Abstract

Dyslipidemia in cancer patients is reported to be linked with cancer risk and progression of the disease. Previous research findings showed that low levels of serum cholesterol and elevated levels of serum triglycerides are associated with risk of overall cancers. However, there are several inconsistencies in the reports regarding the association of dyslipidemia with cancers. In this book chapter we will emphasize on dyslipidemia in relationship to the cancer risk, diagnosis, prognosis and mortality incidents.

Keywords

Serum lipids; Plasma lipids; Cancer; Dyslipidemia; Lipoproteins; Cholesterol; TG; LDL; HDL; VLDL

Abbreviations

TC-Total Cholesterol; TGs-Triglycerides; TG-Triglyceride; HDL-High Density Lipoprotein; VLDL-Very Low Density Lipoprotein; LDL-Low Density Lipoprotein

Introduction

Research on the biochemistry and molecular biology of lipids and lipoproteins has experienced remarkable growth in the past years, particularly with the realization that different classes of lipoproteins play fundamental roles in diseases such as cardiovascular diseases, obesity, diabetes, cancer and several neurodegenerative disorders.
Aberrant blood lipid profiles/dyslipidemia has long been considered as the risk factor of cardiovascular diseases. More recently, various research findings revealed that dyslipidemia is also associated with cancer [1-5]. It has also been known that lipids play crucial role in tumor development and progression [4,6]. The malignant cells manipulate and up-regulate their lipogenic and lipolytic pathways for acquisition of lipids [7,8]. As lipoproteins are the distributors of both endogenous as well as exogenous lipids across the tissues therefore it is suggested that deregulation of lipid metabolic pathways may also affect plasma levels of lipoproteins. Previous studies have demonstrated that almost all cancers are affected with aberrant serum/plasma lipid levels. Serum/plasma lipids-total cholesterol (TC), high-density lipoprotein cholesterol (HDL), low-density lipoprotein cholesterol (LDL), very low-density lipoprotein cholesterol (VLDL) and triglycerides (TGs) are suggested to be associated with cancer development and progression [1-3]. However, there are several discrepancies in the reports regarding the association of dyslipidemia with cancers. The reasons for these inconsistencies in previous research reports might be observed due to the types of cancer or due to related confounding factors including, lifestyle, obesity [5] and effect of antineoplastic therapies [9]. One of the reasons for these contradictory reports could be the fact that various types of cancers exploit different modes for the acquisition of lipids that in turn affect the serum/plasma lipid profiles.

In this chapter we will review the association between dyslipidemia and risk of developing various types of cancers including both hematopoietic malignancies and solid tumors. In order to gain more insight into this complex interplay, some prospective underlying mechanisms will be addressed. Moreover, the potential roles of serum/plasma lipids in promoting carcinogenesis will also be conferred.

**Solid Tumors**

Previous works have demonstrated that cancer patients often display aberrant blood lipid profiles (Table 1). Researchers have also reported association of plasma/serum lipids and lipoproteins with different types of cancers (Table 1). In the subsequent sections we will discuss this association between plasma lipid levels and solids cancers in detail.

**Breast Cancer**

Breast cancer is a heterogeneous disease which is further subdivided into different tumor types on the basis of molecular profile of tumors, patient prognosis and treatment options. Breast cancer is also associated with different cofactors which add up the disease burden such as age, menopausal status, blood lipid profiles and obesity [10]. Abnormal lipid profiles or dyslipidemia are considered as one of the major risk factor of breast cancer.
Many epidemiological studies revealed that breast cancer patients display significantly elevated levels of serum cholesterol [11]. But these observations are not consistent, for example, few longitudinal studies showed that high serum cholesterol levels were associated with increased risk of breast cancer [11]. While some breast cancer related studies showed no association between breast cancer risk and cholesterol [11].

The most striking and frequent of these observations is that; low levels of serum HDL are associated with increased risk of all cancers [11]. There are very few contradictory studies that showed that increased risk of cancer is associated with high levels of serum HDL. For instance it has been reported that women with breast cancer display high levels of HDL in comparison to the healthy women [11]. Although breast cancer patients display reverse relationship; here increased LDL levels are associated with increased breast cancer risk [11].

Moreover, it has been reported that serum lipid profiles of the breast cancer patients with metabolic syndrome are different from those without metabolic syndrome [11]. It has been shown that total cholesterol and triglyceride content in breast cancer patients without metabolic syndrome lies within the normal range [11]. Besides higher levels of serum HDL are shown to be inversely associated with the risk of breast cancer in premenopausal women [11]. Some of the previous works have also studied the possible association of tumor stage or grade with serum lipid profile. It has been shown that breast cancer patients with advanced disease in comparison to the patients with less advanced disease and controls display significantly higher serum TGs and significantly lower serum cholesterol and HDL levels. Moreover, lower serum LDL levels were observed in breast cancer patients with bony metastasis as compared to the patients with liver or liver bony metastasis [11].

Now question arises, how dyslipidemia is associated with the risk of breast cancer? It has been well studied that breast cancer cells have lipogenic phenotype (use de novo fatty acid synthesis pathway). Also, it has been reported that risk of breast cancer is 5 times higher in women of western countries as compared to the Asian women [12]. Moreover, relocation and migrational studies have demonstrated that migration from a region with low incidence to a region with high incidence increases breast cancer incidence in the immigrant population [13]. These epidemiological studies strongly indicated that risk of breast cancer is associated with the diet pattern of women. So, it is hypothesized that dietary lipids might favor the occurrence and progression of breast cancer. Plasma lipoproteins are the major distributor of dietary lipids therefore; blood lipid profiles could be utilized for accessing the early diagnosis and future outcome (prognosis) of disease.
Prostate Cancer

Several epidemiological studies have demonstrated that risk of developing prostate cancer is closely associated with dietary fat consumption [14,15]. In addition to this fat intake also supports the progression of prostate cancer [15]. Fat consumption directly affects the blood lipid profile of an individual therefore; it is suggest that blood lipid profiles might be helpful in early diagnosis of malignant disease.

Several recent research works support inverse association between the intake of statins and advanced stage prostate cancer [11], whereas some reports negate these findings. It has been proposed that the prostate cancer cells exhibit cholesterol feedback dysregulation, hence they might display increased sensitivity to statins [11].

To study the possible and direct role of cholesterol in this observed inverse association between statin intake and advanced stage prostate cancer, a nested case control study was carried out. It was reported that men with low plasma cholesterol had a lower-risk of high-grade prostate cancer and possibly advanced stage disease, but not organ-confined or low-grade disease [11]. Exclusion of the statin-users did not alter these results indicating a direct role of cholesterol in mediating this inverse association between statin intake and advanced stage prostate cancer. Another recent work where statin users were excluded from the study population suggests that men with low cholesterol have a reduced risk of high-grade prostate cancer [11].

Gastrointestinal Cancers

As dyslipidemia is an established risk factor for the other cancers, its role in gastrointestinal malignancies is also well studied. The increasing prevalence of oesophageal, stomach, colon, and rectal cancers may be attributed by plasma/serum lipids. The fat-rich diets, at quantities of 40 to 45% of the total calories ingested by the population, have a close relationship with colorectal cancer incidence [16]. There are several prospective and cohort studies that show conflicting results about colorectal cancers. Here, we present a review of most discrepant findings and their possible explanations.

The main findings of a recent case–cohort study nested in an Italian multicentre cohort suggested that high levels of plasma total and LDL cholesterol increase colorectal cancer risk, particularly in men and postmenopausal women [17]. Another Swedish Apolipoprotein Mortality Risk (AMORIS) cohort study also showed parallel results of total cholesterol (TC) with Italian multicentre cohort study. According to this study, high TC levels were associated with an increased rectal cancer risk whereas high glucose and TG levels were associated with an increased colon cancer risk. An increased risk of oesophageal cancer was also observed in persons with high TG and low LDL, LDL/HDL ratio, TC/HDL ratio, log (TG/HDL),
and apoB/apoAI ratio [18]. According to Wulaningsihet al., 2012, the persistent link between TC and rectal cancer risk as well as between TG and colon and oesophageal cancer risk in normoglycaemic individuals may imply their substantiality in gastrointestinal carcinogenesis [18]. A large prospective study in Korea 2011- restricted to men only-[19] and a study in Sweden 2009 [20] found modest positive association of serum TC with colon cancer. Another study showed positive correlation of serum levels of TC and LDL fraction with the appearance of colorectal cancer [20]. Although the exact mechanisms that how the high total cholesterol levels could lead to an increased risk of colorectal cancers are unclear. McKeown-Eyssen (1994) has also reported an association between high serum triglyceride and colon cancer [21].

In contrast, there are some reports that depict inverse association between blood lipids and colorectal cancers. For example, a study in 1974 [22] which pooled cohort cases from six prospective cardiovascular studies on men, found that the 90 colon cancer cases had lower mean serum cholesterol level than the overall cohort mean. A 1983 review also found an inverse relationship between blood cholesterol and colon cancer [23] as did the Framingham [24] and Honolulu Heart [25] studies. In a cross sectional study, lowest serum TG levels were revealed in colorectal cancers [26]. A large number of prospective studies generally do not support an association between cholesterol and risk of colorectal cancer [19,20,27-31]. The 1991 review of prospective studies found no long-term association of colorectal cancer with low cholesterol [32].

One of the major causes for these aberrant lipid patterns could be the metabolic syndrome; characterized by three or more components among abdominal obesity, high blood pressure, hyperglycemia, hypertriglyceridemia, and low HDL cholesterol [17]. Some recent prospective studies have found that people with metabolic syndrome are at an increased risk of developing colorectal cancer [15,16]. There are several possible mechanisms; mainly involving abdominal obesity and insulin resistance that have been proposed to link the syndrome with colorectal cancer [18]. In particular, the dyslipidemia component of metabolic syndrome is linked to chronic low grade inflammation [19], oxidative stress [20] and insulin resistance [21] – all of which may enhance carcinogenesis. However, some prospective studies exploring the relation of alterations in individual components of blood lipids with colorectal cancer have yielded conflicting results [17,31,33-39]. It is also possible that some genetic factors that affect the metabolism of cholesterol also influence susceptibility to cancer [40]. Hence, apolipoprotein E (apo E) - a multifunctional protein with a role in the transport and metabolism of lipids [40] - has also been considered in the etiology of colorectal cancer [41-43]. In a Brazilian study, the patients had statistically non-significant reduced levels (mean ± SD) of TC and LDL (180.4 ± 49.5 and 116.1 ± 43.1 mg/dL, respectively) compared to controls (204.2 ± 55.6, P = 0.135 and 134.7 ± 50.8 mg/dL; P = 0.330, respectively). The study concluded that presence of the ε4/ε4
genotype only in controls may serve as a protective against colorectal cancers. Lower lipid profile values among patients, even those on lipid-rich diets associated with the APOE*4 allele, suggest alterations in the lipid synthesis and metabolism pathways in colorectal cancers [40].

Hence, on the basis of these studies no clear-cut association between colorectal cancer progression and changes in blood levels of lipids can be decisively stated. For instance, some studies showed a decrease in plasma lipid levels in patients with colorectal cancers, when compared to controls. On the other hand, we have quite a number of reports supporting the opposite association. This may be a consequence upon an increased utilization of blood lipids by malignant cells as a competing factor [44] or some other possible metabolic variability. To understand the role of dyslipidemia in gastrointestinal malignancies, we need to monitor several confounding factors such as classification of cancers, gender, age and body mass index etc.

Liver cancers

Liver cancer is a major public health concern and was considered as fifth common malignant tumor worldwide [45]. It is well known for its poor prognosis. Many previous studies indicate that lower cholesterol levels might increase the risk of cancers. However, this pattern is only consistent in case of preclinical cancers not in all cancers [46,47]. Following this pattern, the patients with severe hepatitis or hepatic failure or chronic liver disease also manifest decline in serum/plasma total cholesterol, TG, HDL, LDL and VLDL cholesterol levels in comparison to the controls [48-61]. This phenomenon could be attributed to the decreased lipoprotein biosynthesis [62]. The negative association between LDL and liver cancer mortality has also been observed in a previous report; showing that low LDL cholesterol may be a predictive marker for death due to liver cancer [50]. Jiang et al., 2008 also reported significantly decreased serum TG, apoAI, HDL and Lp(a) in hepatocellular carcinoma (HCC) patients than in controls, whereas plasma apoM levels were significantly increased in the HCC patients [63]. Moreover, these above mentioned studies were done on a large group of participants and were not gender restricted [46,50]. Though, this would be of prodigious significance to associate dyslipidemia in liver cancer patients with the severity of the disease.

Liver is the main organ that is involved in lipid metabolism. Lipid accumulation in the liver is known as one of the factors for HCC. Liver cancer is followed by liver cirrhosis or chronic hepatitis that may significantly influence lipid and lipoprotein metabolism in vivo [64] and so lowers serum cholesterol [28]. Serum/plasma lipid or lipoprotein levels in liver could be disordered due to cancer, cirrhosis, blocked esterification and evacuation of cholesterol in liver [65-71].
The reduction of TG levels in liver cancers observed by Motta et al. (2001), may be explained on the basis of the relationship between cytokines and lipids [72]. Tumor cells produce such as Tnf-α, IL-1, IL-6, and IFN-α [73,74] that inhibit lipolysis [75]. Hepatic TG lipase activity was also found significantly decreased in hepatocarcinogenesis [76].

Serum Lp(a) level in liver cancer patients decreased strikingly as compared with that of the normal. Lp(a); produced by the liver its malfunction in liver cells may decrease its levels in patients with chronic liver disease [77]. The cause may be involvement of hormones, cytokines, genetics and nutrition in different ways because these influence serum Lp(a) levels in tumors by inducing cachexia that may disorder lipid metabolism [73,78]. Nevertheless, Lp(a) is synthesized and metabolized independently of other plasma lipoproteins so it is not influenced by various dietary manipulations [79]. Lp(a) is a substance involved in both lipid and proteic metabolism, and can be a sensitive and early marker of liver malfunction. It is concluded that Lp(a) might be useful in the follow-up of liver cancer patients and can be used for evaluation of the liver function [66], but in another study the increased Lp(a) serum level was found in hepatoma patients [80].

The quantitative and qualitative difference of lipids, apolipoproteins, enzymes, and lipid transfer proteins results due to various HDL subclasses, which are characterized by differences in shape, density, size, charge and antigenicity [81]. Cholesterol ester transfer protein (CETP) - an important determinant of lipoprotein function especially HDL metabolism—regulates plasma HDL levels [82]. Therefore, HDL plays a key role in the reverse cholesterol transport pathway in liver [83,84]. The primary site of human HDL synthesis is believed to be in the liver [85,86]. Ooiet al. (2005) analyzed lipids in liver diseases such as lower HDL-fraction and higher levels of all other parameters in case of metastatic liver as compared to HCC [67]. Slow α-HDL, abnormal LDL, Lp-X (lipoprotein X) and Lp-Y (lipoprotein Y) were found associated with liver diseases. Slow alpha HDL appeared during slight bile stagnation and was accompanied by increase in the apoE level and the HDL particle size [67]. Hepatic lipase (HL) can adversely affect the HDL2 selectively; hydrolyze the TG and lipoprotein in it [87]. The transgenic over expression of HL in either mice or rabbits decreased HDL levels [88,89]. HL activity is suppressed by estradiol and increased by testosterone [90,91], and when patients’ estradiol level with HCC was high, the secreting ability of testosterone will be cut down, which decreases HDL level too.

Moreover some findings showed virus induced hepatic carcinomas with lower serum cholesterol, TG, HDL and LDL levels [54,92-94]. The possible mechanism behind significantly lower serum cholesterol levels in patients with liver cancer has been clearly explained by Jiang et al., (2007). As liver cancer progresses, tumor cells intake
much exogenous cholesterol that affects endogenous cholesterol to its pathogenic extent [95], and then using this for cytomembrane synthesis [96], duplication of DNA and regulation of oncogene protein [97]. With the reduced synthesis of hydroxy-methylglutarylcoenzyme A (HMG-CoA) reductase, cholesterol synthesis in liver is also reduced and serum cholesterol content gradually depressed, especially in liver cancer [65,67]. Additionally, HDL causes serum cholesterol level to significantly decrease in liver cancer [66]. Moreover, the X protein of hepatitis B virus (HBx)—over expressed in HCC—was shown to down-regulate the transcriptional level of microsomal triglyceride transfer protein, which regulates the assembly and secretion of apoB. Apolipoprotein B (apoB) in the liver is an important glycoprotein for transport of VLDL and LDL. In liver cells hyper-express of HBx, but serum TG level in liver cancer did not obviously decrease compared with Lp(a), total cholesterol and HDL [67].

In most of these above findings, significant negative association of liver cancer incidence and mortality with lower levels of serum/plasma total cholesterol, HDL and LDL was shown but not with TG levels [32,54,98]. Lower HDL levels in Child-Pugh C than Child-Pugh B and in Child-Pugh B than Child-Pugh A and apo-A levels were also found to be the most affected factors in those with liver damage [55].

The study of the argument that there is an association between dyslipidemia and liver cancer showed that condition of liver lipid and lipoprotein metabolism and hepatic cell impairment are related, and will aid in determination of pathogenetic condition, therapeutic effect and prognosis in liver cancer.

Hematopoietic Malignancies

Numerous studies have reported alterations in the plasma lipid profiles in patients with hematopoietic malignancies. However, there are several inconsistencies in these reports [99-104]. The underlying mechanisms for these irregularities have not been clearly elucidated. In general, lipids are known to play a crucial role in tumor development and progression [6]. Lipoproteins are the distributors of both endogenous as well as exogenous lipids across the tissues. Therefore, it is plausible that lipoproteins play a fundamental role in cancer progression via supplying lipids to malignant cells and tumors. These speculations are even more intriguing for the leukemic cells that are in circulation and could attain more direct benefit from the plasma lipoproteins.

Leukemia

Several prospective-cohort studies have previously reported that lower levels of serum cholesterol are associated with high-risk of developing leukemia as well as overall hematopoietic cancers [27,29,105-107] (Table 1).
Moreover, low plasma cholesterol levels were found to be associated with increased risk of mortality in hematopoietic cancer patients [108]. On the contrary, there are few studies that report no association between total serum cholesterol levels and the risk of leukemia [28,109].

The exact cause of the abnormal lipid profiles in leukemia patients is not yet clearly elucidated. The possible role of plasma lipids and lipoproteins in carcinogenesis is also not very well-defined. However, researchers working in this area have made number of suggestions to explain the aberrant plasma lipid profile in leukemia patients [11]. The increased uptake and degradation of LDL cholesterol widely reported in acute myeloid leukemia (AML) cells [110,111]. Thus, it can be speculated that increased uptake of LDL by cancer cells may affect its clearance from circulation and results in decreased serum LDL levels in the cancer patients. Leukemia cells were also shown to display higher uptake of HDL-cholesteryl esters [112]. It has also been reported that the conversion of cholesterol to bile acids is suppressed in the AML patients, a phenomenon that may also result in a decreased intestinal absorption of cholesterol and subsequent hypocholesterolemia [113].

The fatty acid analysis of the triglyceride esters in serum of leukemia patients revealed a high proportion of stearic-acid (18:0) [114], which is associated with a slower in vitro degradation of VLDL by (LPL). Hence, the abnormal composition of triglycerides renders VLDL a poor substrate for lipoprotein lipase (LPL) that may also cause increased serum TG and VLDL levels in leukemia patients.

All of the above mentioned works indicate that the aberrant lipid profiles in leukemia patients are possibly a consequence of cancer. However, several studies have clearly associated the risk of developing leukemia with atypical serum lipoprotein levels (Table 2). Hence, a causative role of aberrant lipoprotein levels is also suggested by previous reports, at least for the malignancies of non-hematopoietic origins. Some researchers have suggested that peroxidation of plasma lipoproteins may also play a key role in cancer development [115]. Lipoproteins are susceptible to peroxidation triggered by reactive oxygen species and reactive nitrogen species. It has been proposed that lipid peroxidation product malondialdehyde, that form adducts with adenosine and cytosine, may contribute to mutagenicity and carcinogenicity in mammalian cells [116]. On the other hand, HDL that due to its lipid and apoprotein content - is less susceptible to peroxidation in comparison to LDL, counters the oxidative damage caused by oxidized LDL [117]. Thereby, HDL prevents the generation of reactive oxygen species and acts as an anti-carcinogen. These speculations provide a possible explanation for the involvement of plasma lipoproteins in carcinogenesis however; further studies are required for the better understanding of this phenomenon.
Multiple Myeloma

Myeloma is the cancer of the plasma cells—white blood cells that produce antibodies. Myeloma cells are produced in the bone marrow. Myeloma cells prevent the normal production of antibodies that makes the immune system weak. Hence the patient is susceptible to infections. The multiplication of myeloma cells also hinders the normal production and function of normal blood cells. In most cases of myeloma there is an excessive production of M-proteins or paraproteins—abnormal antibodies that can cause kidney damage. Additionally, the myeloma cells normally produce substances that may cause bone destruction, leading to bone pain and/or fractures.

Like several solid tumors, hypocholesterolemia is also observed in some types of hematological malignancies, e.g. multiple myeloma (MM). As compared to healthy individuals serum total cholesterol, HDL and LDL levels were found to be significantly lowered in MM patients (p<0.001). Whereas, no difference was observed when TG and VLDL levels were compared between the both groups [118]. Serum lipid levels are also shown to be affected by the type and stage of multiple myeloma [118,119]. One of the plausible reason for hypocholesterolemia in MM patients, could be the increased clearance of LDL and utilization of cholesterol by the myeloma cells [118].

Lymphoma

Lymphoma is a form of hematopoietic cancer of lymphoid origin. It involves lymph nodes and immune cells—lymphocytes. The two major types are Hodgkin lymphoma (HL) and Non-Hodgkin lymphoma (NHL). Like several other types of blood cancers, lymphoma patients often exhibit aberrant lipid metabolism. Previously Lim et al. reported that decreased circulation of HDL particles may take place during lymphomagenesis. However, no correlation for total and non-HDL cholesterol was observed in NHL patients. The inverse association observed between HDL and NHL changed during the follow-up period. It wasn’t confounded by factors like obesity (a putative risk factor for NHL) and physical activity but the gender of the patient affected this association [120]. Further investigations should be conducted to evaluate the etiological role of serum lipids in lymphomagenesis.

Conclusion

Dyslipidemia in cancer patients is reported to be associated with cancer risk, pathogenesis and progression [121,122]. However, there are several discrepancies in the previous reports. Hence the clinical usefulness of plasma/serum lipid levels in risk stratification of a variety of cancers remains elusive. There are several environmental and genetic factors that are known to influence human plasma lipid profile [123]. It is quite possible that the divergent
findings from the previous studies - regarding association between plasma lipid levels and cancers - are due to the fact that these confounding factors were overlooked during analyses. Moreover, these findings may help in outlining the prevalence and types of dyslipidemia in cancer patients that may emerge as diagnostic/prognostic factors for the management of cancer. This knowledge will lead us to the new therapeutic strategies for treatment of cancer. Further investigations are required to clarify this association.

Acknowledgements

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<table>
<thead>
<tr>
<th>Cancer Type Studied</th>
<th>Reference</th>
<th>Lipid Fraction Studied</th>
<th>Cancer Subtype</th>
<th>Sample Size</th>
<th>Results/Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>[124]</td>
<td>Chl</td>
<td>c = 577,330</td>
<td>Overall/Several Cancers</td>
<td>n = 577,330</td>
<td>Lower serum Chl levels were associated with higher risk of all cancers in females. This association is also observed in males for different types of cancers.</td>
</tr>
<tr>
<td>[125]</td>
<td>Chl and LDL</td>
<td>c = 100</td>
<td>(Lymphomas) = 18</td>
<td>n = 100</td>
<td>Significantly lower levels of total serum Chl, cholesterol Chl and LDL were observed in patients in comparison to the control population.</td>
</tr>
<tr>
<td>[126]</td>
<td>Chl</td>
<td>c = 610</td>
<td>(Lung cancer) = 32</td>
<td>n = 610</td>
<td>Lower levels of serum Chl were observed in patients in comparison to the control population.</td>
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<tr>
<td>[127]</td>
<td>Chl</td>
<td>c = 290</td>
<td>(Cervical cancer) = 55</td>
<td>n = 290</td>
<td>Significantly lower serum levels of total serum Chl, esterified Chl were observed in patients in comparison to the control population.</td>
</tr>
<tr>
<td>[128]</td>
<td>Chl</td>
<td>c = 133</td>
<td>(Lung cancer) = 320</td>
<td>n = 131</td>
<td>Significantly lower plasma Chl levels were observed in patients that may emerge as diagnostic/prognostic factors for the new therapeutic strategies for treatment of cancer.</td>
</tr>
<tr>
<td>[129]</td>
<td>Chl</td>
<td>c = 115</td>
<td>(Cancer of the genitourinary system) = 32</td>
<td>n = 115</td>
<td>There was no significant difference between plasma Chl levels of the survivors and non-survivors. Nevertheless, increased mortality was associated with low plasma Chl levels in lung cancer patients but not in stomach, prostate or colorectal cancer patients.</td>
</tr>
<tr>
<td>[130]</td>
<td>Chl</td>
<td>c = 60</td>
<td>(Liver cancer) = 125</td>
<td>n = 61</td>
<td>There was no significant difference between plasma Chl levels of the survivors and non-survivors. Nevertheless, increased mortality was associated with low plasma Chl levels in lung cancer patients but not in stomach, prostate or colorectal cancer patients.</td>
</tr>
<tr>
<td>[131]</td>
<td>Chl, LDL and VLDL</td>
<td>c = 131</td>
<td>(Cancer of upper digestive system) = 108</td>
<td>n = 131</td>
<td>Significantly lower serum Chl, LDL and HDL levels were observed in patients that may emerge as diagnostic/prognostic factors for the new therapeutic strategies for treatment of cancer.</td>
</tr>
<tr>
<td>[132]</td>
<td>Chl, HDL, TGs and LDL</td>
<td>c = 415</td>
<td>(Breast cancer) = 178</td>
<td>n = 415</td>
<td>Significantly lower levels of total serum Chl, esterified Chl were observed in patients in comparison to the control population.</td>
</tr>
<tr>
<td>[133]</td>
<td>Chl</td>
<td>c = 160</td>
<td>(Hematological malignancies) = 97</td>
<td>n = 160</td>
<td>Significantly lower levels of total serum Chl, esterified Chl were observed in patients in comparison to the control population.</td>
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<td>[134]</td>
<td>Chl</td>
<td>c = 84</td>
<td>(Stomach cancer) = 557</td>
<td>n = 84</td>
<td>There was no significant difference between plasma Chl levels of the survivors and non-survivors. Nevertheless, increased mortality was associated with low plasma Chl levels in lung cancer patients but not in stomach, prostate or colorectal cancer patients.</td>
</tr>
<tr>
<td>[135]</td>
<td>Chl, LDL and VLDL</td>
<td>c = 520</td>
<td>(Cervical cancer) = 55</td>
<td>n = 520</td>
<td>There was no significant difference between plasma Chl levels of the survivors and non-survivors. Nevertheless, increased mortality was associated with low plasma Chl levels in lung cancer patients but not in stomach, prostate or colorectal cancer patients.</td>
</tr>
<tr>
<td>[136]</td>
<td>Chl, HDL, LDL and VLDL</td>
<td>c = 32</td>
<td>(Liver cancer) = 125</td>
<td>n = 32</td>
<td>Significantly lower serum Chl levels were observed in patients that may emerge as diagnostic/prognostic factors for the new therapeutic strategies for treatment of cancer.</td>
</tr>
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</table>

Table 1: Overview of the previous studies aimed to evaluate the association between plasma/serum of various lipid fractions and cancer.
Estrogen treatment induced a significant increase in the low serum HDL group. Symptomatic and non-symptomatic patients were significantly increased in comparison to the normal serum HDL group.

**Prostate Cancers**

Significantly lower serum HDL and HDL cholesterol were observed in patients with prostate cancer compared to the controls. HDL levels were significantly lower in patients with prostate cancer than in the controls. HDL levels were significantly lower in patients with prostate cancer than in the controls.

**Bowel Cancers**

Significantly lower serum HDL and HDL cholesterol were observed in patients with bowel cancer compared to the controls. HDL levels were significantly lower in patients with bowel cancer than in the controls. HDL levels were significantly lower in patients with bowel cancer than in the controls.

**Lung Cancers**

Significantly lower serum HDL and HDL cholesterol were observed in patients with lung cancer compared to the controls. HDL levels were significantly lower in patients with lung cancer than in the controls. HDL levels were significantly lower in patients with lung cancer than in the controls.

**Hematopoietic Cancers**

Significantly lower serum HDL and HDL cholesterol were observed in patients with hematopoietic cancers compared to the controls. HDL levels were significantly lower in patients with hematopoietic cancers than in the controls. HDL levels were significantly lower in patients with hematopoietic cancers than in the controls.

**Liver Cancers**

Significantly lower serum HDL and HDL cholesterol were observed in patients with liver cancer compared to the controls. HDL levels were significantly lower in patients with liver cancer than in the controls. HDL levels were significantly lower in patients with liver cancer than in the controls.

**Gastric Cancers**

Significantly lower serum HDL and HDL cholesterol were observed in patients with gastric cancer compared to the controls. HDL levels were significantly lower in patients with gastric cancer than in the controls. HDL levels were significantly lower in patients with gastric cancer than in the controls.

**Prostate Cancers**

Significantly lower serum HDL and HDL cholesterol were observed in patients with prostate cancer compared to the controls. HDL levels were significantly lower in patients with prostate cancer than in the controls. HDL levels were significantly lower in patients with prostate cancer than in the controls.

**Bowel Cancers**

Significantly lower serum HDL and HDL cholesterol were observed in patients with bowel cancer compared to the controls. HDL levels were significantly lower in patients with bowel cancer than in the controls. HDL levels were significantly lower in patients with bowel cancer than in the controls.

**Lung Cancers**

Significantly lower serum HDL and HDL cholesterol were observed in patients with lung cancer compared to the controls. HDL levels were significantly lower in patients with lung cancer than in the controls. HDL levels were significantly lower in patients with lung cancer than in the controls.

**Hematopoietic Cancers**

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**Gastric Cancers**

Significantly lower serum HDL and HDL cholesterol were observed in patients with gastric cancer compared to the controls. HDL levels were significantly lower in patients with gastric cancer than in the controls. HDL levels were significantly lower in patients with gastric cancer than in the controls.
<table>
<thead>
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<th>Reference</th>
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<tr>
<td>[156]</td>
<td>Chl, LDL, VLDL, HDL, TGs, and Free fatty acids</td>
<td>Advanced breast cancer</td>
<td>Increased transaxillary circulating breast cancer risks</td>
</tr>
<tr>
<td>[155]</td>
<td>Chl, LDL, VLDL, HDL, TGs, and Free fatty acids</td>
<td>Advanced breast cancer</td>
<td>Plasma levels of total Chl, free Chl and LDL were significantly higher in postmenopausal breast cancer risk.</td>
</tr>
<tr>
<td>[154]</td>
<td>Chl, LDL, VLDL, HDL, TGs, and Free fatty acids</td>
<td>Untreated Breast cancer patients</td>
<td>Chl, HDL, LDL, and VLDL were observed in patients as compared to the controls. However, Chl and VLDL levels were not significantly different between these two groups.</td>
</tr>
<tr>
<td>[153]</td>
<td>Chl, HDL, TGs Advanced breast cancer</td>
<td>Higher serum levels of Chl and HDL could indicate progression or recurrence of breast cancer.</td>
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</tr>
<tr>
<td>[152]</td>
<td>Chl, HDL, LDL, and VLDL</td>
<td>Breast cancer</td>
<td>n = 105</td>
</tr>
<tr>
<td>[151]</td>
<td>Chl, HDL, LDL, and VLDL</td>
<td>Breast cancer</td>
<td>n = 60</td>
</tr>
<tr>
<td>[150]</td>
<td>Chl, HDL, LDL, and VLDL</td>
<td>Breast cancer</td>
<td>n = 324</td>
</tr>
<tr>
<td>[149]</td>
<td>Chl, HDL, LDL, and VLDL</td>
<td>Breast cancer</td>
<td>n = 12</td>
</tr>
<tr>
<td>[148]</td>
<td>Chl, HDL, LDL, and VLDL</td>
<td>Breast cancer</td>
<td>n = 40</td>
</tr>
<tr>
<td>[147]</td>
<td>Chl, HDL, LDL, and VLDL</td>
<td>Breast cancer</td>
<td>n = 31,209</td>
</tr>
<tr>
<td>[146]</td>
<td>Chl, HDL, LDL, and VLDL</td>
<td>Breast cancer</td>
<td>n = 310</td>
</tr>
<tr>
<td>[145]</td>
<td>Chl, HDL, LDL, and VLDL</td>
<td>Breast cancer</td>
<td>n = 38,623</td>
</tr>
<tr>
<td>[144]</td>
<td>Chl</td>
<td>Breast cancer</td>
<td>n = 79,994</td>
</tr>
<tr>
<td>[143]</td>
<td>Chl</td>
<td>Breast cancer</td>
<td>n = 246</td>
</tr>
<tr>
<td>[142]</td>
<td>Chl</td>
<td>Breast cancer</td>
<td>n = 250</td>
</tr>
<tr>
<td>[141]</td>
<td>Chl</td>
<td>Breast cancer</td>
<td>n = 31,209</td>
</tr>
<tr>
<td>[140]</td>
<td>Chl</td>
<td>Breast cancer</td>
<td>n = 310</td>
</tr>
<tr>
<td>[139]</td>
<td>Chl</td>
<td>Breast cancer</td>
<td>n = 38,623</td>
</tr>
<tr>
<td>[138]</td>
<td>Chl</td>
<td>Breast cancer</td>
<td>n = 79,994</td>
</tr>
</tbody>
</table>

**Abbreviations:** Chl, cholesterol; TGs, triglycerides; HDL, high density lipoprotein cholesterol; LDL, low density lipoprotein cholesterol; VLDL, very low density lipoprotein cholesterol; apo, apolipoprotein; LP, lipoprotein; PUFA, Polyunsaturated fatty acid; CMF, combination of cyclophosphamide, methotrexate and 5-fluorouracil; N, total population studied; n, number of controls; c, number of patients; N/A, not available; OPC, oral precancerous conditions.
Table 2: Association between plasma lipids and risk of hematological cancers: Overview of the data obtained from different prospective-cohort studies.

<table>
<thead>
<tr>
<th>Follow-up Period</th>
<th>Sample Size (n)</th>
<th>Major Findings</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>1990-2004</td>
<td>n = 33,368</td>
<td>No association was observed between total serum cholesterol levels and the risk of leukemia.</td>
<td>[127]</td>
</tr>
<tr>
<td>1971-1984</td>
<td>n = 12488</td>
<td>Inverse association between total serum cholesterol levels and risk of leukemia was observed.</td>
<td>[192]</td>
</tr>
<tr>
<td>1985-2003</td>
<td>n = 172210</td>
<td>Risk of hematopoietic cancer was significantly decreased for participants in the highest total serum cholesterol tertile (≥235.0 mg/dl in men and ≥229.0 mg/dl in women). However, this association was short-term and was only observed for the malignancies diagnosed within 5 months of plasma cholesterol assessments. For the malignancies that were diagnosed after 5 months cancer risk was not significantly associated with total serum cholesterol.</td>
<td>[131]</td>
</tr>
<tr>
<td>1972-2005</td>
<td>n = 577330</td>
<td>Inverse association between total serum cholesterol levels and hematopoietic cancers was observed.</td>
<td>[124]</td>
</tr>
<tr>
<td>1995-2005</td>
<td>n = 6107</td>
<td>In type 2 diabetes patients the association between LDL and leukemia was V-shaped, whereby both low and high levels of LDL were associated with elevated risk of cancer.</td>
<td>[193]</td>
</tr>
<tr>
<td>1985-2003</td>
<td>n = 29,093</td>
<td>Inverse association of total serum cholesterol and HDL-C levels with hematopoietic cancers was observed.</td>
<td>[194]</td>
</tr>
<tr>
<td>1968-1980</td>
<td>n = 39,268</td>
<td>Statistically significant inverse association between total serum cholesterol levels and leukemia was observed during the first years of follow-up, especially for rapidly developing cancers. However, in female participants this association was weaker in comparison to the male counterparts.</td>
<td>[195]</td>
</tr>
<tr>
<td>1960-1976</td>
<td>n = 3102</td>
<td>Statistically significant inverse association between total serum cholesterol levels and leukemia was observed. However, in female participants this association was weaker in comparison to the male counterparts.</td>
<td>[196]</td>
</tr>
<tr>
<td>1965-1968</td>
<td>n = 7716</td>
<td>No significant association was observed between total serum cholesterol levels and the risk of leukemia.</td>
<td>[197]</td>
</tr>
</tbody>
</table>

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