IOSR Journal of Dental and Medical Sciences (IOSR-JDMS)
e-ISSN: 2279-0853, p-ISSN: 2279-0861.Volume 17, Issue 2 Ver. 11 February. (2018), PP 16-23
www.iosrjournals.org

Evaluation of Serum Lipids, Apolipoprotein A1, Apolipoprotein BandLipoprotein(a) In Relation toBreast Cancer Risk

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Abstract: *This study evaluates theassociation of serum lipids and Apolipoproteins with Breast Cancer riskin pre- and post-menopausal breast cancer women. Serum lipids and apolipoproteins were estimated in patients with Breast Cancer and Benign Breast lesion, attending Oncology Department of B.Y.L. Nair Charitable Hospital, Mumbai. The study group comprised of 147 Breast Cancer patients, 27 Benign Breast lesion and 35 normal healthy subjects serving as control group. A total of 100 Breast Cancer patients had Invasive Ductal carcinoma, 17 had Ductal carcinoma in situ and 30 presented with Infiltrating Ductal Carcinoma. Stage II or Stage III Tumour, was present in 78 % patients whereas the remaining 22 % had either Stage I or Stage IV tumour.A highly significant(p=0.0001) increase in Total Cholesterol, LDL-Cholesterol, Triglycerides, Lp(a), and Apo B/Apo A1 ratio and significant decline in HDL-Cholesterolwas presented by patients with Breast Cancer and Benign Breast lesion.The Odds ratio indicated highest risk for development of breast cancer in patients with increased levels of Total Cholesterol, LDL-Cholesterol, Triglycerides, Apo B and Apo B/Apo A1 ratio. Altered lipids and apolipoproteins cannot serve to differentiate Breast Cancer from Benign Breast Lesion.. To reduce the burden of breast cancer, a multi-sectorial approach aiming at early detection of the disease is required.*

Keywords:*apolipoprotein A1,apolipoprotein B, breast cancer, lipids, postmenopausal, premenopausal.*

Date of Submission: 09-02-2018 Date of acceptance: 23-02-2018

I. Introduction

The association of hyperlipidaemiawith various metabolic, cardiovascular and even genetic-based disorders has been well documented.[1, 2] Treating hyperlipidaemia assumes importance not only for treating coronary atherosclerotic disorder, but also for treating malignant disorders.[3-5]It is well-known that malignancy is the second cause of death worldwide with a high disability rate in affected patients.[6]Some studies have documented the changes in lipid levels in the etiology and prognosis of cancer.[7,8] For instance, high cholesterol and low-density lipoprotein (LDL) levels are one of the most important and influential factors in the etiology of cardiovascular disease and has recently been considered as possible risk factor in the etiology of different types of cancers, especially those which are hormone dependent like breast cancer. However, in some types of malignancies, such as oral cancers, reduction of cholesterol is alarming for the progression of cancerous lesions.[9]Various studies have been conducted to find association between dyslipidaemia and breast cancer; but the reports are controversial. It is probable that this relationship may be influenced by the type of tumour and also by role of lipids in the pathophysiological mechanisms related to cancer progression.

Apolipoprotein A1 (Apo A1) is a major structural component associated with high-density lipoprotein (HDL) particles, and plays an important role in reverse cholesterol transport. HDL and Apo A1 are inversely related to the risk for coronary artery disease (CAD) [10] However in breast cancer patients,increased Triglycerides (TG) and LDL levels has been reported; whereas in the same patients, HDL and ApoA1 levels were lowered.[11]Apolipoprotein B (Apo B) is an important component of many atherogenic lipoprotein particles. It occurs as Apo B -48 in intestines and Apo B – 100 in the liver. It is the most important component from the view point of atherosclerosis and cardiovascular risk. It is found in all atherogenic particles like chylomicrons, VLDL, IDL, LDL and Lipoprotein (a) [Lp(a)]particles. Breast cancer risk has been inversely associated with levels of Apo B[12.]Significantly higher levels of Total Cholesterol(TC)and LDL among cases and no difference in HDL and TG levels have been reported[13]In contrast, another study[14]demonstrated no significant differences in TC, HDL, LDL or TG levels between breast cancer cases and controls. It is therefore clear thatcurrently available data regarding the associations between cholesterol, lipoproteins, and breast cancer are inconsistent.

Thus in the present study, we aimed to determine serum levels of lipids and lipoproteins – Lp (a), Apo A1 and Apo B in patients diagnosed with breast cancer and benign breast lesions, and to study association between dyslipidaemia and risk of breast cancer.

II. Methods

This cross-sectional observational study was performed on consecutive patients of breast cancer with positive pathological examinations, who were referred to the Oncology Centre in B. Y. L. Nair Charitable Hospital over a two-year period.Pregnant women, women with lumpectomy done before,those receiving alternative treatment or being treated for hyperlipidaemiaand having major illness in recent past were excluded from the study.Following an initial assessment, 147 patients with breast cancer were included in the study after diagnosis of breast cancer but before initiation of treatment. In the study group, 27patients with benign breast lesions and 35age matched normal healthy subjects serving as control group were also included. Control subjects did not have malignant disease or any serious pathology; but who were being treated for minor conditions. Eligible cases were aged between 26 to 74 years.Demographics, type of cancer, prognostic indicators were ascertained. (Table 1).Ethical Committee approval was obtained for the collection of blood samples from these patients. Patients were staged according to the Tumour-Node – Metastasis (TNM) classification[15]

Plasma Analysis

Approximately 10 ml of blood was collected in heparinised container by venepuncture from all normal subjects and patients. Informed consent was obtained from all subjects. Separated plasma was stored at – 20 ° C until analysis.Plasma levels of TC, including high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), and TGwere measured through enzymatic colorimetric methods. Lp(a), Apo A and Apo B were estimated by immunoturbidimetric method.

Statistical Analysis

Results were presented as mean (and standard deviations) and frequencies for quantitative variables. Statistical analysis was performed using a free and open source OpenEpi statistical software version 3.01. Students t test was used to evaluate differences in selected characteristics. Multivariate logistic regression analysis was used to calculate odds ratio and 95% confidence interval (CI) for lipid parameters associated with breast cancer risk. Clinically significant cut off values (high/exposed or low/nonexposed), were considered for Breast Cancer Group (positive outcome) and Benign Breast Lesion + Control groups (negative outcome).A p-value of 0.05 or less was considered statistically significant.

III. Results

The age of all study subjects spanned from 26 years to 74 years. (Table 1). In each group the age was distributed normally. The selection of control group was age matched with the patient groups (mean age was 44.5 years) and comparison of mean age between the 3 groups showed no statistically significant difference. ($P > 0.5$).

Amongst 147 breast cancer patients, 88 were premenopausal and 59 had reached menopause (Table 2).Invasive ductal carcinoma was the most prominent histopathological type accounting about 100 of total cases in which 58 were premenopausal and 42 were in postmenopausal state. Seventeen patients had Ductal Carcinoma in situ, which included 14 premenopausal and 3 postmenopausal women. Out of 30 cases with Infiltrating Ductal Carcinoma 16and 14 patients were premenopausal and postmenopausal respectively. (Table 2). BMI of patients with Breast Cancer (22.5 Kg/m^2)and Benign Breast lesion (26.1Kg/m^2) did not differ significantly($P > 0.2$), when each group was compared with controls.(Table 1). Mean BMI of 22.9 1Kg/m^2in patients with Ductal Carcinoma in situ ranked lowest within the three-histopathological divisions of Breast Cancer patients.Among all patients, 44 % had Stage II cancer , 34 % had Stage III , whereas Stage I and StageIV was detected in remaining 22 %breast cancer patients.

A highly significant ($P < 0.0001$) elevation in TC levels (216.9 mg/dl), LDL-C (141.3 mg/dl), and TG (168.8 mg/dl) were observed in Breast Cancer patients as compared to control group.The levels of TC(205.6 mg/dl), LDL-C(156.4 mg/dl) & TG (165.7 mg/dl) were also increased in patients with Benign Breast Lesion as compared to control. The levels of TC, and TG in benign breast lesion were marginally lower as compared to Breast Cancer.(Table 3).HDL-C levels declined significantly in Breast Cancer (57.3 mg/dl , $P = 0.002$) and Benign Breast Lesion (54.4 mg/dl, $P = 0.0001$) as compared to control.Levels of HDL- C were altered in nearly 50 % of the patients, whereas, more than 50% of both the groups of patients presented with increased levels TC, LDL–C and TG.(Fig 1)

As shown in Table 4 , levels of Lp(a) (44.8 mg/dl), Apo B (126.8 mg/dl) and Apo B /Apo A ratio(1.9) were increased in patients with Breast Cancer.($P = 0.00008$). Mean Apo A1 levels in Breast Cancer and

controls were nearly equal (P= 0.61). In patients with Benign Breast Lesion a significant (P < 0.0001) increase in Lp(a) (38.3 mg/dl), Apo A1 (148.7 mg/dl) and Apo B/Apo A1 ratio (0.79)& nonsignificant (P = 0.06) increase in Apo B (112.9 mg/dl) was observed, when the levels were compared with control group. The percentage of study subjects with altered apolipoprotein levels is presented in Fig 2.More than 50 % of both the groups of patients presented with increased levels Lp(a), Apo A1, Apo B and ApoB/Apo A1 ratio. (Fig 2). Deviations in levels of all the apolipoproteins was observed in 25 % to 55 % of the control group, as indicated graphically in Fig 2.Table 5 presents Odds Ratio with 95 % Confidence Interval for lipid parameters in relation to Breast Cancer Risk.Odds Ratio > 1 for TC, LDL-C, TG, Apo B and Apo B/Apo A1 ratio were within the span of 95 % Confidence Interval.

IV. Discussion

In the present study, the association of circulating lipids and apolipoproteins with Breast Cancer Risk was investigated.Age, BMI, diabetes, smoking are some of the factors that have been reported to be associated with breast cancer risk.[16] Obesity is a growing health problem in the developed countries and increasingly, around the world. Excess body weight has been linked to an increased risk of postmenopausal breast cancer, and growing evidence also suggests that obesity is associated with poor prognosis in women diagnosed with early-stage breast cancer[17].In this study, no difference in BMI levels was observed within the study groups, ruling out the possibility of association of BMI with Breast Cancer.

This study confirms that dyslipidaemia occurs among women with breast cancer.Increased levels of TC, LDL-C, TG, (P= 0.0001) and decreased HDl-C (p = 0.002) were associated with Breast Cancer and Benign Breast Lesion. These parameters which are risk factors for cardiovascular disease, are alsoshowing evidence of their linkage with breast cancer risk.Many researchers have found increased TC levels in Breast Cancer Patients.[18-20]Cholesterol in tissue and blood has consistently been found to have a prime role in the pathogenesis of coronary artery disease, but an association of cholesterol with breast cancer has also been reported. [21,22]High consumption of fats may increase circulating estrogen levels, thus increasing the possibility of cell damage and proliferation, which is responsible for cancerous growth.[23]

Like other lipids components, there is contrasting evidence on serum LDL-C levels in breast cancer. Some workers have suggested elevation in the levels, while others have found a significant decrease in LDL-C.[18,25]Data available in literature has shown conflicting association of altered HDL-C levels with breast cancer.In one study, HDL-C levels were not significantly different between cases and control group[23.] But Ferraroni[24]et al has shown decreased levels of HDL-C, which is also observed in our present study.Studies suggest that low HDL cholesterol may be a marker of increased breast cancer risk among premenopausal and postmenopausal women.[25,26]However the present study does not indicate low HDL-C levels (Table 5) to be associated with Breast Cancer Risk. (Odds Ratio 0.85, 95 % CI, 0.47-1.55, p = 0.61). A direct association between high LDL level and increased risk for lymph nodes metastasis has been reported.[27]Angiogenesis is a key factor for growing cancer and metastasis, so with an increase in the size of the tumour, the nutritional requirements of the tumour also increase. The growth of tumour and metastasis can be stopped by inhibiting angiogenesis and metastasis. LDL can successfully inhibit the enzymes necessary for angiogenesis.[27]

It seems that the association between serum HDL level and risk for breast cancer can potentially be influenced by menopausal status so it has been shown that premenopausal cases have mean HDL levels lower than matched controls, whereas postmenopausal cases had levels higher than the controls.[28] Elevated TG in Breast Cancer has been reported[29]. In the Danish study[30], the higher serum TG was suggestive of a positive association with breast cancer incidence, but the trend was not significant (P=0.06). However, in the present study, increased serum levels of TG in patients with Breast Cancer indicated Odds Ratio (2.8) within the span of 95% Confidence Interval, suggesting significant (P=0.0008) positive outcome of breast cancer with exposure to increased TG levels. (Table 5). Similarly, for TC (Odds Ratio 2.17, 95 % CI, 1.18 to 3.98, p=0.01) and for LDL-C (Odds Ratio 2.89, 95 % CI, 1.56-5.3, p=0.0007) clearly indicates positively, the odds of these parameters associated with Breast Cancer risk.

Serum levels of Lp(a), Apo A1, Apo B and Apo B/Apo A1 ratio were estimated to evaluate association of apolipoproteins with breast cancer risk.In the present study, not only was a change in serum lipids, but also altered levels of apolipoproteins were recorded in patients.In patients with Breast cancer, except Apo A1 all the other apolipoprotein levels were significantly (p=0.00008) increased. However, in patients with Benign Breast Lesion all apolipoproteins were significantly(p=0.002) increased except Apo B (p=0.06).The relationship between lipids and lipoproteins with atherosclerotic cardiovascular disease (CVD) might provide important clues to the relationship between lipoproteins and breast cancer. Apo A1 is structural component of HDL and is reflective of the number of HDL particles. Apo B is present in LDL, VLDL and Lp(a). Thus, Apo B concentration is a measure of atherogenic particles.

The risk of breast cancer was positively associated with Apo B (Odds Ratio = 1.99, 95 % CI, 1.08 – 3.65, p = 0.02) and Apo B/Apo A1 ratio (Odds Ratio = 3.9, 95 % CI, 2.09 – 7.39); but no association with Apo

A1 (Odds ratio = 0.89, 95 % CI, 0.49 – 1.61, p = 0.70); and Lp(a) [Odds Ratio = 0.92, CI 0.50 – 1.67]. In general,serum lipids and Apolipoprotein levels were not useful in differentiating breast cancer from benign breast lesions. Incidence of StageII and Stage III was higher as compared to Stage I and Stage IV.Stage II was more frequently observed in Pre-menopausal females (45) than in post-menopausal (20); whereasStage III in Post-menopausal cases (30) and pre-menopausal (20). Maximum number of patients presented with Invasive ductal carcinoma (100) than ductal carcinoma in situ (17) and Infiltrating Ductal Carcinoma (30).

This raises question whether, mechanism involved in development of cardiovascular disease due to dyslipidaemia, parallels the mechanism of development of breast cancer?Odds Ratio indicates that exposure to high levels of TC, LDL-C and TG shows increased odds for development of Breast Cancer.Likewise, Lp(a), Apo B and B/A1ratio, already known as risk factors for cardiovascular disease are also found to be associated with Breast Cancer. However,in the present study Odds Ratio indicates only Apo B and Apo B/A1 ratio to be associated with breast cancer risk.

The ability to modulate lipid and cholesterol movement is at the core of apoA-I/HDL's actions resulting in profound physiological and cell phenotypic effects. Changes in cholesterol metabolism or levels of components of cholesterol homeostasis namely apoA-I/HDL, ABCA1, ABCG1, and SR-B1 are known to affect immune responses which in turn impact anti-tumour effects. In cancer, lipid and cholesterol homeostasis is often dysregulated to facilitate the cancer cells' increased demand for these building blocks which are required for proliferation and evasion of apoptosis.[31]To this end, tumour cells can manipulate their intracellular cholesterol level by reducing expression of ABCA1 which effluxes cholesterol and increasing the expression of SR-B1 which influxes cholesterol. This phenomenon has been reported inBreast Cancers[32].

ApoA-I/HDL's anti-tumour effects observed inimmune-competent animals. could be related to (i) the ability of apoA-I/HDL to modulate cholesterol content in immune or tumour cell membrane lipid rafts thus influencing signalling pathways, (ii) the lipid rafts' role as a platform for biologically active lipids and proteins that may impact the immune response, (iii) the cross-talk between the tumour and surrounding stromal cells. The extent to which this activity is consequential in cancers is not clear.

In the context of infection or atherogenesis, apoA-I/HDL modulates macrophages toward an anti-inflammatory M2-like phenotype by effluxing cholesterol. However, in the tumour microenvironment, apoA-I/HDL promotes the accumulation of M1-like macrophages. Now, we do not know the mechanism involved in this process but this apparent dichotomy of apoA-I/HDL functional response in different inflammatory settings underscores the complexity of apoA-I/HDL biology and poses intellectual and experimental challenges toward a better understanding of this multifaceted plasma component.[33]Moreover, the unfavourable hormonal profile (e.g., elevated insulin, oestrogen, or leptin) associated with low levels of high-density lipoprotein (HDL) is thought to increase Breast Cancer risk.[34]The true distribution of induction and promotion times for breast cancer is not known. It is likely that the time window of exposure in this study reflects induction and unlikely that reverse causation by the presence of an established cancer is playing a role. However, it is plausible that the lipid metabolism changed substantially in the period between measurement and diagnosis due to lifestyle changes. Alternatively, it could be possible that the individual develops another co-morbidity (e.g., coronary heart disease, or diabetes) which acts as a competing risk, and may result in death prior to diagnosis of a cancer[35]

V. Conclusion

The current study has shown a significant alteration in the serum lipid profile in Breast Cancer patients, and patients with Benign Breast Lesions. BMI levels were nearly identical in all the study groups. Majority of the Breast Cancer patients had Invasive Ductal Carcinoma. Levels of Lp(a), Apo B and Apo B/Apo A1 ratio, significantly increased in Breast Cancer patients; whereas in patients with Benign Breast Lesions significant increase was observed in levels of Lp(a), Apo A1and Apo B/Apo A1 ratio. Odds Ratio for TC, LDL-C, TG, Apo B and Apo B/ Apo A1 ratio indicated a positive statistically significant association with Breast Cancer Risk. Although there is definitive evidence of a benefit of measuring serum levels of lipids and Apolipoproteins for predicting Breast Cancer; the existence of contrasting reports in literature demands validation of these findings to facilitate future prevention strategies for cancer.Late stage at presentation of breast cancer is the main problem and possesses a challenge to the health care community. The interaction between circulating levels of lipids and breast cancer needs to be further investigated

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Table 1 : Age and BMI of Normal Subjects and Patients

Parameter	Group I Control n = 35	Group II Breast Cancer n = 147	Group III Benign Breast Lesion n = 27
Age (Years) Range Mean ± SD	 27 - 67 44.5 ± 8.1	 26 – 74 45 ± 8.88^{NS}	 26 – 62 43.3 ± 9.19 ^{NS}

BMI (Kg/m^2) Range Mean ± SD	19.5 – 29.6 25.1 ± 3.1	12.5 – 39.2 25.5 ± 5.63 NS	21.8 – 33.6 26.1 ± 3.3 NS
NS : Nonsignificant v/s control			

Table 2 : Age and BMI of Breast Cancer patients as per menopausal status and histopathology

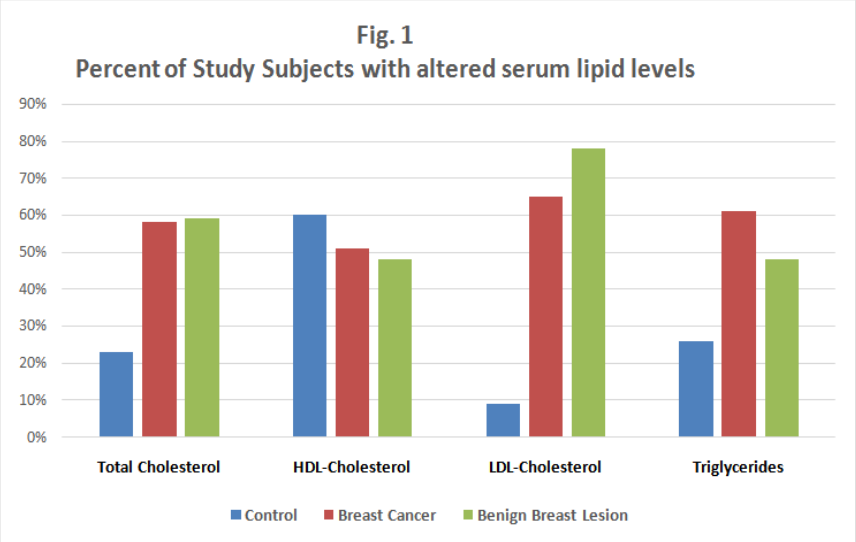
Clinical Data (No. of Patients)		Total No. of Patients	Age (years) Mean ± SD	BMI(Kg/m^2) Mean ± SD
Menopausal Status	Pre-menopausal Stage I - 18 Stage II - 45 Stage III - 20 Stage IV - 5	88	40.1±5.8	25.8 ±5.9
	Post-menopausal StageI - 2 Stage II - 20 Stage III - 30 Stage IV - 7	59	52.3±7.6	24.6±5.3
Histopathology	Ductal Carcinoma in situ (Pre-menopausal-14, Post-Menopausal - 3)	17	49 ± 12.5	22.9 ± 5.1
	Invasive Ductal Carcinoma (Pre-menopausal-58,Post-Menopausal-42)	100	43.5 ± 8.2	25.8 ± 5.6
	Infiltrating Ductal Carcinoma (Pre-menopausal-16, Post-menopausal-14)	30	50.1 ± 6.2	25 ± 5.8

Table 3 : Standard Lipid Profile of Control and Study Groups

Lipid Profile	**Control (n=35) Mean ± SD (Range)**	**Breast Cancer (n=147) Mean ± SD (Range)**	**Benign Breast Lesion (n=27) Mean ± SD (Range)**
Total Cholesterol (mg/dl)	170.1 ± 18.5 (140-199)	216.9 ± 24.6* (180 – 262)	205.6 ± 19.0* (170 – 253)
HDL-Cholesterol (mg/dl)	63.6 ± 6.2 (55-75)	57.3 ± 11.7** (44-76)	55.4 ± 8.7* (44-68)
LDL-Cholesterol (mg/dl)	104.5 ± 11.6 (75 – 135)	141.3± 24.5* (105-180)	156.4 ± 9.7* (130-172)
Triglycerides (mg/dl)	140.1 ± 6.5 (132 - 151)	168.8 ± 35.6* (110-210)	165.7 ± 36.1* (130-241)
Breast Cancer v/s Control *P = 0.0001 **P = 0.002 Benign Breast Lesion v/s Control *P = 0.0001			

Table 4 : Apolipoprotein levels of Control and Study Groups

Apolipoprotein	**Control (n=35) Mean ± SD (Range)**	**Breast Cancer (n = 147) Mean ± SD (Range)**	**Benign Breast Lesion (n = 27) Mean ± SD (Range)**
Lp(a) (mg/dl)	28.7± 11.2 (10 - 45)	44.8 ± 20.5* (16– 75)	38.3 ± 11.8** (25 - 55)
Apo A1 (mg/dl)	141.7± 6.4 (135 - 155)	140.6 ± 12.4 # (130 – 160)	148.7 ± 11.8** (130 - 163)
Apo B (mg/dl)	93.9 ± 20.00 (56 – 125)	126.8± 33.5* (83-175)	112.9 ± 54.3@ (48 - 175)
Apo B/Apo A1 Ratio	0.69± 0.05 (0.41– 0.89)	1.9± 0.21* (0.56-2.28)	0.79 ± 0.44* (0.36-1.2)
Breast Cancer v/s Control *P = 0.00008# P = 0.61 Nonsignificant Benign Breast Lesion v/s Control *P = 0.00007**P=0.002@ P = 0.06 Nonsignificant			



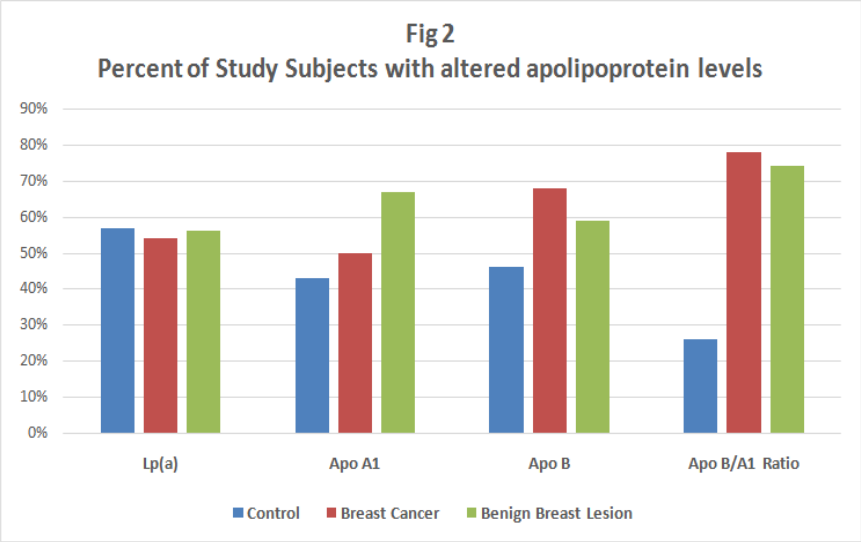


Table V: Odds Ratio , Confidence Interval and Statistical significance of Lipid parameters in relation to Breast Cancer Risk

Parameter	Odds Ratio	95 % CI	P value
Total Cholesterol	2.1707	1.1831 to 3.9826	0.01
HDL-Cholesterol	0.85	0.4729 to 1.556	0.61
LDL-Cholesterol	2.89	1.5674 to 5.3384	0.0007
Triglycerides	2.8	1.5489 to 5.3209	0.0008
Lp(a)	0.92	0.5066 to 1.6747	0.78
Apo A1	0.89	0.4916 to 1.6143	0.7031
Apo B	1.99	1.0872 to 3.6595	0.02
ApoB/ApoA1 Ratio	3.9	2.0902 to 7.3932	0.00008