Malignancy-Associated Dyslipidemia

Agata Bielecka-Dąbrowa[1], Simon Hannam[2], Jacek Rysz[3] and Maciej Banach[1,*]

[1]*Department of Hypertension, Medical University of Lodz, Poland*

[2]*Department of Child Health, King's College London School of Medicine, London, UK*

[3]*Deprtament of Nephrology, Hypertension and Family Medicine, Medical University of Lodz, Poland*

Abstract: Cholesterol and triglycerides, important lipid constituents of cell, are essential to carry out several vital physiological functions. Lipids might be associated with cancers because they play a key role in the maintenance of cell integrity. The pathway for cholesterol synthesis may also produce various tumorigenic compounds and cholesterol serves as a precursor for the synthesis of many sex hormones linked to increased risk of various cancers. In some malignant diseases, blood cholesterol undergoes early and significant changes. The mechanism for the link between cancer and cholesterol remains controversial. The dates from studies are confusing because both hypolipidemia and hypercholesterolemia might be connected with malignancy. Not only cancers but also antineoplastic therapies have an influence on lipid profile. There are also dates suggesting that antihyperlipemic drugs might nfluenced malignancy.

Keywords: Cancer, dyslipidemia, cholesterol, statins.

BACKGROUND

Cholesterol and triglycerides are important lipid constituents of the cell. They play key roles in many vital physiological functions. Cholesterol is vital in the maintenance of the structure and functional integrity of all biological membranes. It is also involved in various other biological functions including; cell growth and division of both normal and malignant tissue, the activity of membrane bound enzymes and stabilizing the DNA double helix.

Cellular uptake and regulation of cholesterol is mediated by lipoprotein receptors located on the cell surface. In plasma, triglycerides and cholesterol are packaged into lipoproteins. These lipoproteins are then taken up and degraded by the cells. In some malignant diseases it has been demonstrated that blood cholesterol levels are significantly altered [1]. It has been proposed that low or high levels of cholesterol in the proliferating tissues and in blood could be reflect a role in carcinogenesis [1].

Lipids might be associated with cancers as they have an integral role in the maintenance of cell integrity. Although, raised lipids are strongly associated with the pathogenesis of coronary heart disease, researchers have also reported an association between plasma/serum lipids and lipoproteins with different types of cancers [2-4].

The main question is to whether hypolipidemia predisposes to cancer or is an effect of the malignancy. Data from studies are conflicting as not only hypolipidemia but also hypercholesterolemia might be connected with malignancy. Furthermore, antineoplastic therapies have an influence on lipid profile.

THE LEVEL OF CHOLESTEROL FRACTIONS AND CANCERS

The exact mechanisms by which lipids and lipoproteins may contribute to carcinogenesis are not clearly understood. Reports suggest however, that the lipid peroxidation product, malondialdehyde, may cross-link DNA on the same and opposite strands [5] *via* adenine and cytosine [6]. This may in theory contribute to carcinogenecity and mutagenecity in mammalian cells [7, 8].

LDL-cholesterol is more susceptible to oxidation in various pathologic conditions, which result in higher LPO (lipid peroxidation) during oxidative stress [9, 10]. HDL-cholesterol, on the other hand, is able to counterbalance the oxidative damage of LDL-cholesterol on cell membrane and prevent LPO. It has been suggested that HDL-cholesterol prevents both enzymatic and nonenzymatic generation of O_2^-, H_2O_2 and OH [11] and thus acts as an anticarcinogen and a powerful antioxidant.

There is evidence that cholesterol has a role in prostate disease. Swyer (1994) reported an increase level of cholesterol in prostatic adenomas compared to normal tissue. Since then, many studies have supported a relationship between cholesterol in prostate tissues or secretions and benign or malignant prostate growth [12]. Magura *et al.* [13] conducted a hospital-based case-control study to examine the possible association between hypercholesterolemia and prostate cancer. Hypercholesterolemia was defined as total cholesterol greater than 5.17 (mmol/l). Univariate logistic regression demonstrated a significant association between hypercholesterolemia and prostate cancer (odds ratio (OR) = 1.64, 95%

*Address correspondence to this author at the Department of Hypertension, Medical University of Lodz, Poland, Zeromskiego 113; 90-549 Lodz, Poland; Tel: +48 42 639 37 50; Fax: +48 42 639 37 50;
E-mail: maciejbanach@aol.co.uk

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confidence interval (CI): 1.19-2.27). This association changed only slightly after adjustment for age, family history of prostate cancer, body mass index, type 2 diabetes, smoking, and multivitamin use. A significant association was also found between a low HDL level and prostate cancer (OR = 1.57, 95% CI: 1.04-2.36). A high LDL level was associated with a 60% increased risk for prostate cancer (OR = 1.60, 95% CI: 1.09-2.34). .

The relationship between lipids and breast cancer is obscure and there are conflicting studies as to whether there is an association between lipids breast cancer. The causes of breast cancer are not known, but presumably it occurs due to a complex interplay of genetic susceptibility and environmental factors [14, 15]. Many studies have suggested that the relative risk of breast cancer is directly associated with the increase in dietary fat intake [16-22].

Ray and Husain [17] demonstrated that plasma total cholesterol, LDL-cholesterol and triglicerides (TG) were found to be significantly elevated among breast cancer patients as compared to the controls. On the other hand, plasma HDL-cholesterol concentration was significantly decreased in breast cancer patients. The maximum increase in plasma total cholesterol was seen in breast cancer patients with stage IV when compared with controls. The Stepsenwol study reported that lipids might primarily affect the gonads [7]. The high concentration of triglicerides may lead a decreased level of sex hormone-binding globulin, resulting in higher amount of free estradiol, which may likely to increase breast cancer risk [8]. The study by Shah *et al.* [23] aimed to examine the role of alterations in the lipid profile in breast cancer. Odds ratio analysis revealed that higher levels of total cholesterol and HDL were significantly associated with a reduction in breast cancer risk (p =0.01 and p =0.0001, respectively), whereas higher levels of VLDL and TG were significantly associated with increased breast cancer risk (p = .001 and p = .002, respectively). The alterations in lipid profile levels also showed a significant correlation with breast cancer risk, disease status, and treatment outcome [23].

A relationship of plasma lipids with gynecologic cancer has also been reported (24. In patients with ovarian cancer, there was a large decrease in the plasma levels of triglycerides (31%) and HDL-cholesterol (39%), with a moderate decrease in cholesterol (28%) and LDL-cholesterol levels (11%). In other gynecologic cancers, there was a significant decrease in plasma levels of the triglycerides (25%), cholesterol (21%), and HDL-cholesterol levels (27%), but a non-significant decrease in LDL-cholesterol (6.2%) when compared with normal subjects. HDL-cholesterol was decreased in all gynecologic cancers [24].

Hypertryglyceridaemia may also predispose to malignancy. Elevated triglycerides levels have been demonstrated in patients with several different types of cancer [18-20]. Alexopoulos *et al.* [18] however, found a non-significant difference in serum triglycerides between controls and cancer patients. The exact mechanism by which hypertriglyceridemia and decreased HDL-cholesterol concentration occur in patients with cancer is not known. It has, however, been suggested that lipoprotein lipase (LPL) may regulate the clearance of TG from blood to tissue and its activity in white adipose tissue is decreased in patients with cancer thus contributing to hypertriglyceridemia [21]. Since precursor particles of HDL-cholesterol are thought to derive from lipolysis of TG, and the LPL activity is decreased in cancer [22], increased plasma TG may be one of the factors that results in lower HDL-cholesterol concentration.

Early studies have reported that the hypolipidemia associated with malignancy may have been due to the direct lipid lowering effect of tumor cells, some secondary malfunction of the lipid metabolism or secondary to antioxidant vitamins used in the treatment of the cancer [25-28]. An inverse trend between lower serum cholesterol and head neck as well as esophageal cancer has been reported [25-30]. Rose *et al.* [31] reported a 66% higher mortality rate in cancer patients with lower plasma cholesterol.

Patel *et al.* [1] demonstrated significantly lower plasma total cholesterol, HDL – cholesterol, VLDL-cholesterol and triglycerides in patients with head and neck cancer and in those with oral precancerous conditions (OPC). A significant decrease in plasma total cholesterol and HDLC was observed in patients with cancer (p=0.008 and p=0.000, respectively) as well as in patients with OPC (p=0.014 and p=0.000, respectively) as compared to the controls [1].

The lower levels of plasma cholesterol and other lipid constituents in patients with some types of cancer might be due to their increased utilization by neoplastic cells for new membrane biogenesis. Whether hypolipidemia at the time of diagnosis, is a causative factor or is a result of the cancer remains unanswered. Lower plasma lipid status however, may be a useful marker in the early neoplastic changes.

Yang *et al.* [32] reported an association between LDL-cholesterol and cancer among patients with type 2 dibetes mellitus. A V-shaped risk relation between LDL cholesterol and all-site cancer was demonstrated. LDL cholesterol levels below 2.80 mmol/L and levels of at least 3.80 mmol/L were both associated with markedly elevated risk of cancer among patients who did not use statins. There was a 50% higher risk of cancer among patients with an LDL cholesterol level either above or below these levels. The associations persisted, with a slight increase in hazard ratios, after exclusion of patients who had been followed for less than 2.5 years [32]. These observations suggest that the increased risk of cancer among patients with high and low LDL cholesterol were probably not attributable to undiagnosed cancer.

ALTERATIONS IN LIPID PROFILE AFTER CANCER THERAPY

Prostate cancer is the leading cancer diagnosis and the second leading cause of cancer-related mortality in men in the USA. Men at risk of prostate cancer represent the same population of men who are at greatest risk for metabolic syndrome, diabetes mellitus, and coronary artery disease (CAD). In addition to risk factors for CAD that are applicable to the general population, men with prostate cancer can be at increased risk for CAD due to long-term androgen deprivation therapy (ADT) administered as treatment for prostate cancer [33].

Androgen deprivation therapy decreases lean mass and increases fat mass. It also decreases insulin sensitivity while increasing LDL- cholesterol, HDL cholesterol and triglycerides levels. [33]. One year of GnRH agonist therapy in a group of 40 men with prostate cancer was later found to cause significant increases in total cholesterol (9.0%), HDL cholesterol (11.3%), LDL cholesterol (7.3%) and triglycerides (26.5%) [34]. In another study men experienced significant increases in total cholesterol and HDL cholesterol during the first three months of GnRH agonist treatment [35].

Bexarotene has been approved for the treatment of cutaneous T cell lymphomas in patients refractory to systemic therapy. Associated hypertriglyceridaemia requires monitoring, but can readily be managed with concomitant medication, such as fenofibrate [36].

Patients suffering from acute lymphoblastic leukaemia (ALL) treated with asparaginase and corticosteroids are at risk of developing severe lipid abnormalities. Hypertriglyceridemia has been successfully managed using plasmapheresis [37]. Pancreatitis due to hypertriglyceridemia during asparaginase treatment for ALL can be prevented by, carrying out plasma exchange using fresh frozen plasma. This reduced both serum triglyceride and total cholesterol levels from 5430 mg/dL to 403 mg/dL and from 623 mg/dL to 204 mg/dL, respectively [38]. Plasmapheresis appears to be safe and effective in reducing hypertriglyceridemia and preventing related complications in ALL.

Patients with malignant disease may need hormonal therapy as primary or adjuvant treatment. Hormonal treatment may alter serum lipid levels and, therefore, may contribute to cardiovascular diseases in patients with cancer [39, 40]. Oestrogen therapy seems to have a mixed effect on serum lipid levels with a significant decrease in the levels of total cholesterol and LDL-cholesterol, an increase in HDL-chlesterol, but an increase in triglyceride concentration [41, 42].

Short term treatment using progestogens decrease total cholesterol, LDL-cholesterol and HDL-cholesterol concentrations and increase TG levels. In long-term treatment, progestogens usually have a small impact on lipid profile [43, 44].

Tamoxifen remains one of the most effective agents in the treatment of breast cancer. The development of persistent side effects from chronic administration of tamoxifen however, remains a concern. Tamoxifen is a selective oestrogen receptor modulator, which binds to oestrogen receptors of tumour cells and prevents the binding of endogenous oestrogen [45]. In the study by Love *et al*. Tamoxifen decreased total cholesterol and LDL-cholesterol levels in postmenopausal women [46]. The long term effects of Tamoxifen therapy on the plasma lipoprotein concentration and lipid transfer activity in postmenopausal women diagnosed with breast cancer have been investigated [47]. A significant decrease in total and LDL - cholesterol levels and a moderate increase in HDL cholesterol levels were observed in plasma samples from postmenopausal women with breast cancer who were administered Tamoxifen for two years. No significant differences in total and lipoprotein C and TG plasma levels were observed in samples from women with breast cancer who had never received tamoxifen. LTP I activity was significantly decreased in patients receiving Tamoxifen compared to patients who had never received tamoxifen [47].

A study in postmenopausal patients receiving adjuvant tamoxifen (10 mg/d) reported a significant increase in serum TG levels after 15 months. Although the increase remained within the reference range for most patients (n=102), severe hypertriglyceridemia developed in four patients after 6 months [48].

These specific tamoxifen-induced effects may be important for a number of reasons. Although the apparent decrease in total cholesterol and LDL- cholesterol levels reduce the risk of cardiovascular disease, the elevated levels of triglycerides have been related to an increased risk of ischemic heart disease.

Tamoxifen has also been associated with hypertriglyceridemia-induced acute pancreatitis [49-53]. These detrimental effects may be attributable to Tamoxifen also being a partial oestrogen agonist, a characteristic associated with the increased incidence of both thromboembolic events and endometrial cancer [49-53].

Aromatase inhibitors which are also frequently used in treating breast cancer, block the cytochrome P450-dependent enzyme aromatase, preventing the conversion of androgens to oestrogens. These third-generation drugs (anastrozole, letrozole and exemestane) are alternative agents to tamoxifen for the treatment of postmenopausal women with hormone-dependent breast cancer [54].

The effects of adjuvant anastrozole (1 mg/d), exemestane (25mg/d), or tamoxifen (20 mg/d) were investigated in postmenopausal women with operable breast cancer. Anastrozole resulted in a non-significant decrease in the levels of total cholesterol, LDL-cholesterol and TG, and a significant increase in HDL- cholesterol concentration [55]. Similar changes were observed after exemestane treatment, although the changes in HDL-cholesterol levels were not significant [56-58]. Long-term studies in postmenopausal women with advanced breast cancer demonstrated that anastrozole did not significantly change TC/HDL-C or LDL-C/HDL-C ratios [56-58].

STATIN TREATMENT AND MALIGNANCY

Although one recent analysis of a large cohort of patients treated with statins showed a greater risk of cancer with low LDL cholesterol levels [59], a more recent study reported otherwise [60]. There is a possibility that statins have anticancer activity [61]. Yang *et al*. found that patients who used statins were less likely to develop cancer, less likely to die and less likely to have the composite outcome of all-site cancer and all-cause death. At enrolment, patients who used statins were more likely to have an LDL cholesterol level of at least 3.80 mmol/L but less likely to have a level of less than 2.80 mmol/L [32]. A recent Canadian retrospective

study of 30 076 patients started on a lipophilic statin after a myocardial infarction reported a reduction of one-quarter in the hazard ratio for cancer incidence with high-dose statin treatment [60]. The findings from observational studies however, are not supported by the results of a meta-analysis of clinical outcome trials conducted by the Cholesterol Treatment Trialists' Collaboration which reported no reduction in cancer incidence [62]. Also three meta-analyses showed that the use of statins, which inhibit cholesterol synthesis, was not associated with any change in the risk of developing cancer [63-65].

Nevertheless, their results cannot completely exclude longer term effects of statins as the mean duration of these trials was only five years.

CONCLUSIONS

The mechanism for any link between cancer and cholesterol remains controversial. The mevalonate pathway, which leads to cholesterol synthesis, can produce molecules such as the isoprenoids farnesol and geranylgeraniol, which are important for a number of signaling proteins such as the GTPases Ras and Rho [66]. The Ras and Rho proteins are known to be involved in cell proliferation, differentiation and apoptosis. Thus, the observations that elevated LDL cholesterol level is associated with increased cancer risk are consistent with experimental findings that the mevalonate pathway may be associated with the development and progression of cancer [66]. The pathway for cholesterol synthesis may produce various tumorigenic compounds. As cholesterol serves as a precursor for the synthesis of many sex hormones there may be a link to an increased risk of various cancers.

Conversely, the underlying mechanism for the risk association between all-site cancer and low cholesterol level is not immediately obvious. One plausible explanation is that low LDL cholesterol may upregulate the activity or responsiveness (or both) of the mevalonate pathway in peripheral tissues. However the relation between low levels of LDL cholesterol and cancer remains controversial and its true mechanism remains elusive [65-68]. In the absence of definite biological mechanisms confirming that low cholesterol levels increase the risk of cancer and given the results of randomized trials indicating no increased risk of cancer with the use of statins, lowering LDL cholesterol still remains a top priority in the treatment of hypercholesterolemia [65-68].

The potential clinical utility of cholesterol fractions to predict cancer risk is still questionable. as there are differences between differenty types of cancer in the plasma lipid profile. The detailed study of cholesterol carrying lipoprotein transport and the efficiency of the receptor system may help in understanding the underlying mechanisms of regulation of plasma cholesterol concentrations in cancer [69-76].

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