



Dyslipidemia and Cancer - More than a Simple Association

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Received: Aug 26, 2022

Accepted: Sep 30, 2022

Published Online: Oct 03, 2022

Journal: Annals of Endocrinology, Diabetes and Metabolism

Publisher: MedDocs Publishers LLC

Online edition: <http://meddocsonline.org/>

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Editorial

The idea that cardiovascular and neoplastic pathologies are two entities that cause a huge "burden" for the public health system especially in developed countries it is currently well accepted. In the last years, starting from a significant improvement in the survival rate of certain cancers and a steady increase in the number of survivors diagnosed with cancer, cardiovascular complications became more frequent in these patients, with a huge impact on both morbidity and mortality. Their recognition and management have become important elements in the general care of cancer patients [1,2]. An overlap in the prevalence of cancer and Cardiovascular Diseases (CVD) is being discussed more and more intensively, as well as the development of cancer therapies in many elderly patients, with a higher incidence

of comorbidities, especially of a cardiovascular nature [3,4]. Starting from this, the approach of the neoplastic patient as a whole requires a new level of complexity. Heart diseases and cancer, apparently two distinct conditions, share a number of common elements, including risk factors, genetic, metabolic and inflammatory components, as well as common prevention strategies. Together, they are the most common causes of death in the United States [5]. In recent years, the synergistic link between CVD and cancer has become increasingly evident through the existence of common risk factors, most of which are modifiable and traditional, such as smoking, obesity, diabetes, type of diet, sedentary lifestyle and alcohol [1]. There are also studies that have highlighted potential common biological mechanisms (inflammation, oxidative stress and an increased



Cite this article: Costache II, Dmour BA, Costache AD, Botnariu B. Dyslipidemia and Cancer - More than a Simple Association. Ann Endocrinol Diabetes Metab. 2022; 1(1): 1001.

release of oxygen free radicals, hormonal factors, cytokine release, growth factors, metabolic reactions), as well as the influence on risk factors by active therapies for cancer [6,7, 8].

In recent years, a synergistic link between CVD and cancer has been highlighted through the existence of common risk factors, most of them modifiable and traditional. However, beyond the existence of risk factors, heart diseases and cancer share a series of common pathophysiological mechanisms from the simplest to the most complicated that include genetic, metabolic and inflammatory components, oxidative stress, altered telomere length, the gut microbiome, and changes in hematopoiesis - involved in the development of certain hematopoietic cancers but also associated with accelerated atherosclerosis and an elevated risk of coronary heart disease [1, 9]. Regarding the risk factors, it can be observed that dyslipidemia is a common element for both pathologies, but the following question arises: DOES DYSLIPIDEMIA PREDISPOSE TO MALIGNANCY OR IS IT A SIDE EFFECT ?

It has been proven that lipids have a central role in cancer biology. Thus, since 2003, the idea has been published that dyslipidemia is associated with increased cancer mortality, starting from the role that cholesterol (Col) and triglycerides (TG) have in:

- Maintaining the structural and functional integrity of the cellular membrane;
- Development, growth and cell multiplication;
- The stability of cellular DNA structure [10].

The role of Col in cancer development still remains a controversial subject. Several studies have highlighted the association between cancer and serum Col levels or statin treatment. A significant finding is related to increased blood Col levels in certain neoplasias. Cancer cells and other types of cells in the tumor microenvironment exploit different ways to capture lipids and extensively reconfigure their metabolism as part of a metabolic reprogramming (influenced by both oncogenic and environmental factors). Most cancers use lipids and Col to meet their unlimited energy demands. In order to obtain lipids and lipoproteins, cancer cells use two mechanisms: absorption of exogenous lipids from their local microenvironment and de novo synthesis of endogenous lipid molecules [11-13].

In addition, cancer cells possess adipocyte characteristics, storing excess lipids in the form of lipid droplets, which provide energy for nutrition, expansion and metastasis. Lipid catabolism is achieved through the Fatty Acid β -Oxidation (FAO) pathway, using both exogenous and endogenous Fatty Acids (FA). Moreover, in some cancers (prostate and lymphoma), the lipid-dependent metabolism that supports cancer cell growth and metastasis becomes a predominant pathway for energy production [14,15]. Another important finding is that rapidly proliferating tumor cells require large amounts of FA and Col. This idea is supported by numerous studies that have confirmed the hyperactivation of de novo lipogenesis in various types of neoplasia. Cancer cells can also rapidly convert exogenous FA into lipids required for proliferation and pro-tumorigenic lipid signaling [15]. There is an increased expression of Low-Density Lipoprotein (LDL) receptors and an increased uptake of LDL in a wide range of tumors, including glioblastoma [16], leukemia [17], pancreatic tumors [18] and lung cancer [19].

Several mechanisms involved in affecting cholesterol homeostasis lead to the development of cancer. In neoplastic cells there is an alteration of the expression and mutation of genes involved in cholesterol homeostasis. Accordingly, the number of genes involved in Col synthesis is increased. Other mechanisms worth mentioning are the increase of Col import through LDL receptors and the decrease in collagen transport so that intracellular collagen increases, which helps in cell proliferation.

Given the close link between altered lipid metabolism and the pathogenic process, the lipid profile may emerge as a disease biomarker, with diagnostic, prognostic and predictive potential. Also, lipid metabolism may become a promising target in oncological strategies to fight cancer. Changes on lipogenesis by inhibiting FA synthase stearoyl-CoA desaturase-1, ATP-citrate lyase or sterol-binding protein was effective in suppressing some tumors [20].

The important role of Col and TG in maintaining the structural and functional integrity of cell membranes is known, while participating in the development, cell multiplication and stability of DNA structures. Thus, the role of dyslipidemia in cancer was studied, either as a predisposing factor for neoplasia or as a side effect. A significant association was identified between elevated LDL-cholesterol (LDL-c) levels and an increased risk for prostate cancer, with elevated HDL-cholesterol (HDL-c) values exhibiting a protective effect [21]. The same lipid profile was correlated with the risk of breast cancer [22].

LDL-c is the fraction most prone to oxidation under pathological conditions, with oxidative stress resulting in increased levels of lipid peroxidation products that can alter the structure of cellular DNA. At the same time, HDL-c is a powerful antioxidant by counterbalancing the oxidative harmful effect of LDL-c, thus becoming an anticarcinogenic potential. At the same time, it has been shown that elevated serum triglycerides are associated with decreased ligands for sex hormones, resulting in increased serum levels of free estradiol involved in breast cancer [23].

On the other hand, cases of cancer associated with hypolipidemia have also been reported, either by secondary impairment of lipid metabolism, or by the direct hypolipidemic effect of tumor cells, or by treatments with antioxidant vitamins used in cancer [24]. This inverse relationship between lipid profile and neoplastic risk has been proven especially for cancers with the primary location in the head or neck, with mortality being significantly higher in patients with low Col [25]. Also, cancers in the gynecological sphere and especially the ovarian one are mentioned as being associated with decreases in lipid values [26]. The importance of these data comes from the usefulness of the lipid profile as an early diagnostic marker in neoplasms.

In the relationship between dyslipidemia and neoplasms, it is worth mentioning the impact of cancer therapy on the lipid profile, with the concomitant influence of the cardiovascular risk. Thus, anti-androgen therapy in prostate cancer has been shown to be associated with significant increases in Col and TG [26,27]. Also, some medications (bexarotene, asparaginase, corticosteroids) used in hematological neoplasms can significantly alter the lipid profile, these patients even needing plasmapheresis to avoid severe complications (acute pancreatitis). Hormone therapy such as tamoxifen may have a mixed effect on the lipidogram, with a decrease in total Col and LDL-c, but with an increase in TG, which may contribute to more frequent thromboembolic events [28].

Statins are the basic treatment in dyslipidemia, with a proven role in the primary and secondary prevention of CVD (acute coronary syndromes, strokes, thromboembolic events). At the same time, however, due to their anti-inflammatory properties, induction of apoptosis, inhibition of tumor growth, angiogenesis and metastases, these drugs seem to have a synergistic action with chemotherapy in improving the prognosis in cancer [7]. Statins have been reported to have a role in preventing breast cancer recurrence due in part to reduced levels of an estrogen receptor ligand (27-hydroxycholesterol), which has been shown to regulate tumor growth dependent on this type of receptor [29]. At the same time, in a study of over 12,000 participants, statins were shown to be useful in reducing mortality in patients with bronchopulmonary cancer [30]. Moreover, recent studies are focused on the effects of statins in reducing the incidence of cancer. The results in this direction are contradictory. However, large meta-analysis studies have not yet shown statistically significant results regarding the role of statins in the prevention of neoplasms [31].

The study of the lipidogram in neoplastic patients also acquires a prognostic role. A 2017 meta-analysis of the prognostic significance of lipids in cancer identifies elevated HDL-c and total Col as positive prognostic markers for the survival of these patients [32]. In the study of breast cancer, elevated LDL-c values correlated with disease progression, being a negative prognostic factor [33,34]. The negative prognostic value of LDL-c has also been demonstrated for small cell lung cancer, prostate cancer, colorectal cancer and esophageal cancer [35-38]. TG have also been shown to be an independent prognostic factor in the progression of hepatocellular carcinoma [39].

Another topic worth discussing is the link between cancer and obesity. It is known that obesity is associated with the presence of dyslipidemia and therefore, we raised the question if obesity can cause cancer. Yihai Cao et al. support this hypothesis by highlighting a strong association between obesity and an increased incidence of several types of cancer including breast cancer, colorectal cancer, multiple myeloma and thyroid cancer. Additionally, obesity is now well acknowledged as a poor prognostic factor for many malignancies. The mechanisms underlying the increase in cancer risk due to obesity are complex from the increase of circulating levels of FA-binding proteins to angiogenesis, inflammation and genomic instability. Interestingly, obese adipocytes provide cancer cells with more FA than nonobese adipocytes, increasing the energy produced by FAO available for tumor development and metastasis. In the tumor microenvironment, cancer-associated adipocytes have a significant impact on tumor development, metastasis, and treatment sensitivity [14,40].

In conclusion, the relationship between cancer and dyslipidemia still remains controversial. The potential clinical utility of Col fractions for predicting cancer risk is still debatable, as there are differences between different types of cancer and the plasma lipid profile. A more in-depth study of Col transporter lipoproteins and the receptor system may help to understand the underlying mechanisms causing the alteration of the lipid profile in cancer and discover new therapeutic targets.

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