

Altered Serum Lipids in the Cases of Head and Neck Cancer Associated with the Habit of Tobacco Consumption

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Abstract

Alterations in serum lipid profile patterns have long been associated with malignancies, and their role remains controversial with respect to head and neck cancer. Due to an increased rate of neoplastic cell multiplication and reduced supply, there is increased utilization of lipids causing Hypolipidemia. Adding to this, tobacco contains carcinogens capable of damaging the cell membrane components including lipids resulting in further hypolipidemia. Thus the purpose of the present case control study is to discuss the alterations in plasma lipid profile in head and neck cancer patients in association with tobacco consumption. This hospital based study includes 80 cases of head and neck cancer patients and 50 controls. Plasma Lipids included are total cholesterol (TC), high density lipoprotein cholesterol (HDL), low density lipoprotein cholesterol (LDL), very low density lipoprotein cholesterol (LDL), triglycerides (TG). Student's "t test" was applied to the data acquired. Values of $P < 0.05$ were considered significant and $P > 0.05$ were considered statistically insignificant.

Keywords

Lipids, Cholesterol, Triglycerides, Head and Neck Cancer

1. Introduction

Lipids are the main cell membrane components that are essential for various biological functions. Cholesterol is an extremely important biological lipid molecule involved in the synthesis of a number of essential vitamins, steroid hormones and bile acids. The cellular requirement of cholesterol is satisfied from two sources: exogenously from receptor mediated uptake of low-density lipoproteins and endogenously from mevalonate. The mevalonate pathway is a sequence of

enzymatic reactions (Figure 1) leading to Farnesyl pyrophosphate, which is the common substrate for the biosynthesis of cholesterol and isoprenoid compounds. Mevalonic acid having an essential role in DNA replication raised the possibility that a derangement in mevalonate synthesis might play a role in carcinogenesis [1]. Since 1980, a number of studies have revealed that there is a loss of cholesterol feedback control in cancer cells. This loss of the cholesterol feedback control leads to uncontrolled synthesis of mevalonate causing damaged DNA synthesis and uncontrolled hypocholesterolemia. Lipids are associated with cancer because they play an important role in cancer cellular integrity [2] [3] Lipids are useful for the study of variation in Cholesterol levels in many diseases.

It has been found that altered Serum Cholesterol levels are associated with breast and colorectal cancers [4] [5] [6]. Head and neck cancer is one of the leading causes of mortality and morbidity in India. Globally, it's the 6th most common cancer in the world [7]. Tobacco is the most important etiological agent in head and neck cancer. There are 72 measurable carcinogens in tobacco and are classified as Group I carcinogens by IARC [8]. The most important players in tobacco causing head and neck cancer are 4-Nitroquinilone-1-oxide (NQO) and Dimethylbenzanthracene (DMBA) [9]. The carcinogen in tobacco stimulates free radicals and reactive oxygen species release which in turn cause increase in Peroxidation and Oxidation of Polyunsaturated fatty acids. Due to enhanced lipid peroxidation, there is a greater consumption of lipids including total cholesterol, triglycerides, and lipoproteins for the synthesis of new cell membranes. To meet the voracious requirement, there is an increased metabolism of

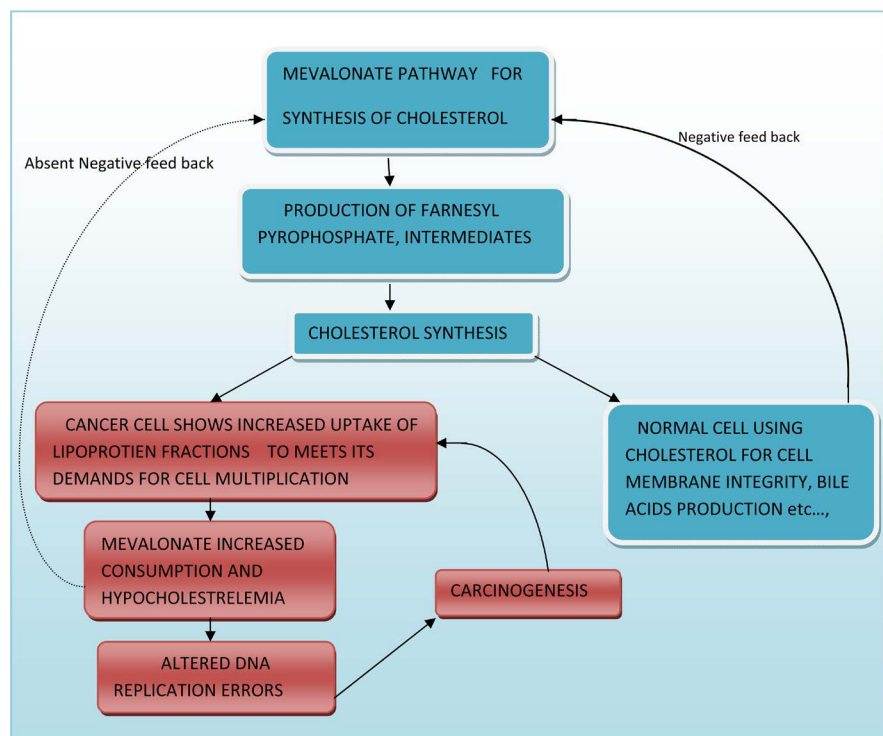


Figure 1. Mevalonate pathway in normal cells and an altered pathway in cancer cells leading to carcinogenesis and Hypocholesterolemia.

lipoprotein fractions such as VLDL, LDL, and HDL. The present study is aimed to evaluate the Plasma lipid profile (including total cholesterol (TC), high density lipoprotein cholesterol (HDL), low density lipoprotein cholesterol (LDL), very low density lipoprotein cholesterol (LDL), triglycerides (TG)) in head and neck cancer patients.

2. Materials and Methods

The following study was conducted in Department of Otolaryngology and Head and Neck surgery at Mahatma Gandhi Memorial Hospital, Warangal during a span of 1 year from January 2016 to January 2017. A total of 80 patients were taken into the study and 50 subjects acted as controls. The controls were selected from the relatives of the patients who accompanied them. The case taken into account were diagnosed both clinically and histo pathologically. All the cases taken into this study had well differentiated Squamous cell carcinoma.

Staging of the cases was done as per AJCC Classification 2009 (7th edition). 28 cases of Stage I, 34 cases of Stage II, 8 cases of Stage III, 8 cases of Stage IV, were included in this study. The patients diagnosed with Head and Neck cancer were having Oral cancer (n = 34), Oropharyngeal cancer (n = 6), Hypopharyngeal cancer (n = 8), Laryngeal cancer (n = 24), Thyroid cancer (n = 6), Unknown primary (n = 2). All the above data is represented in **Table 1**.

Criteria for Cases Selection

Study Inclusion Criteria

- 1) Individuals with habit of smoking tobacco and chewing tobacco.
- 2) Individuals who were diagnosed clinically and histopathologically with Cancer.
- 3) Patients age 25 and above.
- 4) Patients with an Unknown primary, with a histological diagnosis, in form of wedge biopsy/Fine Needle Aspiration Cytology (FNAC).

Study Exclusion Criteria

- 1) Individuals suffering from other diseases that might alter the lipid levels (Hypothyroidism, Hyperthyroidism, Nephritic syndrome, Malabsorbtion, Adrenal Insufficiency, Marfan Syndrome, Hematological diseases, Liver diseases).
- 2) Patients who have habit of Tobacco consumption in any form.
- 3) Patients with History of Head and Neck cancer or treated cancer.
- 4) Patients with Benign head and neck tumors.
- 5) Patients having skin cancer.
- 6) Patients with Lymphomas, Haematological Cancers, Tuberculosis.
- 7) Patient with history of/diagnosed with HIV/AIDS/Tuberculosis and receiving Anti Tuberculosis treatment/Treatment for HIV.
- 8) Patients receiving Hypolipidemia drugs or drugs causing Hypolipidemia were excluded.

Table 1. Clinicopathological details of the cases and controls in the study.

Age of Cases	48
Median	26 - 71
Range	
Age of Controls	
Median	55
Range	37 - 72
Gender of Cases (n = 80)	
Male	62 (77.518%)
Female	18 (22.5%)
Gender of Controls (n = 50)	
Males	46 (92%)
Females	4 (8%)
Site	
Oral Cavity cancer	34 (42.5%)
Oro Pharynx cancer	6 (7.5%)
Hypopharyngeal cancer	8 (10%)
Laryngeal cancer	24 (30%)
Thyroid cancer	6 (7.5%)
Unknown Primary	2 (2.5%)
Stage	
I	28 (35%)
II	34 (42.5%)
III	8 (10%)
IV	8 (10%)
T Stage	
T1	28 (35%)
T2	26 (32.5%)
T3	16 (20%)
T4	8 (10%)
Nodal status	
N ⁺	38 (47.5%)
N ⁻	42 (52.5%)
Cancer in females (n = 16)	
Oral Cavity cancer	8 (10%)
Oro Pharynx cancer	2 (2.5%)
Laryngeal cancer	2 (2.5%)
Thyroid cancer	4 (5%)
Cancer in males (n = 64)	
Oral Cavity cancer	26 (32.5%)
Oro Pharynx cancer	4 (5%)
Hypopharyngeal cancer	8 (10%)
Laryngeal cancer	22 (27.5%)
Thyroid cancer	2 (2.5%)
Unknown Primary	2 (2.5%)
Smoking Tobacco habit in Females	
>10 years	
>20 years	5 (6.25%)
Smoking Tobacco habit in males	
>10 years	18 (22.5%)
>20 years	34 (42.5%)
Female smoking habits	
Tobacco smoking	12 (15%)
Chewing tobacco	8 (10%)
Male Tobacco habits	
Tobacco smoking	48 (60%)
Tobacco chewing	10 (12.5%)

Blood Sample Collection

Fasting serum lipid profile was obtained from both Cases and Controls who were placed on fasting for a minimum of 12 hours prior to obtaining the blood samples. The blood samples were collected at least two times to evaluate the lipid changes in patients. The samples were allowed to clot and the serum obtained was centrifuged in an Automated Alere Cholesterol LDX analyzer.

Habit of Tobacco Consumption in the Subjects

Habit of tobacco consumption in one or the other form of smoking tobacco/chewing tobacco/chewing lime/chewing Areca nut is highly prevalent in India. In our study, 97.5% of the patients with Head and Neck cancer were consuming tobacco in one form or other. The association of cancer of oral cavity and tobacco was 42.5%. The details regarding habit of tobacco consumption in association with head and neck cancer are provided in **Figure 2**. Tobacco chewing form of readily available pouch (Gutka) and/or with lime was common in the patients with Oral cancer and Oropharyngeal cancer. A combination of Bidi and Gutka was more commonly seen in Oral cavity cancer and in the female subjects the habit of Tobacco chewing along with Areca Nut was more commonly seen. Tobacco smoking for more than 10 years was seen in 23 cases (28.75%) and smoking for more than 20 years was seen in 41 cases (51.25).

3. Results

A Significant decrease in Serum Total Cholesterol ($P < 0.001$), HDL ($P < 0.001$), LDL ($P < 0.001$), in Head and Neck cancer patients when compared to Controls. Our results strengthen the evidence of an Inverse relation existing between Serum Lipid levels and Cancer. **Table 2** depicts the data recorded from the cases and controls. **Table 3** shows that significant P values in Stage I, II, III, and IV in TC, HDL, and LDL. Non significant value of P was noted in Stage I, III, IV of VLDL, and TG. The total cholesterol in males and female with cancer in comparison to controls is depicted in **Figure 3**.

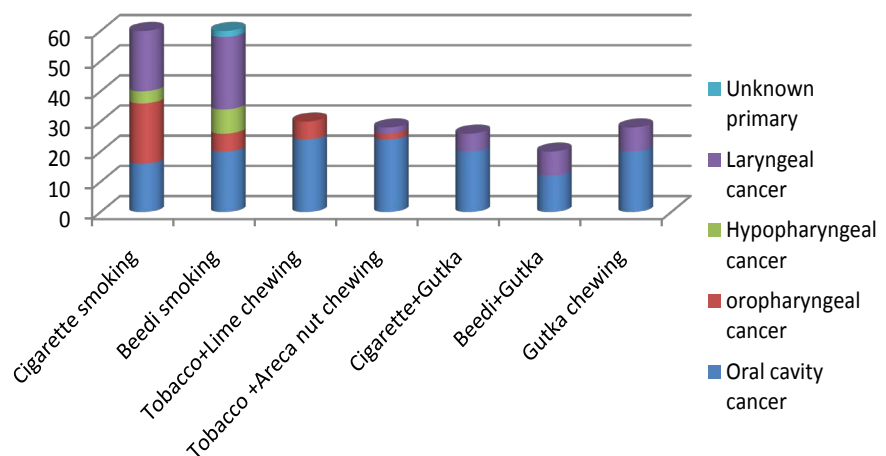


Figure 2. Showing tobacco consumption in various forms in Head and Neck cancer patients.

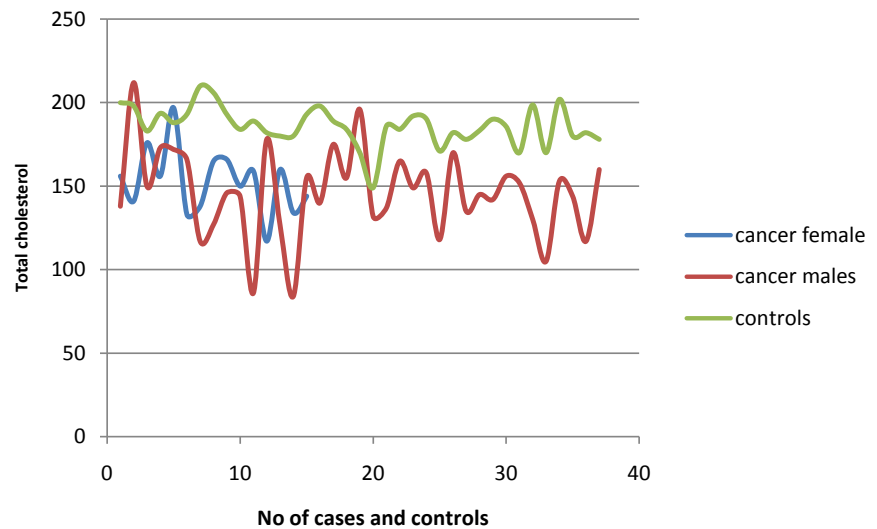


Figure 3. Comparing total cholesterol in cancer in males, female and controls.

Table 2. Comparing lipid profile in cases and controls.

Variables	CASES		CONTROLS		P Value
	Mean \pm SD	Range	Mean \pm SD	Range	
TC	146.8 \pm 26.8	212 - 84	187.1 \pm 11.3	210 - 149	<0.001*
HDL	47.6 \pm 12.1	84 - 27	63.8 \pm 5.4	72 - 50	<0.001*
LDL	70.9 \pm 11.1	118 - 27	92.8 \pm 13.8	113 - 51	<0.001*
VLDL	28.5 \pm 11.1	56 - 14	30.1 \pm 2,5	34.6 - 21.8	0.4321
TG	141.4 \pm 54.4	252 - 70	151.1 \pm 13.2	173 - 109	0.3179

*P < 0.05 is significant.

Table 3. Comparing mean lipid value and P value in different stages of cancer.

Variables	Stage I		Stage II		Stage III		Stage IV	
	Mean \pm SD	P value	Mean \pm SD	P value	Mean \pm SD	P value	Mean \pm SD	P value
TC	138 \pm 27.8	<0.001*	153.6 \pm 25.1	<0.001*	148 \pm 27.9	<0.001*	171 \pm 28.2	0.033*
HDL	45.3 \pm 13.3	<0.001*	46.5 \pm 11.6	<0.001*	47.1 \pm 7.52	<0.001*	48.1 \pm 13.3	<0.001*
LDL	65.4 \pm 24.6	<0.001*	74.3 \pm 20.9	0.0011*	67.8 \pm 29.6	0.0011*	80 \pm 24.9	<0.001*
VLDL	28.6 \pm 15.7	0.56	25.8 \pm 6.94	<u>0.0028*</u>	31.5 \pm 8.23	0.46	32 \pm 13.6	0.48
TG	150 \pm 78.1	0.94	125 \pm 28.2	<u>0.0001*</u>	162 \pm 36.6	0.16	160 \pm 66	0.47

*P < 0.05 is significant

4. Conclusion

Our study reveals that there is a significant reduction in Lipid parameters (TC, HDL, LDL) in cancer patients. The study also reveals Stage II cancer showing Significant reduction in VLDL and TG. Hence in depth study is necessary involving larger populations to confirm this finding.

5. Discussion

The majority of the Cholesterol in the body is in the cell membrane structure

while the rest of it is in blood. Sphingolipids and cholesterol form rafts that move within the cell membrane bilayer. These rafts function as platforms for the attachment of proteins when membranes are moved around inside the cell and during signal transduction [10]. Cholesterol plays important part in membrane trafficking assembly of signaling complexes on the plasma membrane. The Cholesterol presenting in blood is in constant transit between blood and tissue, carried in form of four major Lipoproteins namely HDL, LDL, VLDL, IDL. The normal human body derives energy from break down of free fatty acids and lipoprotein. On the other hand the cancer cell requires a high amount of metabolic intermediates in form of proteins, nucleic acids and lipids, a prerequisite for rapid proliferation [11]. HDL transports cholesterol from peripheral tissue to liver thereby prevents accumulation within tissue. The cancer cell accumulates a large cholesterol intracellularly for its rapid cell growth and division resulting in decreased cholesterol efflux from cancer cell and thus resulting in reduced HDL cholesterol [12]. Cancer cells show *De novo* Lipogenesis [13] to meet their increased requirement but even then this won't be sufficient for oncogenic signaling and its cell membrane synthesis, leading it to derive this from exogenous fatty acids. The oncogenic signals include ceramide-1-phosphate, platelet activating factor, diacylglycerol and lysophosphatidic acid [14] [15] [16]. The *De novo* lipogenesis in cancer cells causes increase in Monosaturated fatty acids which protect the cancer cell from oxidative killing and also chemotherapeutic agents [13]. Furthermore all cases in our study had habit of tobacco consumption in one form or other. Carcinogens in tobacco are responsible for increase in peroxide free radical production due to oxidation/peroxidation of Poly unsaturated free fatty acids [17]. This results in further consumption in lipids adding to already decreased plasma lipids.

In 1974, Rose *et al.* [18] reported that serum cholesterol was found lower in cancer colon patients, followed by Kark *et al.* [19] reporting low cholesterol levels in lung cancer patients. Following these discoveries many researchers found Hypolipedia in several cancers though alterations were seen with respect to LDL, VLDL, TG, reduced levels of HDL seen in most of the studies. Schatzkin *et al.* [2] and Chyou *et al.* [20] observed an inverse trend between lower serum cholesterol in head and neck cancer as well as in esophageal cancers. The lower serum lipid status may be considered a useful indicator for initial changes occurring in the neoplastic cells. In the study done by Omoti *et al.* the mean serum cholesterol & LDL in the cancer patients were significantly lower than those of controls [21]. In one study done at The Edith Wolfson Medical Centre in, Israel they found that the LDL levels showed that a 1 mg/dl increase in LDL was accompanied by a relative 2.4% and 2.5% reduction in odds of hematological cancer and fever/sepsis respectively [22]. This leads to the question if there can be a value so significant that we can determine the prognosis of a patient by the lipid values. Aexopoulos *et al.* [23] had found non-significant difference in serum triglycerides between cases and controls. Study done by Nydegger *et al.* revealed that serum

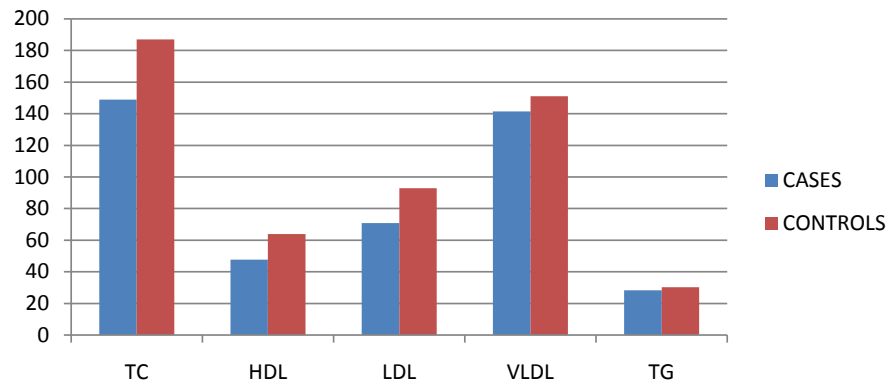


Figure 4. Comparing the lipid parameters between cases and controls.

triglycerides and cholesterol levels were markedly decreased in cancer patients [24].

Figure 4 depicts the different lipid parameters comparing cases and controls. It shows that there is significant difference between cases and controls with respect to TC, HDL, and LDL. In our study we noted that though the mean levels of VLDL, TG in the cases were lower compared to controls, they weren't significant. However values of VLDL, TG in Stage II cancer shows significant P value. Hence to correlate with our findings an in depth study is necessary to find out the changes in lipid levels per stage of cancer by involving a larger populations based study.

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