.26± 11.16,139.9 ± 10.7 & 23.7 ±

3.74,25.89± 2.49,31.71 ± 1.28 in control ,benign and malignant groups respectively (Table-VII).The statistically significant ($p<0.001$) higher LDLc and VLDLc were found in case of malignant tumour as compared to when control group.However the increase in these parameters in benign group was not statistically significant($p>0.05$) when compared with control group. Hansija et al,[29] also found an statistically elevated level of serum LDLc level (150±11.6) as in postmenopausal breast cancer patients as compared to control group and benign group(130±10.9)

In contrast, Gonenc et al[30] have found lower level of LDLc and VLDLc in malignant breast tumour cases than benign groups.

The serum MDA level has positive correlation with serum LDLc and VLDLc level.

To summarize the lipid profile in benign breast tumour patients, the serum HDLc was significantly lower and LDLc was significantly higher but there was no significant difference in all other parameters when compared to controls.In malignant cases all parameters in lipid profile were significantly higher and HDLc was significantly lower when compared to control group. It indicates that in this study dyslipidemia was associated with breast tum-our patients even though they were not obese.

Diets rich in PUFA (poly unsaturated fatty acid) have been shown to be more potent in enhancing tumour growth rate. PUFAs generate free oxygen radicals and lipid peroxides and may stimulate cell proliferation by an effect on cell membrane fluidity, enzymes or receptors[20.] This is particularly evident in cells derived from proliferating mammary tumours which have a higher linoleic acid content than normal mammary cells. It is evident that evident that n-6 PUFAs have a strong promoting effect on growth of human mammary cancer cells in vitro while n-3 PUFA s inhibit the growth of human mammary cells in vitro · (Supplementary fish oil inhibits growth and metastasis in human mammary cells in explants.)[2]

Dietary fat also influences the phospholipid composition of cell membrane leading to changes in cell surface permeability, receptor activity and cell to cell interaction. Membrane changes also effect cell response to hormones which stimulate activation of protein kinase –C,which is a critical factor in control of cell proliferation and differentiation.[31]

Some authors suggest that dyslipidemia may not be the cause but effect of cancer . Changes in the concentration of serum lipids in breast cancer patients could result from increased production of TNF ά by activated macrophases in response to the tumour cells and also due to inhibition of adipose lipo protein lipase activity by the action of insulin .This would impair the catabolism of VLDLc leading to an increase in serum TG level and decrease in serum HDLc level[32]. In present study the lipid parameters such as total cholesterol , triglyceride, LDLc were significantly higher ($p<0.001$) in malignant group compared to control group suggesting dyslipidemia in case of malignant group.

Although cancer is a disease of mutation (DNA damage) almost all cancers are due to environmental factors rather than heredity.The predominant initiators are chemical agents such as aflatoxin,ROS or free radicals, the poly cyclic hydro carbons, radiation,virus etc[33].Free radicals are generated both physiologically and pathologically by a number of processes in mammalian tissues. Oxidative stress arises when there is an imbalance between OFR formation scavenging by antioxidants. Excess generation of OFR can cause oxidative damage to biomolecules resulting in lipid peroxidation, mutagenesis and carcinogenesis .MDA which is an intermediate product of lipid peroxidation can be TBA reaction.

In present study lipid peroxidation was assessed by measurement of serum MDA (an intermediate product in lipid peroxidation) by reacting with TBA by Satoh et al method.

In our study serum MDA level in µ mol/L of control, benign and malignant cases were

1.77±0.33,3.23±0.3&4.76±0.38 respectively (Table- VII). The serum MDA level was significantly high($p<0.001$) in both benign and malignant cases when compared with healthy controls.(Table-VIII). Serum MDA has positive correlation with Tch,TG,LDLc,VLDLc which are statistically significant ($P<0.001$) & it has negative correlation with HDLc which is also stastistically significant.($p<0.001$)

Our finding was consistent with the findings of Rajneesh C .P et al [15] who have reported a statistically significant increase in .serum MDA level in malignant tumour cases as compared to control

Krishna Mohan Supraneniet al[16]. have observed that there was a significant increase($p<0.001$) in MDA level in malignant tumour cases (4.62±0.58) as compared to healthy controls. (3.37±0.516). Aghvamiet al.[36] reported a significantly increased plasma MDA in nmol /ml level in malignant group(1.76±0.47) as compared to controls(1.57±0.45). Our finding is also supported by the observations of Kumar et al[35], Hristozov et al [36]and Huang et al[37].

In contrast, A. Gonenc et al have found a significantly lower level of MDA in case of malignant breast tumour than benign breast tumour. Lipid peroxidation mediated by free radicals is considered as an important factor in tissue damage induced by various pathophysiologies (Tas F et al[38]) Oxidative stress caused by increased free radical generation or decreased antioxidant status in the target cells and tissues has been suggested to play an important role in carcinogenesis. (Diplock, 1991; Halliwell and Gutteridge,1999; Huang et al,1999) Damage to breast epithelium by OFR can lead to fibroblast proliferation , epithelial hyperplasia ,cellular atypia and breast cancer. Studies have shown increased lipid peroxidation in solid tumours. In our study Mean ±SD of age of menarchae was found to be 13.43± 0.67,12.45± 0.6 , 12.21± 0.83 . Age of menopause was found to be 47.16 ± 1.19, 50 ± 1.14,51± 1.13 & parity was found to be 2.83± 1.07,1.35± 1.05, 1.31± 1.04 in case of control, benign and malignant cases respectively (Table-V).Thus a statistically significant($p<0.001$) early menarche was found in case of both benign and malignant cases as compared to control group. .Late age of menopause was found in case of benign and malignant groups as compared to control groups which was statistically significant .($p<0.001$) .Statistically significant lower parity was found among benign and malignant group as compared to malignant group.

Thus women with early menarche, late menopause and low parity (more exposure to estrogen) are more prone to breast tumour development (both benign and malignant).

Estrogen and their metabolic products are shown to induce direct and indirect free radical mediated DNA damage, genetic instability and mutations in culture cells suggesting a role of free radical in breast cancer intiation[65].

CONCLUSION

From the above findings it can be concluded that obesity is not an important risk factor in development breast tumour. Early menarche, late menopause and low parity are definite risk factors .Dyslipidemia is definitely associated with breast tumour whether it is a cause or effect of tumour it is not exactly known. There is definite increase in ROS production oxidative stress is more in case of breast tumour patients both in benign and malignant group.

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