



HDL in Endocrine Carcinomas: Biomarker, Drug Carrier, and Potential Therapeutic

Emily E. Morin^{1,2*}, Xiang-An Li³ and Anna Schwendeman^{1,2*}

¹ Department of Pharmaceutical Sciences, College of Pharmacy, University of Michigan, Ann Arbor, MI, United States,

² BioInterfaces Institute, University of Michigan, Ann Arbor, MI, United States, ³ Department of Physiology, Saha Cardiovascular Research Center, College of Medicine, University of Kentucky, Lexington, KY, United States

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*Correspondence:

Emily E. Morin
emmorin@med.umich.edu
Anna Schwendeman
annaschw@med.umich.edu

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High-density lipoprotein (HDL) have long been studied for their protective role against cardiovascular diseases, however recently relationship between HDL and cancer came into focus. Several epidemiological studies have shown an inverse correlation between HDL-cholesterol (HDL-C) and cancer risk, and some have even implied that HDL-C can be used as a predictive measure for survival prognosis in for specific sub-population of certain types of cancer. HDL itself is an endogenous nanoparticle capable of removing excess cholesterol from the periphery and returning it to the liver for excretion. One of the main receptors for HDL, scavenger receptor type B-I (SR-BI), is highly upregulated in endocrine cancers, notably due to the high demand for cholesterol by cancer cells. Thus, the potential to exploit administration of cholesterol-free reconstituted or synthetic HDL (sHDL) to deplete cholesterol in endocrine cancer cell and stunt their growth of use chemotherapeutic drug loaded sHDL to target payload delivery to cancer cell has become increasingly attractive. This review focuses on the role of HDL and HDL-C in cancer and application of sHDLs as endocrine cancer therapeutics.

Keywords: High-density lipoprotein (HDL), Apolipoprotein A-I (ApoA-I), endocrine cancer, cholesterol, cancer therapy

INTRODUCTION

Endocrine cancers are defined as those affecting the hormone secreting tissues of our body, including cancers of the adrenal, thyroid, parathyroid, prostate, pancreatic, and reproductive tissues. A rare subset of endocrine cancers, called neuroendocrine tumors (NETs), are neoplasms originating in endocrine tissue that migrate to form hormone-secreting tumors in other organs of the body, including intestine, lung, and pancreas (1). While specific molecular signatures may vary among the different types of endocrine cancers, they all share a common modality which is essential for tumor cell proliferation and overall survival: a high demand for cholesterol (2–4).

Cholesterol is a precursor molecule for steroid synthesis and bile acid production, making it essential for hormone production by endocrine tissue (5). Cholesterol is also an important component of cellular membranes, offering structure and rigidity to the plasma membrane as well as clustering with sphingolipids and glycerophospholipids to form highly-stable membrane microdomains or “lipid rafts” that host a number of proteins and lipids involved in key cell signaling pathways (6). In cancer, rapid cellular division is needed for the growth and survival of the tumor. Hence, a large demand for cholesterol is needed to facilitate the rapid formation of new membranes (3). Endocrine cancers in particular, display an even higher demand for cholesterol due to increased hormone and steroid production by these cells (7, 8).

A hydrophobic molecule, cholesterol has very poor aqueous solubility and thus is transported throughout the body by lipoproteins. Under normal conditions, HDL is a key participant in the reverse cholesterol transport (RCT) pathway, a process by which excess cholesterol from peripheral tissue is taken up by HDL and transported back to the liver for secretion in the bile or for redistribution to endocrine tissue for steroid production. Historically, HDL-C has been the focus of lipid metabolism modulating therapeutics for cardiovascular diseases, as high HDL-C or “the good cholesterol” and low LDL-C “bad cholesterol” have been well established as markers of cardiovascular health. Specifically, nascent HDL has the ability to reduce the burden of atherosclerosis by depleting foam-cell macrophages of their cholesterol and reducing inflammation and oxidation in the surrounding atheroma environment (9, 10). In this review, we will summarize what is known about the association between HDL-C levels and cancer and examine the utility of reconstituted or synthetic HDL as a potential therapeutic and drug delivery vehicle for endocrine cancers.

HDL-C IN CANCER

HDL is an endogenous, nanosized particle composed of apolipoproteins, and lipids (11). Naturally, these particles range in shape, size, density, and charge depending on their lipid composition, protein cargo, and degree of maturation (11). The main protein component of HDL, apolipoprotein A-I (ApoA-I), is initially synthesized in the liver where it is subsequently secreted into the circulation. Once secreted, ApoA-I picks up a small amount of lipid to form pre- β HDL particles. These nascent, cholesterol-poor discs can then further interact with cholesterol-rich cells of the periphery to take up and deliver that cholesterol back to the liver where it is taken up via scavenger receptor type B-I (SR-BI) for secretion or further processing. Once picked up by HDL, cholesterol is esterified by lecithin:acyl cholesterol transferase (LCAT) to form cholesterol ester. Cholesterol ester is then buried within HDL's hydrophobic lipid core, inducing the maturation and formation of larger, spherical HDL particles. Spherical HDL particles contain not only ApoA-I, but also ApoE, which facilitates the growing load of CE into the hydrophobic core since ApoA-I can only facilitate a limited amount of CE in the HDL core. ApoE is also useful in that it is a substrate for low-density lipoprotein receptor (LDLR) and can deliver HDL cargo to hepatic LDLR for biliary excretion or to endocrine tissue expressing LDLR or SR-BI for use in steroid production (12, 13).

HDL is highly heterogeneous and is present in a variety of different forms depending on its size, shape, density, and lipid/protein composition. This is a result of HDL remodeling, which is a continuous process involving several endogenous enzymes (14). Put simply, HDL can be continually and reversibly recycled between lipid-poor apoA1, discoidal HDL, and small/large/larger spherical HDLs. These subsets of HDL are classified into two groups, HDL₂ and HDL₃, based on their densities (11, 15). HDL₂ is lipid-rich and less dense

(1.063–1.125 g/mL) than its HDL₃ counterpart, which is dense (1.125–1.21 g/mL) protein-rich in comparison (11). Both HDL₂ and HDL₃ can be further divided into 2 and 3 subclasses, respectively, based on their size; HDL₃ ranges in size from roughly 7–9 nm in diameter while HDL₂ ranges from about 9–12 nm (11). To further complicate things, HDL can also be classified according to its surface charge and shape. Spherical, more neutral HDL particles are classified as α -HDL, while nascent, discoidal HDL particles, known as β -HDL, are poorly lipidated and more negative in overall charge.

In addition to the existing variety of subpopulations in healthy individuals, HDL particle makeup can vary significantly among patients of different disease states (16). Particularly, recent studies have identified changes in the diverse proteome of HDL particles in the various disease states (17, 18). While ApoA-I is the main protein in HDL, other proteins including ApoA-II, ApoC, paraoxanase (PON), ApoM, and serum amyloid A (SAA) have been identified and can be altered under disease conditions (19–21). The lipid composition of HDL particles can also vary with disease (22), and chronic changes in the HDL lipidome have been attributed to the high inflammatory state of various diseases, including the presence of lysophosphatidic acid (LPA), a phospholipid implicated in the progression of several endocrine cancers (23–25). Under such conditions, including atherosclerosis and lupus, HDL isolated from patients is said to be dysfunctional or proinflammatory, and its abilities to carry out cholesterol efflux and exert anti-inflammatory properties are lost (26–31). Similarly, studies have shown that HDL can promote breast cancer metastasis, which is attributed to the alterations in HDL's lipid and protein compositions under inflammatory and oxidative conditions (32, 33).

Epidemiology

A number of observational studies and retrospective study analyses have shown that plasma HDL-C and ApoA-I levels are significantly reduced in cancer patients, including those with breast, ovarian, colon, prostate, and pancreatic carcinomas (34–50). These studies are summarized in **Table 1**. A number of studies also sought to investigate the predictive power of HDL-C or ApoA-I levels in subsets of cancers and found that, when combined with other traditional cancer biomarkers cancer antigen 125 (CA125) and transthyretin (TTR), either ApoA-I or HDL-C levels significantly increased the power of these panels to predict patient prognosis (52, 54–58). In some cases, however, there were no significant associations between HDL-C, ApoA-I, and cancer risk (51). This is likely due to differences in study design and evaluation as well as the methods used to quantify HDL-C and ApoA-I. For example, direct measurements of HDL-C are generally performed by mass precipitation and can be confounded by the presence of ApoE and other proteins. Other methods directly measure HDL particles via size and charge separation using density gradient ultracentrifugation, gel filtration, high performance liquid chromatography (HPLC), and nuclear magnetic resonance (NMR) among others. Each of these techniques has its drawbacks, and is generally bias toward one or more subpopulation of HDL or risks chemical modification of

TABLE 1 | Clinical relationships between HDL-C and endocrine cancers.

Cancer	Study design	Major findings	References
Breast	<ul style="list-style-type: none"> Preoperative serum lipid profile (TC, TG, HDL-C, LDL-C, ApoA1, ApoB) and the clinical data were retrospectively collected for 1,044 breast cancer patients undergoing operation Kaplan-Meier method and the Cox proportional hazards regression model were used in analyzing the OS and DFS 	<ul style="list-style-type: none"> Preoperative lower TG and HDL-C level were risk factors of breast cancer patients Decreased HDL-C associated with lower OS rate Decreased TG associated with lower DFS rate 	(49)
Multiple	<ul style="list-style-type: none"> Twenty-six studies including 24,655 individuals identified via PubMed and EMBASE Meta-analysis to investigate the prognostic significance of serum blood TC, TG, HDL-C, and LDL-C for cancer 	<ul style="list-style-type: none"> Patients with higher HDL-C had a 37% reduced risk of death compared with lower HDL-C DFS patients with higher HDL-C level had the risk of disease relapse reduced by 35% compared with patients with lower levels. 	(50)
Breast	<ul style="list-style-type: none"> Examined the possible association of low HDL-C with incidence of breast cancer using data from the Atherosclerosis Risk in Communities Study (ARIC) cohort Among 7,575 female members of the ARIC cohort, 359 cases of incident breast cancer were ascertained during the follow-up from 1987 through 2000 	<ul style="list-style-type: none"> No association of low baseline HDL-cholesterol (<50 mg/dL) with incident breast cancer in the total sample and a modest association among women who were pre-menopausal at baseline. No association was observed among women who were post-menopausal at baseline Low HDL-cholesterol among pre-menopausal women may be a marker of increased breast cancer risk 	(51)
Multiple	<ul style="list-style-type: none"> Assess the relationships of TC, TG, HDL-C, ApoA, ApoB-100, Lp(a) with risk of common cancer forms, and total cancer mortality in comparison to incidence and mortality of CVD Case-cohort sample out of the prospective EPIC-Heidelberg study, including a random subcohort ($n = 2,739$), and cases of cancer ($n = 1,632$), cancer mortality ($n = 761$), CVD ($n = 1,070$), and CVD mortality ($n = 381$). 	<ul style="list-style-type: none"> High TC, HDL-C, ApoA, and Lp(a) levels were associated with a reduction in total cancer mortality High levels of apoB-100 and TG were inversely associated, and high HDL-C levels were positively associated with breast cancer risk Higher levels of Lp(a) were associated with an increase in prostate cancer risk 	(48)
Multiple	<ul style="list-style-type: none"> Serum TC, LDL-C, HDL-C, and TG were analyzed in 530 patients with newly diagnosed cancer (97 with hematological malignancies, 92 with tumor of the lung, 108 of the upper digestive system, 103 of colon, 32 of breast, and 98 of the genitourinary system) and in 415 non-cancer subjects 	<ul style="list-style-type: none"> TC, LDL-C, HDL-C, SA, and BMI were significantly lower in cancer than in non-cancer subjects; similar trend for metastatic vs. non-metastatic cancer patients Lowest values of TC, LDL-C, and HDL-C recorded in patients with hematological malignancies Highest values of TC, LDL-C, and HDL-C in patients with breast tumor 	(36)
Renal cell carcinoma	<ul style="list-style-type: none"> Preoperative serum lipid-profile (TC, TG, HDL-C, LDL-C, ApoA- I, and ApoB) were retrospectively performed in 786 patients with RCC 	<ul style="list-style-type: none"> Patients with low ApoA-I (<1.04) had significantly lower OS than the high ApoA-I In the 755 patients with nonmetastasis, the low ApoA-I group was also associated with shortened DFS time compared to the high ApoA-I group 	(47)
Pancreatic	<ul style="list-style-type: none"> Identify and validate new biomarkers in PCa patient serum samples 96 serum samples from patients undergoing PCa surgery was compared with sera from 96 healthy volunteers as controls. 	<ul style="list-style-type: none"> Apolipoprotein A-II, transthyretin, and apolipoprotein A-I were identified as markers These identified proteins were decreased at least 2-fold in PCa serum compared with the control group. 	(52)
Multiple	<ul style="list-style-type: none"> A retrospective cohort study of 14,169 men and 23,176 women with type 2 diabetes to investigate the relationship between HDL cholesterol (HDL-C) and cancer risk among type 2 diabetic patients During a mean follow-up period of 6.4 years, 3,711 type 2 diabetic patients had a cancer diagnosis 	<ul style="list-style-type: none"> A significant inverse association between HDL-C and the risk of cancer was found among men and women Suggests an inverse association of HDL-C with cancer risk among men and women with type 2 diabetes, whereas the effect of HDL-C was partially mediated by reverse causation Each 15 mg/dL increase in baseline HDL-C was associated with an 8–10% decreased risk of cancer in men and a 1–7% decreased risk of cancer in women with type 2 diabetes 	(44)
Breast	<ul style="list-style-type: none"> Review and meta-analysis of prospective studies investigating associations between TC, HDL-C, and LDL-C levels and the risk of breast cancer 	<ul style="list-style-type: none"> Evidence of a modest inverse association between TC and more specifically HDL-C and the risk of breast cancer No association observed between LDL-C and the risk of breast cancer 	(45)

(Continued)

TABLE 1 | Continued

Cancer	Study design	Major findings	References
Multiple	<ul style="list-style-type: none"> Evaluated the prospective association of total, breast, colorectal, and lung cancers and cancer mortality with lipid biomarkers in 15,602 female health professionals in the Women's Health Study (aged ≥ 45 y, free of cardiovascular disease and cancer, and without hormone replacement therapy or lipid-lowering medications at baseline) Included 2,163 incident cancer cases (864 breast, 198 colorectal, and 190 lung cancers) and 647 cancer deaths 	<ul style="list-style-type: none"> Total cancer risk significantly lower for the highest quartile of ApoA-1 Significant associations included colorectal and lung cancer risk with HDL cholesterol LDL cholesterol was not significantly associated with risk of total cancer or any site-specific cancers 	(46)
Multiple	<ul style="list-style-type: none"> Prospective examination of the association between TC and cancer incidence among 1,189,719 Korean adults enrolled in the National Health Insurance Corporation Over follow-up, 53,944 men and 24,475 women were diagnosed with a primary cancer 	<ul style="list-style-type: none"> High TC (≥ 240 mg/dL) was positively associated with prostate cancer and colon cancer in men and breast cancer in women Higher TC was associated with a lower incidence of liver cancer, stomach cancer, and, in men, lung cancer TC was inversely associated with all-cancer incidence in both men and women TC was associated with the risk of several different cancers, although these relationships differed markedly by cancer site 	(42)
Multiple	<ul style="list-style-type: none"> Examined the relationship between serum HDL-C and risk of overall and site-specific cancers among 29,093 Finnish male smokers in the Alpha-Tocopherol Beta-Carotene (ATBC) study cohort 7,545 incident cancers were identified during up to 18 years of follow-up 	<ul style="list-style-type: none"> Higher serum TC inversely associated with cancer risk Greater HDL-C levels associated with decreased risk of cancer of the lung, prostate, liver, and hematopoietic system Largely explained by reverse causation 	(40)
Multiple	<ul style="list-style-type: none"> Systematic analysis of 24 lipid intervention randomized controlled trials (76,265 intervention patients and 69,478 control patients) Examined association between baseline and on-treatment HDL-C levels and cancer risk 	<ul style="list-style-type: none"> Significant inverse association between HDL-C and cancer risk For every 10 mg/dL increase in HDL-C, 28–36% lower risk of developing cancer 	(41)
Ovarian, breast, prostate, colon	<ul style="list-style-type: none"> A five-center case-control study, involving a retrospective sample of 645 serum specimen Serum proteomic expressions were analyzed on 153 patients with invasive epithelial OC, 42 with other OC, 166 with benign pelvic masses, and 142 healthy women Utilized a ProteinChip Biomarker System and SELDI-TOF-MS 	<ul style="list-style-type: none"> Three biomarkers identified as biomarkers for OC: ApoA-1 (\downarrow in cancer); TT (\downarrow); and a cleavage fragment of ITIH4 (\uparrow) 	(53)
Ovarian	<ul style="list-style-type: none"> Serum analysis from 31 healthy individuals and 43 from patients with ovarian tumors Use of micro-LC-MS/MS followed by Western/ELISA to identify five serum protein biomarkers previously reported using SELDI-TOF-MS (54) 	<ul style="list-style-type: none"> TT (\downarrow), beta-hemoglobin (\uparrow), ApoA-1 (\downarrow), and transferrin (\downarrow) in early-stage OC When combined with CA125, biomarkers should significantly improve the detection of early stage ovarian cancer 	(55)
Ovarian	<ul style="list-style-type: none"> Evaluated markers identified by Zhang et al. (53) in an independent study population Sera from 42 women with OC, 65 with benign tumors, and 76 with digestive diseases Measured levels of various posttranslationally forms of TTR, apolipoprotein A1, and CA125 using SELDI-TOF-MS Examined power of markers to discriminate sera from women with ovarian cancer from sera from women with other diseases 	<ul style="list-style-type: none"> Confirmed findings by Zhang et al. (53) ApoA-I and TT levels were lower in disease states compared to controls Markers used alone improved detection of controls with CA125 levels ≥ 35 units/mL but lost sensitivity for late-stage cases. 	(56)
Ovarian	<ul style="list-style-type: none"> Evaluated multiplexed bead-based immunoassay of OC-associated biomarkers (TTR and ApoA-1, together with CA125) using serum of 61 healthy individuals, 84 patients with benign ovarian disease, and 118 patients with OC 	<ul style="list-style-type: none"> Panel of ApoA-I, TT, and CTAPIII combined with CA125 increased sensitivity for detection of early stage OC Combination of three markers offered maximum separation between non-cancer and stage I/II or all stages of disease 	(57)

(Continued)

TABLE 1 | Continued

Cancer	Study design	Major findings	References
Ovarian	<ul style="list-style-type: none"> Development of multiplexed bead-based immunoassay for detection of known serum biomarkers of cancer (118 OC, 84 benign ovarian disease, 61 healthy controls) 	<ul style="list-style-type: none"> Combination of transthyretin, and ApoA-I with CA125 improved sensitivity and specificity of OC diagnosis 	(58)
Ovarian, breast	<ul style="list-style-type: none"> Measured ApoA-I and GPX3 mRNA levels via qRT-PCR in 121 effusions (101 OC, 20 BC) and 85 solid OC specimens (43 primary carcinomas, 42 metastases) 	<ul style="list-style-type: none"> APOA1 and GPX3 transcript levels were higher in ovarian carcinoma compared with breast carcinoma effusions APOA1 and GPX3 mRNA levels can effectively differentiate ovarian from breast cancer 	(59)
Breast	<ul style="list-style-type: none"> Fasting serum samples analyzed for lipid fatty acid and lipoprotein levels Malignant breast tissue analyzed for hormone receptor binding 100 women with breast masses (50 malignant, 50 benign) 	<ul style="list-style-type: none"> Serum lipid and apolipoprotein components of LDL were increased in fibrocystic disease and early stage cancer but decreased in women with early recurrence Ratio of serum ApoA-1/ApoB levels at time of biopsy was the best predictor of cancer recurrence 	(34)
Breast	<ul style="list-style-type: none"> Nested case-control study to examine association between HDL-C and breast cancer risk Serum lipid profiles from 200 age-matched (100 diagnosed before age 50 and 100 at age 50 or older) case-control BC patients 	<ul style="list-style-type: none"> No difference in HDL-C between BC and control samples Pre-menopausal cases had significantly lower HDL-C levels than controls In pre-menopausal cases, each 1 mg/dL increase in HDL-C is associated with a 4% reduction in risk of BC 	(35)
Breast	<ul style="list-style-type: none"> Estimated the relative risk of breast cancer associated with HDL-C levels using serum samples of 38 823 Norwegian women aged 17–54 years at time of entry 708 BC cases identified over median follow up time of 17.2 years 	<ul style="list-style-type: none"> Low HDL-C, as part of the metabolic syndrome, is associated with increased postmenopausal BC risk 	(37)
Breast	<ul style="list-style-type: none"> Examined relationship between breast cancer and lipid profiles in Taiwanese women Lipid profiles in fasting serum of 150 BC patients before treatment and 71 healthy controls 	<ul style="list-style-type: none"> BC patients had significantly lower HDL-C and apoA-I, lower apoA-I/apoB ratios, and higher VLDL-C levels than controls Lower ApoA-1 and HDL-C levels associated with higher incidence of BC 	(38)
Breast	<ul style="list-style-type: none"> Nested case-control study from trial containing 4,690 women with extensive mammographic density Examined whether serial measures of serum lipids and lipoproteins were associated with risk of BC Measured lipids in an average of 4.2 blood samples for 279 invasive breast cancer case subjects and 558 matched control subjects 	<ul style="list-style-type: none"> HDL-C and apoA-I were positively associated with BC risk only when HRT was not used 	(60)
Endometrial	<ul style="list-style-type: none"> Case-control study nested within the European Prospective Investigation into Cancer and Nutrition (EPIC) Examined the relation between prediagnostic plasma lipids, lipoproteins, and glucose, metabolic syndrome, and EC risk in 284 women with EC and 546 matched controls 	<ul style="list-style-type: none"> HDL-C levels were inversely correlated with the risk of developing EC Metabolic abnormalities and obesity may act synergistically to increase risk of developing EC 	(39)
Prostate	<ul style="list-style-type: none"> Examined the association between serum lipids and prostate cancer risk A cohort ($n = 69,735$) of all men aged 35 years or older were selected from the Apolipoprotein MOrtality RiSk (AMORIS), Levels of TG, TC, glucose, LDL-C, HDL-C, ApoB, and ApoA-I were measured at baseline, was database 2,008 men developed prostate cancer 	<ul style="list-style-type: none"> ApoA-I and HDL levels were inversely associated with prostate cancer risk Low HDL and ApoA-I as well as increased lipid ratios are related to increased risk of prostate cancer No association between ApoB, LDL, and non-HDL with prostate cancer risk 	(43)

ApoA-I, apolipoprotein A-I; ApoA-II, apolipoprotein A-II; ApoB, apolipoprotein B; BC, breast cancer; CA125, cancer antigen 125; CTAPIII, connective tissue activating protein III; CTC, circulating tumor cells; DFS, disease-free survival; DMFS, distant-metastasis-free survival; EC, endometrial cancer; HDL-C, High-density lipoprotein cholesterol; IMRT, intensity-modulated radiation therapy; ITIH4, inter-trypsin inhibitor heavy chain H4; LDL-C, low-density lipoprotein cholesterol; OC, ovarian cancer; OS, overall survival; PCa, pancreatic cancer; SELDI-TOF-MS, surface-enhanced laser desorption/ionization time-of-flight mass spectrometry; TC, total cholesterol; TF, transferrin; TG, triglycerides; TT, truncated transthyretin; TTR, transthyretin; VLDL-C, very low-density lipoprotein cholesterol.

the particles during sample preparation (61). In addition other confounding factors such as lifestyle factors, co-morbidities, and physiological factors (i.e., pre- vs. post-menopausal women), all contributed to heterogeneity of the results since most of the analyses were done retrospectively using the existing body of publicly available clinical trial data. On the other hand, there are studies describing positive correlations between HDL-C and cancer risk, namely in breast cancers (60). However, given the high heterogeneity in HDL proteome, lipidome, and subclass distribution between patients in different disease settings, it is reasonable that such variability exists between studies. While the verdict is still out on the utility of HDL-C and ApoA-I as predictive biomarkers in cancers, there is clearly a role for HDL in this complex disease which will be discussed in more detail to follow.

Mechanism

Whether decreased levels of HDL-C are a causal or consequential factor to cancer progression is yet to be elucidated, however we are logically drawn to the latter. It is known that cancer cells, in particular prostate, adrenal, and breast cancer cells, highly express the SR-BI on their plasma membrane (62–64). Because of their high-demand for cholesterol, cancer cell upregulation of SR-BI is likely a survival mechanism to increase HDL-C recruitment and, thus, increase cholesterol uptake needed for proliferation and hormone production while consequently decreasing circulating HDL-C. That being said, this argument could also be used to explain why, in some reports, HDL-C is associated with an increased risk of cancer, as it continues to provide additional cholesterol to and fuel the growth of the tumor. Regardless, we can take away several key points from these findings: (i) SR-BI is overexpressed in cancer cells, (ii) HDL-C levels are significantly affected by the presence and development of cancer, and (iii) the high affinity between SR-BI and HDL facilitates the transport of cholesterol to/from HDL and the cancer cell. In addition, HDL is known to have potent antioxidant activity and both endogenous and reconstituted HDL particles were shown to inhibit oxidative-stress induced proliferation of pancreatic cells *in vitro* (65). And although the details of the epidemiology can be disputed, there are clear opportunities for therapeutic intervention by utilizing the HDL/SR-BI axis, of which will be discussed below.

SYNTHETIC HDL PRODUCTS

As previously mentioned, the main focus of HDL research over the past several decades has been surrounding its role in cardiovascular disease. Because of its role in facilitating RCT, several “HDL mimetics” have been developed and tested clinically in humans for their ability to reduce the burden of atherosclerosis and number of events following an acute coronary event (66–69). These HDL-mimicking particles, termed reconstituted HDL (rHDL) or synthetic HDL (sHDL), are cholesterol-free HDL particles prepared from plasma purified or recombinantly expressed ApoA-I or short synthetic ApoA-I mimetic peptides complexed with phospholipids. Since they

lack cholesterol, these “empty” particles are highly effective in effluxing cholesterol from lipid-laden cells both *in vitro* and *in vivo* (9, 70, 71). In addition to their augmented efflux capacity, these particles offer a natural ability to target SR-BI-expressing cells. When combined, the ability of rHDL/sHDL to deplete cellular cholesterol, target SR-BI expressing cells, along with the biocompatibility of the individual components and proven clinical safety make the application of sHDL for cancer therapy increasingly attractive.

Clinically Tested sHDL Products

The concept of utilizing sHDL and ApoA-I mimetic peptides as a cholesterol depletion therapy has been around for decades, but focused primarily in the context of cardiovascular diseases. In fact, several sHDL therapies have been developed and tested in various stages of human clinical trials (66, 69, 72). The purpose of such sHDL infusion therapies was to efflux cholesterol and reduce plaque size and vulnerability following an initial coronary event, in order to decrease the occurrence of secondary events. Early sHDL clinical trials utilized lipid-free ApoA-I protein or mimetic peptides, such as ApoA-I milano, D-4F, and L-4F, however it was shown that the naked proteins and peptides themselves had a very short plasma half-life, and their pharmacological effect suffered as a consequence (73, 74). Formulation of peptide or full-length ApoA-I protein with phospholipid, forming sHDL, was shown to markedly improve plasma half-life and thus its overall therapeutic effect (75). Moreover, studies have shown that the phospholipid component of sHDL therapies is a driving determinant of the overall pharmacokinetic and pharmacodynamic effect (71).

Measurable improvements in the pharmacokinetic and pharmacodynamic effects of sHDL therapies has led to their progression from bench to bedside in both early and late stage clinical trials. Such sHDL products include peptide-based sHDLs, including ETC-642 (22A peptide/dipalmitoylphosphatidylcholine/sphingomyelin), and ApoA-I protein based sHDLs, including ETC-216 (recombinant ApoA-I/palmitoylphosphatidylcholine) and CER-001 (recombinant ApoA-I/sphingomyelin/dipalmitoylphosphatidylglycerol), among others. These products were all shown to be safe at high doses of up to 100 mg/kg in humans and possess potent cholesterol efflux abilities (76, 77). More recently CSL-112, reconstituted ApoA-I/soybean phosphatidylcholine, has advanced to a 17,000 patient Phase III clinical trial after showing promising ability to reduce atheroma burden and decrease secondary coronary events in earlier trials (78–80). Given their proven clinical safety and ability to facilitate cholesterol removal, sHDL products could be easily translated for use as cholesterol depleting therapies in cancer.

SHDL FOR CANCER THERAPY

Cholesterol Depletion

Given the dependence of endocrine cancers on cholesterol, cholesterol-targeting therapies have gained increasing attention.

TABLE 2 | Experimental studies utilizing HDL for endocrine cancer therapy.

Cancer	Treatment	Model	Major findings	References
Ovarian	<ul style="list-style-type: none"> L-4F peptide or sc-4F ctrl - 10 mg/kg/day S.Q. for 5 wks, starting either the day of ID8 cell injection or 2 wks post-ID8 injection L-5F peptide - 10 mg/kg/day S.Q. for 5 wks (for S.Q. tumors) or 9 wks (for I.P. tumors) Compared to buffer treated control mice D-4F peptide - 300 µg/mL (129.8 µM) in drinking water, starting immediately post-ID8 injection - Compared to normal drinking water 	<ul style="list-style-type: none"> Female C57BL/6/J mice, 9 wk old ID8 cells given: <ul style="list-style-type: none"> - S.Q. (5 wk flank tumor model) - I.P. (9 wk tumor model) 	<ul style="list-style-type: none"> L-4F: <ul style="list-style-type: none"> - Smaller flank tumor volumes when given both immediately following or 2 wks post-ID8 injection (5 wk S.Q. tumor model) L-5F: <ul style="list-style-type: none"> - Flank tumor size decreased (5 wk S.Q. tumor model) - Number of tumor nodules decreased (9 wk I.P. tumor model) D-4F: <ul style="list-style-type: none"> - Smaller flank tumor volume (5 wk S.Q. tumor model) - Fewer number of tumor nodules (9 wk I.P. tumor model) 	(86)
Ovarian	<ul style="list-style-type: none"> L-5F peptide - 10 mg/kg/day S.Q. for 5 wks, starting immediately after ID8 cell injections 	<ul style="list-style-type: none"> Female C57BL/6 mice ID8 cells injected S.Q. 	<ul style="list-style-type: none"> Decreased the number of perfused vessels within tumors Decreased size of total vessels within tumor Decreased VEGF levels in both serum and tumor tissue 	(87)
Ovarian	<ul style="list-style-type: none"> L-4F peptide - 10 mg/kg/day S.Q. for 3 wks, starting 2 weeks post-ID8 injection - Compared to sc-4F peptide treated mice 	<ul style="list-style-type: none"> Female C57BL/6 mice, 9 wk old ID8 cells injected S.Q. 	<ul style="list-style-type: none"> Decreased expression and activity of HIF-1α in tumors Reduced the number of vessels and overall angiogenesis within tumors 	(88)
Breast	<ul style="list-style-type: none"> L-4F peptide 10 mg/kg S.Q. daily from weaning to 45 days, and 3x per wk until 19 wks of age 	<ul style="list-style-type: none"> Mammary PyMT transgenic mice 	<ul style="list-style-type: none"> Significantly increased tumor latency and inhibited tumor development Decreased plasma levels of oxLDL 	(89)
Pancreatic	<ul style="list-style-type: none"> L-4F peptide - 10 mg/kg/day I.P. for 1 week, starting immediately post-H7 injection - Compared to sc-4F peptide treated mice 	<ul style="list-style-type: none"> Female C57BL/6 mice, 6–8 w/o H7 cells injected directly into pancreas 	<ul style="list-style-type: none"> Reduced tumor size and weight Reduced number of inflammatory tumor infiltrating cells, including Th17 and Th1 lymphocytes Decreased mRNA expression of inflammatory cytokines in tumors Decreased % of M2 macrophage polarization in tumors 	(90)

D-4F, D-amino acid version of L-4F; I.P., intraperitoneal; L-4F, DWFKAFYDKVAEKFKAEAF; L-5F, DWLKAIFYDKVFEKFKEFF; oxLDL, oxidized low-density lipoprotein; PyMT, mammary tumor virus-polyoma middle T-antigen; sc-4F, scrambled-4F peptide; S.Q., subcutaneous; Th1, T-helper cell 1; Th17, T-helper cell 17; VEGF, vascular endothelial growth factor; wk, week.

One approach is to directly deplete cholesterol from cells using cholesterol scavenging therapies. In addition to cholesterol being essential for the formation of new membranes during cell division, it is also vital for the formation of lipid rafts in the plasma membrane. These lipid rafts are rich in cholesterol and sphingolipids and house many proteins and transporters involved in key signaling pathways, including the Akt signaling pathway implicated in the migration, proliferation, and survival of cancer cells (81). By depleting cholesterol from cells, lipid rafts are disrupted and the proteins they house internalized, drastically reducing the cell's ability to carry out its functions and often triggering cell death (4). In cancer cell lines, treatment with cyclodextrins induced marked cell death, and that cells with a higher abundance of lipid rafts were more susceptible to such treatments (82–84). More recently, Taylor et al. showed that HAC15 adrenal carcinoma cells treated with ETC-642, a clinically tested sHDL, displayed

marked reduction in cellular cholesterol levels in addition to inhibition of aldosterone, cortisol, and androstenedione production (85). Thus, the application of cholesterol-depleting therapies, namely sHDL, for endocrine cancer deserves further investigation.

sHDL Peptides

Several recent studies have investigated the use of HDL-mimetics, including sHDL, ApoA-I protein, and ApoA-I mimetic peptides, for cancer treatment, outlined in **Table 2**. In addition, treatment of cells with both sHDL and chemotherapeutic drugs was able to reduce the overall effective dose (91). Other studies utilizing ApoA-I protein or mimetic peptides L-4F, L-5F, and D-4F have shown that treatment of tumor-bearing mice with either protein or peptide can reduce both tumor volume and angiogenesis in tumor tissues when compared to control mice (87–90, 92–94). For example, in a mouse model of ovarian cancer, Gao et al.

show that L-4F peptide, when administered subcutaneously at 10 mg/kg/day for 3 weeks, could reduce overall angiogenesis and vessel number within the tumor tissue, which was connected to a decrease in expression levels of hypoxia inducible factor-1 α (HIF-1 α) (88). In a similar study, they also show that L-5F peptide could exert similar anti-angiogenesis effects and led to decreased levels of serum vascular endothelial growth factor (VEGF) (87). In a separate study utilizing a similar ovarian cancer mouse model, Su et. al. demonstrated that both L-4F and L-5F peptides could decrease the overall volume of tumors in both flank and intraperitoneal tumors when given 10 mg/kg/day over the course of 5 or 9 weeks, respectively (86). They postulate that the antitumorogenic effect could be related to peptides' abilities to reduce circulating levels of LPA, and they were found to have significantly greater binding affinity for LPA when compared to full length ApoA-I protein. In a study by Peng et. al. L-4F peptide given at 10 mg/kg/day for 1 week was able to not only reduce size and weight of H7 pancreatic tumors in mice, but also significantly reduce several markers of inflammation within the tissue as well (90).

While the above studies also included extensive screening of ApoA-I and mimetic peptides for viability and anti-proliferative activity in a broad range of cancer cell lines *in vitro*, there are also reports describing the ability of HDL to induce proliferation, migration, and survival in cancer cell cultures (32, 33, 95, 96). Consistent with previously mentioned clinical findings showing a positive association between HDL-C and cancer risk, these studies support the notion that HDL-C may promote the progression of cancer by supplying the tumor cells with their increasing demand for cholesterol. However, a distinction should be made between the epidemiology of HDL and cancer and the utility of HDL in cancer treatment: namely, that the use of HDL in cancer therapy referred to in this review involves the administration of "empty" cholesterol-free particles. These particles are the nascent, discoidal HDL particles with high cholesterol efflux activity as proven both in basic and clinical research. Of course, studies utilizing plasma purified HDLs should be considered differently. Plasma HDLs contain a variety of different components, including signaling lipids responsible for many of HDLs pro-angiogenic and Akt-activating properties (22, 97), and namely cholesterol capable of being delivered to cells (98, 99). While such studies are integral to understanding the role of endogenous HDL in cancer pathogenesis, they should not be confused with therapeutic implications utilizing sHDL or mimetic peptides with a defined molecular makeup and superior cholesterol efflux capacity.

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Targeted Drug Delivery

Given the very poor solubility of many chemotherapeutic drugs, the hydrophobic lipid core of HDL presents an attractive environment and alternative strategy for delivery and formulation of this class of drugs. Not only is it possible to lower the overall dose of drug given by improving its solubility, but the SR-BI targeting ability of these sHDL nanoparticles affords the additional benefit of site-specific, cytosolic drug delivery to SR-BI over-expressing tumor cells while subsequently reducing systemic toxicity (72, 94, 100). Others have, with varying success, shown anti-tumorogenic by introducing HDL surface modifications to augment the targeting capacity and to extend particle half-life (101). The use of HDL-mimetics for targeted drug delivery has been extensively reviewed elsewhere (72, 102) and is beyond the scope of this review, however, its importance and growing relevance warrant mentioning.

SUMMARY AND PERSPECTIVE

Decades of epidemiological evidence suggests that, notably -C, plays a role in the incidence and progression of cancer. Whether or not this role is causal or consequential, or whether the risk association is positive or negative under specific conditions is still left for debate. Despite, we know from years of clinical and basic cardiovascular research that is an intimate player in the RCT process and has specific and potent cholesterol efflux ability both *in vitro* and *in vivo*. We also know that cholesterol is a vital resource for cancer cells, which require a constant supply to maintain and facilitate their rapid proliferation and overall survival. Endocrine cancers, in particular, are at an increased demand for cholesterol given their additional need for steroid production making them even more susceptible to cholesterol depletion interventions and targeting by due to upregulation of SR-BI.

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All authors listed have made a substantial, direct and intellectual contribution to the work, and approved it for publication.

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Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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