

Association of Dyslipidemia, Increased Insulin Resistance, and Serum CA 15-3 with Increased Risk of Breast Cancer in Urban Areas of North and Central India

Poonam Kachhawa, Kamal Kachhawa¹, Divya Agrawal², Vivek Sinha, Purnima Dey Sarkar³, Sanjay Kumar⁴

Department of Biochemistry, Saraswathi Institute of Medical Sciences, Hapur, Uttar Pradesh, ¹Department of Biochemistry, Mahaveer Institute of Medical Sciences and Research, Bhopal, ³Department of Biochemistry, Mahatma Gandhi Memorial Medical College, Indore, Madhya Pradesh, Departments of ²Anatomy and ⁴Pharmacology, GSL Medical College, Rajahmundry, Andhra Pradesh, India

ABSTRACT

Objective: This study aims to determine the association of dyslipidemia and increased insulin resistance (IR) with increased breast cancer (BC) risk. **Materials and Methods:** The study group comprised 110 premenopausal and 143 postmenopausal, untreated female BC patients in the age range of 29–72 years. Control group consisted of 117 premenopausal and 141 postmenopausal healthy females in the age range of 23–75. Approximately 8-ml blood samples were drawn to measure various biochemical parameters. Serum glucose, total cholesterol, triglyceride (TG), and high-density lipoprotein-cholesterol were measured. Very low-density lipoprotein-cholesterol (VLDL-C) and LDL-C were calculated using Friedewald's formula. Serum insulin and serum CA 15-3 were estimated by immune enzymatic assay. IR was assessed using homeostasis model assessment IR index (HOMA-IR). **Results:** Clinical variables in the case and control groups were compared using the unpaired Student's *t*-test. The crude and adjusted odds ratios (ORs) and 95% confidence intervals (CIs) were calculated by binary logistic regression analysis. Pearson's correlation analysis was used to determine the association between CA 15-3 and variables of interest. Total cholesterol, TG, LDL, VLDL, serum glucose, serum insulin, HOMA-IR, and serum CA 15-3 were significantly higher ($P < 0.001$) in BC patients compared to those in controls. Significant adjusted ORs with 95% CI were found to be fasting glucose, total cholesterol, and TGs. We also found a significant positive correlation between total cholesterol, TG, LDL, serum glucose, serum insulin, HOMA-IR, and serum CA 15-3. **Conclusion:** This study confirms the association between dyslipidemia, IR, and increased BC risk.

KEYWORDS: Breast cancer, cholesterol, homeostasis model assessment-insulin resistance, risk factors

INTRODUCTION

Breast cancer (BC) is the most common cancer affecting female individuals in the world with an estimated 1.67 million new cancer patients diagnosed in 2012. In India, the incidence of BC is significantly lower than in western countries. With an annual incidence of approximately 144,000 BC has now become the most common cancer affecting female individuals in urban India.^[1] The incidence of BC in India varies from 5/100,000 women per year in rural areas to 30/100,000 women per year in urban areas.^[2] The incidence of BC

increases with age in India, as is the case in the rest of the world. Genetic predisposition is the main risk factor in 5%–10% cases of BCs. Risk factors identified for the remaining 90% spontaneous BCs are reproductive, lifestyle, or environmental factors, primarily through their influence on the hormonal milieu. The precise

Address for correspondence: Dr. Sanjay Kumar, Department of Pharmacology, GSL Medical College and GSL General Hospital, Rajahmundry - 533 296, Andhra Pradesh, India. E-mail: sanjaykumarimssum@gmail.com

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How to cite this article: Kachhawa P, Kachhawa K, Agrawal D, Sinha V, Sarkar PD, Kumar S. Association of dyslipidemia, increased insulin resistance, and serum CA 15-3 with increased risk of breast cancer in urban areas of North and Central India. *J Mid-life Health* 2018;9:85-91.

Access this article online	
Quick Response Code: 	Website: www.jmidlifehealth.org
	DOI: 10.4103/jmh.JMH_77_17

etiology of BC is unknown. However, the female sex hormone, estrogen, is reported to be carcinogenic, promoting cell proliferation in breast tissues and reproductive organs. In addition, environmental factors such as exposure to radiation and chemicals may trigger the onset of BC.^[3] Important lifestyle factors believed to contribute toward the development of BC include obesity after menopause, decreased physical activity, high-fat diet, use of contraceptives, and lack or short duration of breastfeeding.^[4]

In the past few years, extensive efforts have been dedicated to understanding the relationship between dyslipidemia, insulin resistance (IR), type 2 diabetes mellitus and metabolic syndrome, and BC risk.^[5-9] Several reports showed that the levels of circulating lipids and lipoproteins are high in pre- and postmenopausal BC patients.^[5-7,10,11] It has been postulated that changes in the concentration of serum lipids in the BC patients could result in an increased production of tumor necrosis factor-alpha and inhibition of adipose lipoprotein lipase activity by insulin.^[12] These changes impair the catabolism of very low-density lipoprotein-cholesterol (VLDL-C), leading to an increase in high-density lipoprotein-cholesterol (HDL-C). Epidemiology studies reveal that HDL-C and BC are influenced by variables such as dietary fat intake, alcohol consumption, body weight, country of residence, pregnancy, endogenous hormones, smoking, exercise, and socioeconomic status.^[13] HDL-C level has been shown to be higher in participants with mammography dysphasia and family history of BC.^[14,15] However, it has also been reported that HDL-C level was either elevated or depressed in women with BC.^[9] Thus, HDL-C level alone, at present, cannot be taken into consideration as a causative factor. It was found that patients with more advanced Breast Cancer have significantly lower concentration of HDL-C than do patients with less advanced disease.^[12,16] Plasma total cholesterol and LDL-C were found to be significantly elevated whereas HDL-C was significantly decreased in BC patients. These studies suggest that higher level of total cholesterol may play an important role in carcinogenesis.^[9,17,18] The role of lipoprotein levels in the development and advancement of BC has been reported in many *in vitro* studies.^[19-21] The role of different lipids in cancer has been studied extensively in developed countries, but it is still a matter of controversy.^[11,20,21] Levels of exposure to carcinogens and prevalence of established risk factors may be different in developing and developed nations.

This study aims to compare the serum lipid levels in female BC patients with those in normal healthy controls and to discover the effect of dyslipidemia and increased IR on BC risk.

MATERIALS AND METHODS

Subjects

The case group comprised 110 premenopausal and 143 postmenopausal female BC patients. A case was defined as an untreated female patient with histopathologically confirmed BC. The age group of the cases ranged from 29 to 72 years. Control group consisted of 117 premenopausal and 141 postmenopausal healthy women in the age range of 23–75. These were apparently healthy volunteers, who were not taking oral contraceptives or any form of hormonal medication. Women were classified as postmenopausal if they had no menstrual cycles during the preceding 3 years or if they had undergone a hysterectomy without complete oophorectomy before menopause and were 47 years of age or older.

Exclusion criteria

Patients were excluded if they were suffering from diabetes mellitus or dyslipidemia and those taking statins or any drugs that interfere with blood glucose, serum lipid profile, and serum insulin.

Blood sample collection and preparation

Approximately 8-ml blood sample was withdrawn from the antecubital vein after overnight fasting. The blood sample was collected in plain vacutainers. Serum was separated from the clotted blood by centrifugation for 15 min at 3000 rpm at room temperature. All serum samples were stored at -80°C until use.

Biochemical assays

Serum total cholesterol (normal value: 150–200 mg/dl), HDL-C (normal value: 35–70 mg/dl), and triglycerides (TGs) (normal value: 60–170 mg/dl) were measured using commercially available kits for autoanalyzer. VLDL-C (normal value: 12–34 mg/dl) and LDL-C (normal value: 50–100 mg/dl) were calculated by Friedewald's formula. Serum glucose level (normal value: 70–140 mg/dl) was estimated by glucose oxidase and peroxidase method. All biochemical investigations were performed using a fully automated analyzer, Turbo cam 100 (CPC Diagnostics Pvt. Ltd., Alwarpet, Chennai, Tamil Nadu, India). Serum insulin (normal value: <10 $\mu\text{IU/ml}$) was measured using enzyme-linked immunosorbent assay (ELISA), a solid-phase two-site enzyme immunoassay (Calbiotech, Inc., Insulin ELISA kit, Catalog No. IS130D, 96 Tests). Serum CA 15-3 (normal value: <35 U/ml) was measured using the CA 15-3 ELISA kit (Calbiotech, Inc., Catalog No. CA153T). All assays were performed according to the respective manufacturer's instructions. Homeostasis model assessment-IR index (HOMA-IR) to indicate IR was calculated as: "fasting glucose (mg/dl) \times fasting insulin ($\mu\text{IU/ml}$)/405." The cutoff point was 2.5 or

greater. Body mass index (BMI) was calculated as “weight in kilograms/height in meters squared (kg/m^2).” Blood pressure (systolic and diastolic) was measured in the sitting position after a 10-min resting period.

Statistical analysis

Statistical analysis was performed using SPSS version 21 (SPSS Inc., 233, South Wacker Drive, 11th Floor, Chicago, IL, 60606-6412, USA). Metabolic parameters such as BMI, systolic blood pressure (SBP), diastolic blood pressure (DBP), lipid profile, serum glucose, serum insulin, HOMA-IR, and serum CA 15-3 were compared between cases and controls, using an unpaired Student's *t*-test. Crude odds ratios (ORs) and 95% confidence intervals (95% CIs) were calculated using crosstab analysis. In univariate analysis, the significance level was <10%. The binary logistic regression analysis was done using the presence of BC as dependent variable and parameters of interest (age, menopausal status, BMI, total cholesterol, TGs, HDL, fasting glucose, serum insulin, and HOMA-IR) as independent variables. Pearson's correlation analysis was used to determine the association between serum CA 15-3 and variables of interest. $P < 0.05$ was considered statistically significant.

Ethics statement

The study was approved by the Ethical Committee of the Institute. Informed consent was obtained from each patient.

RESULTS

Table 1 highlights the clinical characteristics of BC cases and healthy controls. Data revealed that BC cases had significantly higher ($P < 0.001$) SBP, DBP, fasting glucose, total cholesterol, triglyceride, LDL-C, VLDL-C, serum insulin, HOMA-IR, and serum CA 15-3 than did the controls. There was no significant difference in age, BMI, and HDL-C between the cases and controls.

Table 2 shows the comparison of biochemical parameters between premenopausal and postmenopausal BC cases and healthy controls. The data indicated that SBP, DBP, total cholesterol, LDL-C, TGs, VLDL-C, serum glucose, HOMA-IR, and CA 15-3 were significantly different ($P < 0.001$) between premenopausal and postmenopausal cases and controls. Serum insulin was significantly high ($P < 0.05$) only in postmenopausal cases compared to that in postmenopausal controls. The differences in BMI and HDL-C between premenopausal and postmenopausal cases and controls were not significant. Similarly, there was no significant difference in serum insulin levels between premenopausal cases and controls.

Table 3 shows crude and adjusted ORs and 95% CIs for BC in relation to age, menopausal status, BMI, total

Table 1: Clinical characteristics of breast cancer cases and healthy controls

Parameters	Mean±SD		P
	Case (n=253)	Control (n=258)	
Age (year)	50.5±10.8	49.5±11	0.35 (NS)
BMI (kg/m^2)	23.5±2.39	23.1±2.36	0.070 (NS)
SBP (mmHg)	124.7±7.4	118.7±4.8	<0.001
DBP (mmHg)	81.1±4.7	78.5±3.8	<0.001
Total cholesterol (mg/dl)	239.1±29.8	196.7±27.3	<0.001
HDL-C (mg/dl)	44.9±9.01	45.4±6.94	0.51 (NS)
LDL-C (mg/dl)	161.4±31.7	125.3±27.9	<0.001
Triglycerides (mg/dl)	163.1±18.5	130.1±17.4	<0.001
VLDL-C (mg/dl)	32.6±3.71	26.04±3.48	<0.001
Fasting glucose (mg/dl)	112.2±22.5	98.6±14.2	<0.001
Serum insulin ($\mu\text{IU/ml}$)	14.08±6.29	12.56±5.36	<0.05
HOMA-IR	4.08±2.48	3.18±1.83	<0.001
CA 15-3 (U/ml)	68.54±24.5	23.18±6.22	<0.001

$P < 0.05$ significant, $P < 0.01$ highly significant. BMI: Body mass index, SBP: Systolic blood pressure, DBP: Diastolic blood pressure, HDL-C: High-density lipoprotein-cholesterol, LDL-C: Low-density lipoprotein-cholesterol, VLDL-C: Very low-density lipoprotein-cholesterol, HOMA-IR: Homeostasis model assessment index, NS: Not significant, SD: Standard deviation, CA: Carcinoma Antigen 15-3

cholesterol, HDL-C, TGs, fasting glucose, insulin, and HOMA-IR. Crude ORs with 95% CI ($P < 0.001$) were significant for fasting glucose (3.83 [2.64–5.55]), total cholesterol (8.23 [5.26–12.8]), TGs (11.13 [7.37–16.8]), and HOMA-IR (2.14 [1.49–3.07]). On the other hand, HDL-C had a mitigating effect on the risk of developing BC (OR [95% CI]: 0.86 [0.59–0.99]), $P < 0.001$. In univariate analysis, the significant variables were taken for binary logistic regression. Significant adjusted OR with 95% CI and $P < 0.001$ were found to be fasting glucose (4.87 [2.73–8.70]), total cholesterol (6.76 [3.98–11.5]), and TGs (10.49 [6.50–16.9]).

Table 4 shows Pearson's correlation analysis between CA 15-3 and variables of interest. Figures 1-4 also depict the correlation [Figures 1-4] between CA 15-3 and other variables. The results showed that serum CA 15-3 was significantly positively associated with fasting glucose ($r = 0.35$, $P > 0.001$) shown in [Figure 4], serum insulin ($r = 0.29$, $P > 0.05$), HOMA-IR ($r = 0.36$, $P > 0.001$) shown in [Figure 3], total cholesterol ($r = 0.48$, $P > 0.001$) shown in [Figure 1], TGs ($r = 0.34$, $P > 0.001$), LDL-C ($r = 0.49$, $P > 0.001$), and VLDL-C ($r = 0.34$, $P > 0.001$) and significant negative association with HDL-C ($r = -0.26$, $P < 0.05$) shown in [Figure 2]. No significant correlation was found with age, BMI, SBP, and DBP.

DISCUSSION

BC results in the death of millions of women worldwide

Table 2: Comparison of biochemical variables between premenopausal and postmenopausal breast cancer cases and healthy controls

Parameters	Premenopausal women			Postmenopausal women		
	Case (n=110), mean±SD	Control (n=117), mean±SD	P	Case (n=143), mean±SD	Control (n=141), mean±SD	P
Age (years)	40.1±5.40	39.5±5.06	0.41 (NS)	58.5±5.93	57.8±7.36	0.33 (NS)
BMI (kg/m ²)	22.8±2.25	22.1±1.96	0.06 (NS)	24.11±2.35	24.10±2.30	0.99 (NS)
SBP (mmHg)	121.6±6.13	117.1±5.04	<0.001	127.1±7.53	120.1±4.28	<0.001
DBP (mmHg)	79.4±4.31	77.6±3.55	<0.05	82.5±4.60	79.2±3.92	<0.001
Total cholesterol (mg/dl)	235.8±30.4	196.5±27.5	<0.001	241.4±29.47	197.1±27.46	<0.001
HDL-C (mg/dl)	45.9±9.48	46.0±6.97	0.93 (NS)	44.19±8.62	44.91±6.96	0.47 (NS)
LDL-C (mg/dl)	157.8±33.45	124.4±27.98	<0.001	164.3±30.41	126.1±28.15	<0.001
Triglycerides (mg/dl)	160.6±18.97	130.4±17.91	<0.001	164.5±17.96	130.1±17.05	<0.001
VLDL-C (mg/dl)	32.12±3.79	26.08±3.58	<0.001	32.90±3.59	26.04±3.41	<0.001
Fasting glucose (mg/dl)	109.6±20.02	93.91±13.71	<0.001	113.7±22.8	102.1±13.8	<0.001
Serum insulin (µU/ml)	13.40±6.19	12.05±5.47	0.07 (NS)	14.53±6.25	12.93±5.28	<0.05
HOMA-IR	3.78±2.30	2.92±1.82	<0.05	4.25±2.45	3.37±1.82	<0.05
CA 15-3 (U/ml)	68.55±23.62	22.72±6.58	<0.001	68.23±25.35	23.41±5.93	<0.001

$P < 0.05$ significant, $P < 0.01$ highly significant. BMI: Body mass index, SBP: Systolic blood pressure, DBP: Diastolic blood pressure, HDL-C: High-density lipoprotein-cholesterol, LDL-C: Low-density lipoprotein-cholesterol, VLDL-C: Very low-density lipoprotein-cholesterol, HOMA-IR: Homeostasis model assessment index-insulin resistance, SD: Standard deviation, CA: Carcinoma Antigen 15-3

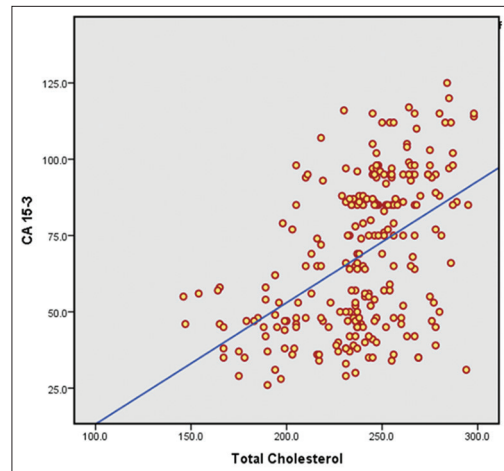
Table 3: Crude and adjusted odds ratios and 95% confidence interval for breast cancer with respect to menopausal status, age, body mass index, total cholesterol, high-density lipoprotein-cholesterol, triglycerides, fasting glucose, insulin, homeostasis model assessment index-insulin resistance, calculated using binary logistic regression

Parameters	Crude OR (95% CI)	Adjusted OR (95% CI)
Menopausal status	1.06 (0.74-1.50)	
Age	1.11 (0.62-1.96)	
BMI	1.35 (0.91-2.00)	
Fasting glucose	3.83 (2.64-5.55)*	4.87 (2.73-8.70)*
Total cholesterol	8.23 (5.26-12.8)*	6.76 (3.98-11.50)*
HDL-C	0.86 (0.59-0.99)*	0.75 (0.45-1.25)
Triglycerides	11.13 (7.37-16.81)*	10.49 (6.50-16.92)*
Serum insulin	1.30 (0.70-2.41)	
HOMA-IR	2.14 (1.49-3.07)*	1.13 (0.66-1.95)

*OR is significant at the <0.001 level (Chi-square tests), $P < 0.05$ significant, $P < 0.01$ highly significant. BMI: Body mass index, HDL-C: High-density lipoprotein-cholesterol, HOMA-IR: Homeostasis model assessment index-insulin resistance, OR: Odds ratio, CI: Confidence interval

every year. This study confirms the occurrence of dyslipidemia and IR in women with BC. In this study, we have found higher levels of total cholesterol, TGs, LDL-C, VLDL-C, fasting glucose, fasting serum insulin, and HOMA-IR in BC cases compared to those in healthy controls.

Ray *et al.* suggested that an increased serum total cholesterol level may play a significant role in carcinogenesis.^[22] Some of the studies also find similar

**Figure 1: Positive Pearson's correlation between serum CA 15-3 and total cholesterol**

results.^[23-25] A few other studies reported that plasma total cholesterol level was significantly lower in patients with BC.^[26,27] Agurs-Collins *et al.* and Hoyer and Engholm did not find any significant difference in the serum total cholesterol levels between BC patients and controls.^[28,29]

In our study, TG levels were significantly higher in both pre- and postmenopausal BC patients than in controls. These results are consistent with those of other studies.^[10,23,28,30] Bani *et al.* showed that there was a significant increase in the TG levels in postmenopausal cancer patients.^[11] Goodwin *et al.* reported elevated serum TG levels in premenopausal BC patients.^[31] The high concentration of TGs may lead to a decreased level of sex hormone-binding globulin, resulting in higher levels of free estradiol, which may increase BC risk.^[32]

Table 4: Pearson’s correlation coefficient (*r*) between serum CA 15-3 and various metabolic variables of breast cancer patients

Parameters	<i>r</i>	<i>P</i>
Age	0.05	NS
BMI (kg/m ²)	0.17	NS
Total cholesterol (mg/dl)	0.48**	<0.001
HDL-C (mg/dl)	-0.26*	<0.05
LDL-C (mg/dl)	0.49**	<0.001
Triglycerides (mg/dl)	0.34**	<0.001
VLDL-C (mg/dl)	0.34**	<0.001
SBP (mmHg)	0.06	NS
DBP (mmHg)	0.02	NS
Fasting glucose (mg/dl)	0.35**	<0.001
Serum insulin (μU/ml)	0.29*	<0.05
HOMA-IR	0.36**	<0.001

P<0.05 significant, *P*<0.01 highly significant. BMI: Body mass index, SBP: Systolic blood pressure, DBP: Diastolic blood pressure, HDL-C: High-density lipoprotein-cholesterol, LDL-C: Low-density lipoprotein-cholesterol, VLDL-C: Very low-density lipoprotein-cholesterol, HOMA-IR: Homeostasis model assessment index, CA: Carcinoma Antigen 15-3

In this study, we did not observe any significant difference in the HDL-C levels in pre- and postmenopausal BC patients and controls. Ray *et al.* and Kachhawa *et al.* reported that plasma HDL-C levels were significantly lower in BC patients.^[22,23] At least two prospective studies reported the association between low HDL-C levels and increased risk of BC.^[29,33] Since endogenous sex steroids are closely associated with the development of BC, it has been hypothesized that cholesterol is an important risk factor for the development of BC.^[34] It has also been reported that low HDL-C is a marker of relative androgen excess.^[35] Aromatization of the excess androgen in the body promotes BC development.

The LDL-C level was significantly higher in pre- and postmenopausal BC patients than in controls in this study, consistent with results reported in other studies.^[22,23] The elevated serum LDL-C, which is more susceptible to oxidation, may result in high lipid peroxidation in BC patients. This may cause the accumulation of reactive oxygen species and free radicals (oxidative stress), which may, in turn, lead to cellular and molecular damage, ultimately resulting in malignant transformation.

High blood glucose was associated with increased BC risk in five of seven cohort studies,^[36-42] but the association was significant only in three.^[36-38] Some other studies have reported higher fasting blood glucose, serum insulin, and HOMA-IR in BC patients.^[36,41,43,44] The results of the present study are consistent with these findings. Muti *et al.* and Stattin *et al.* have reported that elevated blood glucose levels were associated with

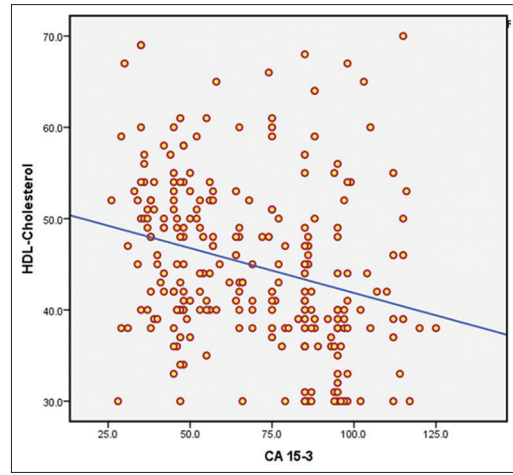


Figure 2: Negative Pearson’s correlation between serum CA 15-3 and high-density lipoprotein-cholesterol

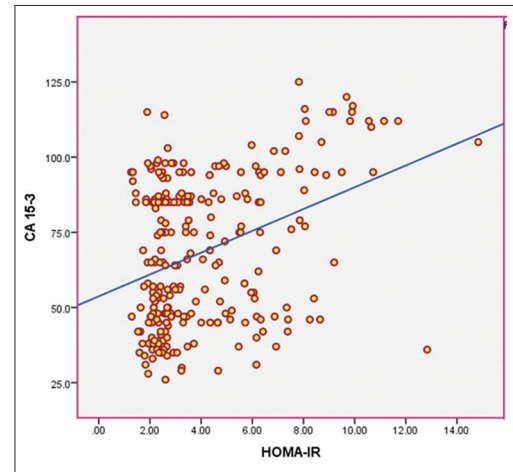


Figure 3: Positive Pearson’s correlation between serum CA 15-3 and homeostasis model assessment-insulin resistance

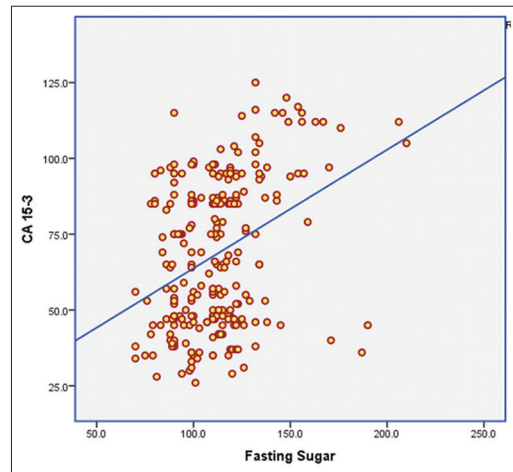


Figure 4: Positive Pearson’s correlation between serum CA 15-3 and fasting sugar

a significantly higher risk of BC in premenopausal women, compared to the lower risk in postmenopausal

women.^[36,38] A study conducted with 77,228 women participants, during a screening program in Austria, found that elevated blood glucose was associated with BC risk. The risk was the highest among those older than 65 years of age.^[42]

Only one of the four cohort studies that have examined fasting insulin levels in relation to BC risk reported a significant positive association.^[40,45-47] HOMA-IR, based on a measurement of fasting insulin and glucose, by the euglycemic clamp method, has been shown to reflect IR more accurately than fasting insulin alone.^[48] Thus, the positive association of HOMA-IR with BC risk adds to the evidence for a possible role of IR in the etiology of BC. The results of the repeated measures analysis supported the findings of the analyses using baseline values for glucose, insulin, and HOMA-IR.

CONCLUSION

Our study suggests that dyslipidemia and disturbed glucose metabolism are correlated with BC and supports the hypothesis that total cholesterol, LDL-C, and TGs and serum glucose are important risk factors in the development of BC. It also reinforces the importance of controlling these factors, thereby reducing the incidence and mortality associated with BC. Our study has particularly highlighted the significant differences in metabolic indices and lipid profile between BC patients and controls. Among the biochemical parameters, serum glucose, total cholesterol, TG, LDL-C, VLDL-C, serum insulin, HOMA-IR, and serum CA 15-3 are significantly elevated in patients with BC compared to those in controls, suggesting a significant positive correlation between serum CA 15-3 and total cholesterol, TGs, LDL-C, serum insulin, and HOMA-IR in BC patients. There was no significant difference between the serum HDL-C levels in BC patients and controls. There was a negative correlation between serum HDL-C and CA 15-3. HOMA-IR is an indicator of IR, which is an important risk factor in the development of BC. Our study confirms that total cholesterol, TG, serum glucose, and HOMA-IR are important risk factors for BC.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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