MAK HILL Publications Research Journal of Medical Sciences

Research Article
doi: 10.36478/makrjms.2024.9.95.99

OPEN ACCESS

Key Words
Plasma lipid profile, cervical cancer, HDL

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Received: 18 June 2024
Accepted: 4 August 2024
Published: 10 August 2024

Citation: Nimmala Niharika, P.S.L.K. Prasanthi and T.G.V.R.L. Hanumanth Jyothsna, 2024. Plasma Lipid Profile in Cervical Cancer Patients: Clinical Study. Res. J. Med. Sci., 18: 95-99, doi: 10.36478/makrjms.2024.9.95.99

Plasma Lipid Profile in Cervical Cancer Patients: Clinical Study

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ABSTRACT

Cervical cancer is a multi-factorial disease process and risk factors associated are early age of intercourse, multiple sex partners, low socioeconomic status and human papilloma virus infection. Cancer development is a complex mechanism comprising of proliferation, apoptosis and differentiation and the interplay between these intricate processes decides tumor development and progression. A total number of 60 women were recruited in our study after taking written and informed consent. Out of these 60 women, 30 were cases and 30 were healthy controls. The 30 cases were clinically and histologically confined cases of carcinoma cervix of various stages. The 30 controls were matched with cases for age and BMI. It was seen that the mean serum total cholesterol levels were lesser in carcinoma group (131.7 mg/dl) than in the control group (176.3 md/dl) which was statistically strongly significant ($p<0.001$). It was seen that the mean serum triglycerides levels were lesser in carcinoma group (107.77mg/dl) than in the control group (183.57 md/dl) which was statistically strongly significant ($p<0.001$).

INTRODUCTION

Cancer is defined as a relatively autonomous growth of tissue. It is a genetic disorder caused by DNA mutations that are acquired spontaneously or induced by environmental insults[1]. Cervical cancer is the third most common cancer in women worldwide accounting for 9% of all female cancer and 9% death in females due to cervical cancer. Worldwide it is seventh cancer with estimated 5, 30, 000 new cases in 2008 accounting for 4% of cancer worldwide. The world age adjusted rate is 15.2/100,000 population. More than 85% of the global burden is seen in developing countries and it accounts for 13% of all female cancer. In India, 1, 34, 000 women were detected to have cervical cancer, out of which 72,825 women died of cervical cancer in 2008[2]. According to Surendra Shastri, 1, 82, 027 new cases and 77,096 deaths occurred in India in 2010 due to cervical cancer 3[4]. Cervical cancer is a multi-factorial disease process and risk factors associated are early age of intercourse, multiple sex partners, low socioeconomic status and human papilloma virus infection[4]. Cancer development is a complex mechanism comprising of proliferation, apoptosis and differentiation and the interplay between these intricate processes decides tumor development and progression[5].

Lipids are major cell membrane components that are essential for various biological functions, such as maintaining cell integrity, cell growth and division of normal and malignant cells. Researchers have reported an association of plasma/serum lipids and lipoproteins with different cancers[6]. Reports suggest lipid peroxidation product malondialdehyde may cross link DNA on the same and opposite strands via adenosine and cytosine and may contribute to carcinogenicity and mutagenicity[7]. Because of the lipid peroxidation there is a greater utilization of lipids probably total cholesterol, lipoproteins and triglycerides for the new membrane biogenesis in neoplastic state[8].

The purpose of the present study is to give an insight on the basics of lipids and also to evaluate alterations in plasma lipid profile in cervical cancer patients and its association with histological grading thus assisting in better understanding of these complex phenomena.

MATERIALS AND METHODS

Source of Data: A total number of 60 women were recruited in our study after taking written and informed consent. Out of these 60 women, 30 were cases and 30 were healthy controls. The 30 cases were clinically and histologically confined cases of carcinoma cervix of various stages. The 30 controls were matched with cases for age and BMI.

Sample Size Calculation

The sample size was calculated by the formula:

- $2S^2(Z\alpha+Z\beta)^2/d^2$
- Zα=standard normal variation at 95% confidence interval.
- Zβ=Power at 80%.
- d=difference of mean between two groups.
- S=standard deviation

Inclusion Criteria: Patients who were diagnosed to have cervical cancer of any clinical stage confirmed by biopsy were included as cases.

Exclusion Criteria:

- Obese individual with BMI >30.
- Patients having other medical illness including diabetes, hypertension, hypothyroidism which interfere or alter lipid profile.
- Patients who had previously taken or were at time of study on radiotherapy or chemotherapy.
- Patients who were on medications such as statins, corticosteroid which are known to alter the lipid profile for past one month.
- Patients who have undergone surgeries like bariatric surgery which are known to alter lipid levels.

All patients were explained the details of the study and written, informed consent was taken from all cases and controls who were willing to participate in our study. All clinically suspected patients of carcinoma cervix underwent punch biopsy and endocervical sampling under aseptic precautions. The samples were sent to histopathological examination to confirm cervical cancer.

An overnight fasting blood sample of minimum 8 hours was collected from both cases and controls for estimation of serum lipid profile and apolipoprotein A. All possible standard precautions were used for sample collection. The blood was drawn from the left antecubital vein in sitting posture. Standard procedures were followed at every step to prevent hemolysis. 5ml of venous blood was drawn in plain vacutainer. It was centrifuged for 10 minutes at 3000rpm so as to separate out 2 ml of the serum. The serum was collected in aliquot tube and stored in the freezer at -800 c till analysis. Serum apolipoprotein A was analyzed by immunoturbidimetry. Lipid parameters were analyzed using Vitros 250 dry chemistry auto analyzer from Johnson and Johnson.

- Total cholesterol.
- Triglycerides.
- HDL cholesterol.

Calculated Parameters:

- LDL cholesterol by friedewald's formula.
- LDL = TC-[(TG/5) + HDLc]
- Apolipoprotein A.

RESULTS AND DISCUSSION

While comparing HDL levels between cases and controls we observed that cases had lower HDL levels compared to controls. Amongst cases, 15 patients (50%) had HDL levels <35 mg/dl and 15 patients (50%) had HDL levels >35 mg/dl. Amongst controls, no control had HDL below 35 mg/dl, 27 women (90%) had HDL levels between 35-60 mg/dl and 3 women (10%) had HDL level more than 60 mg/dl. The difference in HDL levels between cases and controls was statistically significant. (p<0.001).

In cases, 9 patients (30%) had LDL levels less than 70 mg/dl and 21 patients (70%) had LDL levels between 70-190 mg/dl. Amongst controls, no control had LDL levels below 70 mg/dl. All 30 women (100%) had LDL levels between 70-190 mg/dl. The difference in LDL levels in cases and controls was statistically significant (p<0.002).

Amongst cases, 28 patients (93.3%) had triglycerides levels less than 150mg/dl and 2 patients (6.7%) had LDL levels between 150-500 mg/dl. Amongst controls, 3 women (10%) had triglycerides levels below 150 mg/dl and 27 (90%) had triglycerides levels between 150-500mg/dl. The difference in the triglycerides levels in cases and controls was statistically significant (p<0.001).

In cases, all 30 patients (100%) had total cholesterol levels below 200 mg/dl and no patient had cholesterol above 200 mg/dl. Amongst controls, 24 women (80%) had total cholesterol levels below 200 mg/dl and 6 women (20%) had total cholesterol levels between 200-280 mg/dl. The difference in total cholesterol levels in cases and controls showed strong statistical significance (p< 0.001).

The mean serum HDL levels were lesser in cases (35.67 mg/dl) than in the controls (50.47mg/dl) which was statistically strongly significant (p<0.001). The mean serum LDL levels were lesser in cases (79.47mg/dl) than in the controls (117.57 mg/dl) which was statistically strongly significant (p<0.001).

The mean serum triglycerides levels were lesser in cases (107.77mg/dl) than in the controls (183.57 md/dl) which was statistically strongly significant (p<0.001).

The mean serum total cholesterol levels were lesser in cases (131.7 mg/dl) than in the control (176.3 md/dl) which was statistically strongly significant (p<0.001). There was statistically strong significant difference between the mean value of HDL, LDL, triglycerides and total cholesterol between the cases and controls.

Among the cases, 19 patients (63.3%) had apolipoprotein A value between 150-200 mg/dl, 7 cases (23.3%) had apoprotein A levels below 150mg/dl, 4 cases (23.3%) had apoprotein A levels <200 mg/dl. The mean value of apolipoprotein A in cases was 169.19±24.6 mg/dl.

Among controls, 27 women (90%) had apolipoprotein A value <150 mg/dl and 3 women (10%) had apolipoprotein A value between 150-200 mg/dl. No cases had apolipoprotein A >200mg/dl The mean value of apolipoprotein A in control was 128±18.6 mg/dl. There was statistically strong significant difference between the mean values of apolipoprotein A in cases and controls (p< 0.001).

The above table showing the comparison of total cholesterol with different cancers. It was seen that the mean serum total cholesterol levels were lesser in carcinoma group (131.7 mg/dl) than in the control group (176.3 md/dl) which was statistically strongly significant (p<0.001). Similar results were seen in studies done by Naik P.P *et al.* (p<0.001), Patel P.S *et al* (p<0.008), Raju K *et al* (p<0.079).The serum total cholesterol were elevated in study done by Ali *et al* (p<0.039)

In breast cancer the total cholesterol is elevated compared to controls. zhang xi et al reported that adult weight gain or increased BMI is a strong predictor of breast cancer risk. Cholesterol is essential for maintenance of the structural and functional integrity of all biological membranes. Cholesterol is an essential constituent of lipoprotein fraction. Low serum levels of cholesterol could be due to the ongoing process of oncogenesis.

The above table showing the comparison of triglycerides with different cancers. It was seen that the mean serum triglycerides levels were lesser in carcinoma group (107.77mg/dl) than in the control group (183.57 md/dl) which was statistically strongly significant (p<0.001). Similar results were seen in studies done by Patel P.S *et al* (p<0.059), Raju K *et al* (p<0.02), Neerupakam M *et al* (p<0.001).The triglycerides values were elevated in studies by Ali et al (p<0.043), Naik. P.P *et al* (p<0.001) which was not correlating with present study. The possibilities for decrease triglycerides may be due to decreased synthesis or increased catabolism or synthesis of lipoproteins and cholesterol by the liver could be inhibited by tumour metabolites.

The above table showing the comparison of HDL with different cancers. It was seen that the mean serum HDL levels were lesser in carcinoma group (35.67 mg/dl) than in the control group (50.47mg/dl) which was statistically strongly significant

Table 1: Difference in lipoproteins values in case and control.

Lipoproteins	Cases (n=30)		Controls (n=30)		
	Number	percentage	Number	percentage	p-value
HDL (mg/dl)					
<35	15	50.0	0	0.0	<0.001**
35-60	15	50.0	27	90.0	
>60	0	0.0	3	10.0	
LDL (mg/dl)					
<70	9	30.0	0	0.0	<0.002**
70-190	21	70.0	30	100.0	
>190	0	0.0	0	0.0	
Triglycerides (mg/dl)					
<150	28	93.3	3	10.0	<0.001**
150-500	2	6.7	27	90.0	
>500	0	0.0	0	0.0	
Total Cholesterol (mg/dl)					
<200	30	100.0	24	80.0	<0.001**
200-280	0	0.0	6	20.0	
>280	0	0.0	0	0.0	

Table 2: Comparison of mean value of lipoproteins in cases and controls.

Lipoproteins	Cases	Controls	p-value
HDL (mg/dl)	35.67±8.16	50.47±7.04	<0.001**
LDL (mg/dl)	79.47±14.97	117.57±22.89	<0.001**
Triglycerides (mg/dl)	107.77±28.11	183.57±32.93	<0.001**
Total Cholesterol (mg/dl)	131.70±20.32	176.3±24.24	<0.001**

Table 3: Apolipoprotein A distribution in cases and controls

Apolipoprotein A (md/dl)	Cases		Controls	
	Number	%	Number	%
<150	7	23.3	27	90.0
150-200	19	63.3	3	10.0
>200	4	13.3	0	0.0
Total	30	100.0	30	100.0
Mean ± SD	169.19±24.60	128.70±18.60		

p<0.001**, Significant, Student t test

Table 4: Comparison of means of total cholesterol in different cancers

Authors	Cancer type	Control			Cases		
		Mean	Standard deviation	Number	Mean	Standard deviation	Number
Naik. P.P *et al*. 2006[9]	Leukemia and Hodgkin's	153.88	18.98	52	136	35.04	105
Neerupakam M *et al.* 2014[10]	Oral cancer	183.73	24.28	15	170.43	26.21	15
Patel P.S *et al*. 2012[11]	Head and neck	206.76	10.07	52	167.59	4.93	184
Ali *et al*. 2014[12]	Breast cancer	175.6	43.5	27	207.9	49.5	76
Raju K *et al*. 2014[13]	Cancer cervix	166.3	34.7	35	155.1	23.8	99
Present study	Cancer cervix	176.3	24.24	30	131.7	20.32	30

Table 5: Comparison of means of triglycerides with different cancers:

Authors	Cancer type	Control			Cases		
		Mean	Standard deviation	Number	Mean	Standard deviation	Number
Naik.P.P *et al.* 2006[9]	Leukemia and Hodgkin's	73.9	22.47	52	136.0	35.04	105
Neerupakam M *et al.* 2014[10]	Oral cancer	131	101.19	15	113.8	54.34	15
Patel P.S *et al*.. 2012[11]	Head and neck	105.6	12.7	52	95.57	3.91	184
Ali *et al.* 2014[12]	Breast cancer	173.6	43.43	27	227.7	94.5	76
Raju K *et al.* 2014[13]	Cancer cervix	166.4	88.1	35	87.9	27.1	99
Present study	Cancer cervix	183.5	32.93	30	107.7	28.11	30

Table 6: Comparison of means of HDL Cholesterol with different cancers

Authors	Cancer type	Control			Cases		
		Mean	Standard deviation	Number	Mean	Standard deviation	Number
Naik. P.P *et al.* 2006[9]	Leukemia and Hodgkin's	35.76	6.68	52	25.15	9.88	105
Neerupakam M *et al.* 2014[10]	Oral cancer	44.27	6.28	15	36	5.53	15
Patel P.S *et al.* 2012[11]	Head and neck	40.32	2.33	52	28	0.8	184
Ali *et al.* 2014[12]	Breast cancer	46.8	9.8	27	45.4	12.7	76
Raju K *et al.* 2014[13]	Cancer cervix	36.6	8.2	35	38	5.9	99
Present study	Cancer cervix	50.47	7.04	30	35.67	8.16	30

Table 7: Comparison of means of LDL cholesterol in different cancers.

Authors	Cancer type	Control			Cases		
		Mean	Standard deviation	Number	Mean	Standard deviation	Number
Naik. P.P *et al.* 2006[9]	Leukemia and Hodgkin's	104.54	18.79	52	81.7	32.78	105
Neerupakam M *et al.* 2014[10]	Oral cancer	115.67	22.48	15	88.27	21.68	15
Patel P.S *et al.* 2012[11]	Head and neck	122.87	10.72	52	118.42	5.02	184
Ali *et al.* 2014[12]	Breast cancer	116.7	27.8	27	122.5	25.8	76
Raju K *et al.* 2014[13]	Cancer cervix	97.1	30.8	35	131.8	26.4	99
Present study	Cancer cervix	117.57	22.89	30	79.47	14.97	30

Table 8: Comparison of mean of Apolipoprotein A in cases and controls.

Apolipoprotein A	Case	control	p-value
Mean ± SD	169.19±24.60	128.70±18.60	p<0.001**,

(p<0.001).Similar results were seen in studies done by Naik P.P *et al.* (p<0.001), Neerupakam M *et al.* (0.043), Patel P.S *et al.* (p<0.001). No statistical difference in mean serum HDL levels were seen in study by done Raju K *et al.* (p<0.355), Ali *et al.* (p<0.32). As tumour cells accumulate cholesterol as CE in lipid droplets and efflux less cholesterol to HDL, thus results in decreased HDL cholesterol.

The above table showing the comparison of LDL with different cancer. It was seen that the mean serum LDL levels were lesser in carcinoma group (79.47mg/dl) than in the control group (117.57 mg/dl) which was statistically strongly significant (p<0.001). Similar results were seen in studies done by Naik. P.P *et al.* (p<0.001), Neerupakam M et al. (p<0.004), Patel P.S (p<0.04). No statistical difference in mean serum LDL levels were seen in study done by Raju K *et al.* (p<0.119), Ali *et al.* (p<0.18).

The decreased may be due to elevated expression of LDL-R in malignant cells increases the uptake of LDL via receptor mediated endocytosis. High consumption of LDL by cancer cells may cause depletion of LDL from serum of cancer patients.

Feng Sua and colleagues studied Apolipoprotein A-I (apoA-I) and apoA-I mimetic peptides inhibit tumor development in a mouse model of ovarian cancer and concluded mice expressing a human apoA-I transgene had increased survival (p< 0.0001) and decreased tumour development (p< 0.01), when compared with littermates, following injection of mouse ovarian epithelial papillary serous adenocarcinoma cells (ID-8 cells). ApoA-I mimetic peptides reduced viability and proliferation of ID8 cells and cis-platinum–resistant human ovarian cancer cells, and decreased ID-8 cell-mediated tumour burden.

Research has shown that exogenous ApoA1 prevents tumour development in mice, while lowered APoA1 levels are associated with ovarian cancer. ApoA1 has been shown to have anti-inflammatory and antioxidant capabilities in addition to counteracting atherogenesis[14]. No studies are done regarding the association of apolipoprotein A and carcinoma cervix. In present study. it was seen that the mean serum Apoprotein A levels were greater in carcinoma group (169.19 mg/dl) than in the control group (128.7mg/dl) which was statistically strongly significant (p<0.001).

CONCLUSION

Our study concluded that the lipid parameters and apolipoprotein A were significantly different in cases and controls. The mean serum HDL cholesterol, LDL cholesterol, triglycerides and total cholesterol were found to be significantly lower in patients with cervical cancer when compared to healthy controls. The mean serum Apolipoprotein A was found to be significantly levated in cases when compared to healthy controls. Periodic estimation of lipid profile in patients with suspected cases of cervical neoplasia will help us to establish the association between lipid parameters and cervical cancer. Thus the lipid profile can be used as a diagnostic or prognostic marker for cervical cancer.

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