LDL, HDL and endocrine-related cancer: From pathogenic mechanisms to therapies

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Abstract:

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1. Introduction

Cholesterol plays a critical role in cancer progression by enhancing cell proliferation, migration, and invasion [1]. Endocrine-related cancers include those affecting the hormone secreting tissues, such as the adrenal, pancreatic, thyroid, and reproductive tissues, but also the main endocrine target tissues [4] such as the breast and prostate.

Intestinal cholesterol absorption is highly variable, but on average only 30% of serum cholesterol in humans derive from the diet in humans [5,6]. All endocrine cells can synthesize their own cholesterol, but circulating cholesterol is primarily synthesized in the liver and is mainly transported to cells through low-density lipoproteins (LDL) [6]. Indeed, circulating cholesterol balance is mainly determined by the hepatic synthetic rate of cholesterol and th rate of excretion from the body, either as cholesterol or bile [5,6].

Intracellular cholesterol homeostasis is tightly regulated in most cell types (MACROFAGOS NO) [7]. Acetyl-CoA is the major precursor of cholesterol synthesis, producing hydroxyl methylglutaryl-CoA (HMG-CoA). The rate limiting step in the cholesterol biosynthetic pathway is the reduction of HMG-CoA to mevalonate reaction catalyzed by the enzyme HMG-CoA reductase (HMGCR). Alternatively, cells may increase exogenous cholesterol uptake by upregulating the LDL receptor (LDLR) and other lipoprotein receptors, such as LDLR-related protein 1 (LRP1) and scavenger receptor type BI (SR-BI). A reduction of endoplasmic reticulum cholesterol levels triggers the translocation of the transcriptional factor sterol regulatory element–binding protein-2 (SREBP-2) to the nucleus, thereby iincresing expression of t HMGCR and and LDLR expression, promoting both cholesterol biosynthesis and uptake [8]. Conversely, intracellular cholesterol accumulation inactivates the SREBP-2 pathway. Excess of intracellular unesterified cholesterol can be accumulated as cholesterol esters, mainly by the action of acyl-coenzyme A: cholesterol acyltransferase (ACAT) 1

High-density lipoprotein (HDL) is the main lipoprotein cholesterol transporter to the major steroidogenic organs. The adrenal and ovary preferentially take up cholesterol from HDL via the SR-BI [9]. In contrast, the interaction between HDL and the membrane ATP-binding cassette transporter (ABC) A1 has a key role in HDL-mediated

efflux of cellular unesterified cholesterol. Some functional oxysterols, such as 24-hydroxycholesterol (HC), 25-HC, or 27-HC, are significant activators of liver X receptors (LXRαβ ¡¿¿Y LRX ALFA’??) which can upregulate ABCA1, but also repress LDLR pathway [10,11]. Furthermore, HDL, mainly through apolipoprotein (APO) A1 and paraoxonase (PON) 1, exhibit potent antioxidant and anti-inflammatory properties, thus potentially antagonizing two main hallmarks of cancer progression (reviewed in [12,13]).

In this article, we aimed to review the progress to date in the studyof e LDL and HDL on intracellular cholesterol homeostasis impacting carcinogenic pathways in endocrine-related cancers. For this analysis, PubMed was searched comprehensively with combinations of the keyword breast, prostate, thyroid, pancreatic, ovarian, testicular, and adrenal cancer and the rest of keywords related with intracellular cholesterol, LDL, and HDL, as well as those with statins, ezetimibe, proprotein convertase subtilisin/kexin 9 (PCSK9), fibrates, niacin, cholesterol ester transfer protein (CETP) and cancer.

2. Breast cancer

Breast cancer was the third most common cancer worldwide in 2016. About 1.7 million incident cases were estimated, increasing by 29% between 2006 and 2016. Moreover, breast cancer was the fifth leading cause of cancer deaths , and the leading cause of cancer death for women. Concretely, it is estimated that 1 in 20 women developed breast cancer over their lifetime [14].

Breast cancer is a complex disease which includes a variety of entities with differences in clinical, morphological, and molecular attributes. Taking into account the expression of estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2), breast cancers can be classified for predicting prognosis and response to treatment [15]. The presence or absence of these biomarkers identifies the three main sub-types of breast cancer: luminal (ER-positive), HER2-like (mainly ER-negative and HER2-positive), and basal-like (mainly ER-negative, PR-negative, and HER2-negative, also known as triple-negative) [16]. The two last sub-types are the most aggressive [17].

2.1. Cholesterol and breast cancer

Some studies have been published studying the relationship between total serum cholesterol levels and risk of breast cancer, despite reporting divergent results. A large prospective study performed in Korea found that high total cholesterol (≥ 240 mg/dL) was positively associated with breast cancer in women compared with low cholesterol levels (< 160 mg/dL) [18]. In contrast, total cholesterol was found inversely associated with breast cancer risk in a French cohort [19], and other studies failed in finding association [20–24]. These discrepancies may be due to differences in the impact of cholesterol on the breast cancer sub-types, although this possibility needs further research [25]. Moreover, dietary cholesterol intake was found positively associated with the risk of postmenopausal breast cancer in a Canadian case-control study [26], results that were corroborated by a meta-analysis, which reported that a cholesterol intake greater than 370 mg/day increased the risk of breast cancer [27].

The pathogenic role of cholesterol in breast cancer has also been investigated in different experimental mouse models. In this sense, MMTV-PyMT mice fed a high-fat/high-cholesterol (HFHC) diet showed accelerated and enhanced tumor progression

[28]. These mice are transgenic for the viral polyoma middle-T (PyMT) antigen under the control of the murine mammary tumor virus (MMTV) promoter, that specifically directs expression to the mammary epithelium, and are a model of luminal ER-positive breast cancer [29]. Similarly, HFHC diet administration to immunodeficient mice implanted orthotopically with the triple-negative breast cancer cells MDA-MB-231 induced angiogenesis and accelerated breast tumor growth [30]. The effects of hypercholesterolemia on mammary tumor growth and metastasis were also explored in APOE knockout mice, which exhibit marked dyslipidemia with elevated cholesterol remnant lipoproteins. APOE knockout mice were fed HFHC diet and injected with non-metastatic Met-1 and metastatic Mvt-1 mammary cancer cells obtained from PyMT mice and c-Myc/VEGF tumor explants, respectively. Results showed that APOE knockout mice displayed increased tumor growth only when the HFHC diet was administered, not in standard chow diet, thereby indicating that high dietary fat and cholesterol are necessary to promote tumorigenesis. Moreover, these mice exhibited a greater number of pulmonary metastases [31]. Finally, two studies evaluated the effects of a high-cholesterol diet, in order to specific address the effects of cholesterol, without the interference of high saturated fat, in breast cancer development. PyMT mice developed palpable tumors earlier when fed a high-cholesterol diet compared to those fed a chow diet [32]. Similarly, high-cholesterol diet promoted breast tumor growth in xenograft models of breast cancer, which presented lung metastases more frequently [33]. Overall, these studies revealed that HFHC diet had deleterious effects in breast cancer development, at least in part attributed to its high-cholesterol content.

2.2. LDL and breast cancer

LDL cholesterol (LDL-C) levels, at diagnosis of breast cancer, were found as a prognostic factor of breast tumor progression in a prospective study in Portugal. In this sense, patients with higher levels of LDL-C at diagnosis had larger tumors, with higher differentiation and proliferative rate, and with more frequent HER2-like phenotype [34]. A Mendelian randomization study showed that genetically raised LDL-C was associated with higher risk of breast cancer, and specifically ER-positive breast cancer [35]. However, no association was found between LDL-C and breast cancer risk in another Mendelian randomization analysis [36], or in other meta-analyses and

prospective studies [21,37–40]. In contrast, two studies found that LDL-C or non-HDL-cholesterol were inversely associated with the risk of breast cancer [20,41].

The impact of LDL-C on breast cancer cells is divergent depending on their expression of the main lipoprotein receptors. LDL-C promoted proliferation [42–44] and migration [33,45], mainly in ER-negative cell lines, but not in ER-positive cells. LDL-C also induced proliferation in the HER2-positive cell line BT-474 [33]. These differences may be explained by the increased LDL-C internalization and esterification in HER2-like or triple-negative cells, as they presented with increased expression of *LDLR* and increased expression and activity of ACAT1 [43,46].

A recent study reported that the treatment of mouse breast cancer 4T1 cells with LDL increased the levels of reactive oxygen species (ROS), which in turn, induced cell migration. These effects were counteracted by the addition of an inhibitor of xanthine oxidase, an enzyme that generates ROS [47]. Similarly, mice that exhibited high LDL-C levels due to a HFHC diet which were injected with these cells showed increased tumor growth and metastasis compared to that fed with chow diet, and both were markedly inhibited by xanthine oxidase inhibition, mainly through ERK signaling pathway inhibition [47].

Beyond LDL-C levels, the enhanced production of oxidized LDL (oxLDL) is a common feature of both dyslipidemia and carcinogenesis. Patients with breast cancer showed increased serum levels of oxLDL, and circulating levels of oxLDL were positively associated with breast cancer risk [48]. The uptake of oxLDL is also increased in breast cancer, as the lectin-like oxLDL receptor 1 (OLR1) is overexpressed in breast cancer tissue [49], as well as in the breast cancer cell line HCC1143 compared to the NO SE PORQUE DICES NORMAL, NO ES TUMORAL? mammary epithelial cell line MCF10A [50]. In line with these results, upregulation of *OLR1* in breast cancer cell lines enhanced cell migration [50,51]. Moreover, ORL1 depletion or inhibition significantly repressed the invasion and migration of breast cancer cells [50–52]. One of the mechanisms by which oxLDL promotes breast carcinogenesis could be the stimulation of miR-21 and the consequent activation of the PI3K/Akt pathway, as was described in MCF10A cells treated with oxLDL [53]. Further oxLDL and OLR1 activate the inflammatory pathway through the nuclear factor κB (NF-κB), leading to

transformation [54]. Accordingly, forced overexpression of *OLR1* resulted in upregulation of NF-κB and target pro-oncogenes involved in apoptosis inhibition and cell cycle regulation in both HCC1143 and MCF10A cells [50]. Moreover, *TBC1D3*, a hominoid-specific oncogene, induced the expression of *OLR1* in breast cancer cells, regulated by NF-κB signaling [52]. Therefore, *OLR1* may act as an oncogene by activation of NF-κB target genes responsible for proliferation, migration, and apoptosis inhibition [50].

2.2. HDL and breast cancer

Controversy also exists about the association between HDL-cholesterol (HDL-C) levels and breast cancer risk. Two different Mendelian randomization studies found that genetically raised HDL-C increased the risk of breast cancer [35,36]. Conversely, a prospective study found that HDL-C levels were inversely associated with breast cancer risk [19]. In line with these findings, a retrospective study reported that low HDL-C levels were significantly associated with worse overall survival in breast cancer patients [55]. Other studies found the same association taking into account the menopausal status; some found that low HDL-C among premenopausal women increased breast cancer risk [37,56,57], whereas others found the same association only in postmenopausal women [21,58]. Finally, some studies did not find association between HDL-C and breast cancer risk [38,39,59] or survival [59]. Some *in vitro* analyses supported the positive association of HDL-C in breast cancer risk, as HDL increased proliferation in breast cancer cell lines [44,60], and stimulated migration through the Akt and ERK1/2 signal transduction pathways [61]. In contrast, the protective role of HDL in breast cancer can be attributed to some of their components, *e.g.* PON1 or APOA1, which possess antioxidant and anti-inflammatory properties. PON1 activity was found lower in patients with breast cancer compared to controls [62–64]. PON1 activity was found unchanged between metastatic and non-metastatic cancer patients [62], but it was found lower in patients who needed neoadjuvant chemotherapy [64]. Moreover, genetic polymorphisms in the antioxidant enzyme PON1 could influence individual susceptibility to breast cancer. In the case of Q192R polymorphism, QQ homozygotes had higher risk of the breast disease [63,65,66]. These effects could be due to the differences in the activity of the Q and R alleles toward some substrates [67]. However, other studies did not find association between Q192R genotypes and breast cancer risk [68–71]. Concerning L55M polymorphism, carriers of at least one M allele

had increased risk for breast cancer [65,66,68–72], probably due to the lower levels of mRNA and activity of the PON1-55M isoform compared to the 55L isoform [67]. Therefore, L55M polymorphism could be considered as a molecular biomarker to identify susceptible women to breast cancer. On the other hand, APOA1 levels were found inversely associated with breast cancer risk [19,73,74]. However, human APOA1 transgenic mice with increased APOA1-containing HDL was not able to delay or reduce breast tumor development in PyMT mice despite reducing oxLDL levels [75]. This point could be related with the large cholesterol-containing HDL particles of PyMT mice expressing human APOA1 [75]; they could constitute an extra cholesterol source for the tumor. In contrast, APOA2 (which possesses proinflammatory actions and decreased capacity to protect against LDL oxidation) overexpression increased breast tumor burden in PyMT mice [76]. *In vitro* experiments have demonstrated that overexpression of APOA1 in breast cancer cells increased the aggressive potential of the ER-positive MCF-7 cells, while decreased the aggressiveness of the triple-negative cell line MDA-MBA-231. In this way, overexpression of APOA1 decreased proliferation and migration in MDA-MBA-231 cells, accompanied by increased *ABCA1* levels and increased transfer of cholesterol to the plasma membrane. The opposite effects were observed in MCF-7 cells, in which the transfer to the plasma membrane seemed to be inefficient, thereby leading to intracellular accumulation of free-cholesterol [77].

Women with type 2 diabetes mellitus (T2DM) have an increased risk of developing breast cancer [78,79]. This association between T2DM and breast cancer could be attributed, at least in part, to the formation of functionally deficient HDL particles in T2DM, which involves glycation and oxidation of APOs and other HDL-components of HDL [80]. Accordingly, HDL from T2DM patients (and also glycated and oxidized HDL particles produced *in vitro*) promoted cell proliferation, migration, and invasion of breast cancer cells through the Akt/ERK pathway [81]. When breast cancer cells were pre-treated with these modified HDLs and injected into mice, a promotion of pulmonary and hepatic metastasis was found compared to cells pre-treated with normal HDL [82]. Moreover, these pre-treated breast cancer cells also showed increased adhesion to human umbilical vein endothelial cells (HUVEC) and extracellular matrix *in vitro*, mainly due to elevated protein kinase C (PKC) activity and integrin secretion, which are vital in promoting breast cancer cell metastasis [82]. Similarly, HDL isolated from

breast cancer patients complicated with T2DM promoted breast cancer cells adhesion to HUVECs by activating PKC, which in turn stimulated the expression of intercellular adhesion molecule 1 (ICAM-1) and vascular cell adhesion molecule 1 (VCAM-1), compared to HDL isolated from healthy or breast cancer patients. Thus, HDL from breast cancer and T2DM subjects can elevate the levels of ICAM-1 and VCAM-1 in cells in circulation, but not within the tumor tissue, contributing to metastasis [83].

2.4. Intracellular cholesterol metabolism and breast carcinogenesis

In order to supply the augmented need of cholesterol, proliferating breast cancer cells can increase cholesterol uptake from the circulation. In this way, both *LDLR* and *SCARB1* expression, which codifies SR-BI, were found upregulated in breast cancer tissue, which could (ATENCIÓN A INFERIR FUNCIONES A PARTIR DE DATOS DE RNAm) increase the uptake of LDL-C and HDL-C from the bloodstream, respectively [84,85]. As indicated above, tumors with higher LDLR (SI ES RNA VA EN ITALICAS) expression were HER2-like and triple-negative, had higher histological grades, Ki-67 expression, and tumor necrosis [46,86], and high LDLR expression was associated with decreased recurrence-free survival, particularly in patients treated with systemic therapies [87]. Similarly, high SR-BI expression was associated to tumor aggressiveness and poor prognosis in breast cancer [46,86,88,89]. SR-BI expression was upregulated concomitantly with the increase in the number and the size of the tumors in PyMT mice fed a HFHC diet [28]. Moreover, *in vitro* knockdown of SR-BI in breast cancer cells inhibited proliferation and migration, as well as decreased tumor burden when injected to mice, effects that were associated with a reduction of Akt and ERK1/2 activation [61].

In contrast, loss of ABCA1 protein expression was found associated with a more aggressive phenotype in human breast cancer patients [90], which was in accordance with the notion that ABCA1 exerts antitumor effects by preventing the accumulation of free cholesterol in cancer cells, inhibiting the release of tumor necrosis factor progression [91]. However, in a recent report, the expression of ABCA1 in triple-negative breast cancer was found higher than in non-cancerous mammary tissue, whereas ABCG1 levels were not differentially expressed [92]. These discrepancies could be explained by a study that found that ER-positive cells were more sensitive to

LXR induced G0/G1 arrest than ER-negative cells, but that LXR stimulation led to higher induction of *ABCA1* in ER-negative than in ER-positive cells [93].

Apart from bloodstream uptake, cells can obtain cholesterol by *de novo* biosynthesis. This pathway was found increased in cancer stem cells derived from ER-negative breast cancers, which exhibit resistance to conventional therapy. Moreover, increased cholesterol biosynthesis showed correlation with shorter relapse-free survival in a large breast cancer cohort [94].

Once inside the cell, cholesterol can be esterified or metabolized. One of the most prevalent oxysterols is 27-HC, generated by sterol 27-hydroxylase CYP27A1, and catabolized by oxysterol 7α-hydroxylase CYP7B1 [95]. 27-HC was increased in human breast cancer tissue, concomitant with *CYP7B1* downregulation, whereas *CYP27A1* remained unchanged [96]. Furthermore, *CYP7B1* gene (UP-REGULATION??) expression was found to correlate with better survival [96], whereas CYP27A1 protein expression was increased in higher grade tumors [32]. *In vivo*, 27-HC increased tumor growth in murine or human cancer cell xenografts and in PyMT mice, in which 27-HC also hastened metastasis to the lungs, an effect that implicated LXR activation [32,96]. Moreover, 27-HC was found to stimulate the proliferation of ER-positive MCF-7 cells, but not that of ER-negative cells, associated with increased protein levels of the E3 ubiquitin protein ligase mouse double minute 2 (MDM2) and decreased levels of the tumor suppressor protein p53 [97]. It was also found to activate Myc (a critical oncoprotein that can promote the proliferation, migration and invasion of cancer cells) by increasing its protein stability [98]. 27-HC also induced angiogenesis by enhancing the expression of vascular endothelial growth factor (VEGF) by the classical ERα/VEGF signaling pathway in ER-positive breast cancer cells, or by promoting the generation of ROS, which in turn activated the signal transducer and activator of transcription (STAT)3/VEGF signaling in an ER independent manner [99]. Moreover, 27-HC induced epithelial-mesenchymal transition (EMT) by decreasing the expression of E-cadherin and β-catenin [100], and by increasing the phosphorylation of STAT3, that in turn promoted *MMP9* expression [101]. Tumor associated macrophages (TAMs) are the main source for local 27-HC production in breast tissues, and the hypermethylation of the *CYP7B1* promoter in breast cancer cells further attenuates de degradation of 27-HC, resulting in its accumulation in tumor tissue [102]. The elevated

27-HC levels, a part from inducing cell proliferation and migration, increased the secretion of chemokines such as CCL2, CCL3, and CCL4 from TAMs, which further attract monocytes to tumor sites, and can be polarized to M2 type macrophages, which woud further produce 27-HC [102].

Collectively, these results indicate that targeting cholesterol uptake and conversion to 27-HC could be a good strategy for the treatment of breast cancer patients. A summary of the main lipoprotein-mediated uptake and cholesterol-related downstream pathways and their effects on oncogenic signaling pathways in breast cancer cells is shown in **Figure 1A**.

3. Prostate cancer

Prostate cancer is the most commonly diagnosed cancer in men older than 50 years of age and more than 98% have a glandular origin. Nevertheless, the anatomopathological studies conducted in autopsies have also revealed their presence in men younger than 30 years of age, without previous symptomatology, suggesting that these tumors are able to have a slow growth. In 2018, this disease represented the 7.1 % of all cancers diagnosed in men, causing the 3.8% of all deaths, being in this sex the second most common cause of cancer-related mortality in developed countries after lung cancer [103]. SIMPLISTA The main biomarker for the prostate tumors screening is prostate-specific antigen (PSA) serum level. PSA serum levels above 4.0 ng/mL represents a suspicion of neoplasia. However, this marker alone is not enough for diagnosis of prostate cancer, because the false-negative and also false-positive test results are frequent [104]. The degree of malignancy of the tumor is determined by the Gleason Score, based on histological analysis, thereby grading the prostate cancer from low-grade (score 6) to high-grade cancers (8 to 10 score) [105].

3.1. Cholesterol and prostate cancer

Some evidence indicates that high serum levels of cholesterol are associated with the risk of developing aggressive prostate cancer, thus indicating that hypercholesterolemia could be a critical factor for prostate cancer progression. A large prospective study conducted in Korean adults, with a follow up to 14 years, showed that plasma cholesterol levels were positively associated with the risk of prostate cancer, particularly when individuals with total cholesterol levels ≥ 240 mg/dL) werecompared with those with < 160 mg/dL [18]. In line with these findings, a prospective trial reported that men with cholesterol levels < 200 mg/dL had a lower risk of high-grade prostate cancer [106]. However, higher total cholesterol levels were associated with increased short-term prostate cancer risk but an inverse risk association was observed with 20-year lag time [107].

Two meta-analysis did not find association of serum cholesterol levels with the risk of prostate cancer [108] or with prostate cancer recurrence after radical prostatectomy [109]. Similarly, the Swedish “Apolipoprotein MOrtality RISk” (AMORIS) prospective study did not provide evidence for an association between serum total cholesterol and prostate cancer risk [110].The REDUCE randomized trial conducted in men that

presented elevated PSA and a negative baseline biopsy, did not demonstrate that the total cholesterol levels were related to either overall or low-grade prostate cancer risk. However, the stratification of the patients with high total serum cholesterol showed positive association with the increase risk of high-grade prostate cancer diagnosis [111]. Overall, these findings do not convincingly support the association between high serum cholesterol levels and prostate cancer risk.

Some epidemiological studies showed that Western diets with an excess of saturated fat and cholesterol promoted prostate cancer development in association with increased androgens levels [112,113]; however but the role of dietary cholesterol is unclear. Several preclinical models have assessed the effects of dietary cholesterol in the development of prostate cancer. A HFHC diet promoted tumor growth and intratumoral levels of testosterone in xenograft mice bearing LNCaP, androgen-dependent human prostate cancer cells. These results suggested that the diet-induced increase in tumor androgen concentrations is due to *de novo* synthesis from exogenous cholesterol [114]. Interestingly, intra-epithelial neoplasia was also enhanced by the HFHC diet in C57BL/6:129Sv mice, but this increase was dependent on the accumulation of cholesterol in the prostatic gland under LXRαβ deficient conditions [115]. It is noteworthy that these dietary interventions used distinct high saturated fat diets and do not allow to determine a direct, independent effect of the cholesterol content. Therefore, the translation of these experimental results into humans could not be anticipated [116]. Rather surprisingly, a large Canadian population-based case-control study found an inverse association between dietary cholesterol intake and the risk of prostate cancer [26]. Also, cholesterol intake was not associated with prostate cancer risk in another case-control study conducted in Italy [117], suggesting that higher cholesterol intake *per se* does not increase prostate cancer in humans.

3.2. LDL and prostate cancer

Few epidemiological studies investigated the association between LDL-C and malignant prostate disease or with their aggressiveness, but results were contradictory. Several studies did not support the association between LDL-C and the risk of aggressive prostate cancer, as reported in a meta-analysis of 14 prospective studies that failed to show association between risk of prostate cancer and blood levels of LDL-C [108].

Furthermore, data from a French prospective study with a follow-up time of 11.5 years did not show association between the prostate cancer risk and serum concentrations of LDL-C or APOB100, HDL-C or APOA1 [19], similarly than a nested case-control study conducted in U.S. with a follow-up of 2-years [118]. In contrast, another prospective study from the Netherlands showed that LDL-C levels were associated with an increased risk of prostate cancer, and also with its aggressive behavior [119]. Interestingly, a large Mendelian randomization study found a weak evidence that higher-C LDL levels increase aggressive prostate cancer risk [120]. These divergent results may be explained by the heterogeneity in the approaches used and the large differences on follow-up of these studies.

Other experimental approaches showed increased proliferative effect of LDL on different cancer prostatic cell lines, compared with that of normal prostate cells. These findings were concomitant with an upregulation of HMGCR, whereas ABCA1 was downregulated [121]. The LDL-mediated effects on proliferation of prostate cancer cells were induced by PTEN loss and activation of the Akt and ERK signaling pathways, which in turn upregulate LDLR [122].

Some studies pointed out to oxLDL, and its main receptor OLR1, in prostate cancer. In this way, oxLDL levels were found to correlate with prostate cancer stage, and *OLR1* expression correlated with lymph node metastasis [123]. oxLDL levels were increased in benign prostatic hyperplasia, but not in prostate cancer patients of another small cohort [124]. *OLR1* was also overexpressed in prostate adenocarcinomas and inassociation with high Gleason score [125]. *In vitro*, oxLDL stimulated proliferation, migration, and invasion of prostate cancer cells, in part by promoting β-catenin, cMyc, NF-κB, STAT1, and STAT3 signaling pathways [123]. OLR1 was also found overexpressed in prostate cancer cell lines, and its activation by oxLDL promoted EMT by increasing mesenchymal markers (vimentin, N-cadherin, snail, slug, MMP2, and MMP9) and reducing epithelial markers (E-cadherin and plakoglobin) [125]. OLR1 silencing in prostate cancer cells exhibited lower tumorigenic potential in a xenograft mouse model [125]. These data indicates that both oxLDL and OLR1 are major determinants of accelerated prostate tumor progression and metastatis.

3.3. HDL and prostate cancer

A randomized, controlled trial in men with elevated PSA and a negative baseline biopsy found that elevated serum HDL-C was associated with increased risk of both overall and high-grade prostate cancer [111]. However, as occurred with LDL-C, some studies did not support this association. A meta-analysis of 14 large prospective studies did not find any association between HDL-C and high-grade prostate cancer [108]. Also, a large Mendelian randomization trial reported above did not find evidence that genetically predicted changes in HDL-C changed prostate cancer risk [120]. The lack of androgen-dependent status data in some studies could explain the divergent results on the association between HDL-C and prostate cancer risk [126].

Since HDL also exhibited antioxidant properties, a recent report investigated the potential of HDL or reconstituted APOA1-containing HDL on prostate cancer cell proliferation induced by oxidative stress. Both native HDL and small APOA1-containing HDL reduced ROS levels in prostate cancer cells, thus inhibiting ROS-induced cell entry in the G2/M phase. Of note, these effects were independent of androgen receptor activation or the modulation of the cell cholesterol content [127]. On the other hand, HDL induced cell proliferation and migration of androgen-independent prostate cancer cells through ERK1/2 and Akt, but these effects were not found in androgen-dependent prostate cancer cells [128]. HDL also promoted migration and invasion, concomitant with the increase of Ser727 phosphorylation of STAT3 via ERK1/2 in androgen-independent prostate cancer cells, which was dependent on the delivery of sphingosine-1-phosphate (S1P) [129]. SEGURO QUE S1P ES PROCANCERIGENO EN ESTAS CIRCUNSTANCIAS?? These findings emphasize the critical role of S1P in HDL-induced cell progression of androgen-independent prostate cancer cells.

3.4. Intracellular cholesterol metabolism and prostate cancer

Cholesterol was found increased in the cytoplasmic fractions of prostate cancer tissue, along with an upregulation of LDLR and the peripheral-type benzodiazepine receptor involved in transferring cholesterol from the cytosol to the inner mitochondrial membrane [130]. Cholesterol levels were also increased in the nucleus fraction, concomitant with a high expression of Cyclin E, which could be enhancing cell division

[130]. The accumulation of cholesterol esters in lipid droplets was also found in high-grade and metastatic human prostate cancer tissue, but not in normal prostate, benign prostatic hyperplasia, prostatitis, or prostatic intraepithelial neoplasia [122]. As commented above, PTEN loss activated PI3K/Akt signaling leading to accumulation of cholesterol by increasing cholesterol uptake and, also, esterification *in vitro* [122]. Importantly, the pharmacological inhibition of cholesterol esterification via ACAT1 significantly suppressed cancer proliferation, migration, invasion, and tumor growth in xenograft mice [122], thereby indicating that cholesterol esters serve as a reservoir of cholesterol for prostate cancer cell proliferation. However, dedifferentiated tumors and those with lethal outcomes had lower expression of *LDLR* and *ACAT1*, but higher levels of squalene monooxygenase, the second rate-limiting enzyme of cholesterol synthesis, thus indicating a greater reliance on cholesterol synthesis than uptake in aggressive prostate cancer [131]. Another report also found that cholesterol accumulation also promoted EMT in prostate cancer cells via the ERK1/2 pathway; epidermal growth factor receptor and adipocyte plasma membrane-associated protein accumulation in lipid rafts [132]. These findings indicate that cholesterol biosynthesis and uptake during cancer progression is extremely complex and remains to be clarified.

Noteworthy, androgen receptor has also been linked to cholesterol synthesis in prostate cancer cells [133]. It is known that the androgen receptor binds an androgen-response element within an intron of SCAP, upregulating SCAP expression and resulting in a shift in the cellular equilibrium between SCAP and Insig, thereby promoting SREBP2 [134,135]. Thus, androgen receptor signalling may affect cholesterol synthesis [135]. In line with these findings, an androgen responsive element can upregulate the enzyme 3β-hydroxysterol Δ24- reductase (DHCR24) in androgen receptor-positive prostate cancer cells, thereby promoting cholesterol accumulation. Furthermore, the amount of DHCR24 protein and mRNA expression was higher in prostate cancer tissues than in adjacent normal tissues [136].

Importantly, HDL did not affect the cholesterol content ofprostate cancer cells and the (lower response DE QUE TIPO?) of androgen-dependent cancer cells correlated with a low level of ABCA1 [128]. It should be noted that androgens inhibit *ABCA1* expression in androgen-dependent prostate cancer cells, and this change enhanced growth rate [128,137]. ¿¿¿NO SE ENTIENDEThese latter findings were not related with HDL???

[133]. Taken together, these findings support a role of ABCA1 on prostate cancer growth,but would seem independent of cell cholesterol content. Furthermore, an analysis of clinical prostate samples for mRNA and prostate tissue biopsy cores for protein expression found a higher SR-BI expression in high Gleason grade versus low Gleason grade prostate cancer samples, but their consequences in HDL-C uptake or oncogenic signaling remain to be clarified [138]. Overall, these findings emphasized the critical role of ABCA1 and SR-BI on cell progression of prostate cancer cells, although the role of ABCA1 is highly-dependent of androgen status.

Some metabolites of cholesterol such as 22(R)-hydroxycholesterol and 24(S)-hydroxycholesterol are natural ligands of LXR and its activation inhibits prostate cancer cell proliferation [139]. In the same way, LXR can prevent cholesterol accumulation in the prostate and protect from abnormal cell proliferation when exposed to high dietary cholesterol, mainly by downregulating LDLR and upregulating ABCA1 protein expression [115]. A link was found between cholesterol accumulation and the proliferative process through the oncogene and histone methyl transferase Enhancer of Zeste Homolog 2 (EZH2) [115], which has been associated with aggressive human prostate carcinomas [140]. Also, cholestane-3β, 5α, 6β-triol suppressed proliferation in human prostate cancer cells and reduced the growth of tumor xenografts in nude mice [141]. This treatment reduced the expression of Akt1, c-Myc, and Skp2 protein levels whereas increased the cell cycle inhibitor p27(Kip) levels and the main proteins associated with EMT. However, 27-HC stimulated the proliferation of prostatic cells and induced the expression of PSA by increasing androgen receptor transcriptional activity in prostate epithelial cells [142]. Also, 27-HC suppressed apoptosis induced by docetaxel [142]. Consistently, CYP7B1, the main enzyme involved in 27-HC catabolism, was highly expressed in high-grade prostatic intraepithelial neoplasia and adenocarcinomas [143].

Overall, these results indicate that targeting cholesterol uptake, synthesis and efflux and their effects on intracellular cholesterol storage and conversion to 27-HC could be a good strategy for the treatment of prostate cancer (summarized in **Figure 1B)**.

4. Epithelial thyroid cancer

Thyroid cancer is a common endocrine malignancy whose incidence has increased in the last past decades. This neoplasia corresponds the 2.1% of all cancer diagnoses worldwide, affecting more women than men. Approximately 95% of thyroid cancer cases have the origin in the follicular epithelium with an array of different histological patterns and biological behavior [144,145]. Thyroid cancer is classified in two major types. First, the well-differentiated thyroid carcinomas (DTC) which include the papillary thyroid cancer (PTC), representing about 80 % of cases, is more common in women, and can metastasized throughout lymph nodes in the neck or close to the thyroid. This group also include the non-invasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP); and the follicular thyroid cancer (FTC), that represents about 5 to 10% of the diagnostic cases and can spread throughout lungs or bones. The second group of tumors correspond to dedifferentiated thyroid cancer, that include the poorly differentiated thyroid carcinoma (PDTC), formed by heterogeneous tumors with a prevalence of 0.23% to 2.6%, and associated with high risk of cancer recurrence including spread to lung and/or bones. This second group also include the anaplastic thyroid carcinoma (ATC), represents 1% to 2% of thyroid cancers , an is the tumor with the most aggressive behavior [4].

4.1. Cholesterol and thyroid cancer

Only few studies have investigated the association between serum cholesterol levels and thyroid cancer. A retrospective study investigated the lipoprotein profile of Chinese patients with thyroid cancer. Serum cholesterol levels were lower in subjects with thyroid cancer, mainly including patients with PTC and FTC [146]. This study also reported significant differences between the metastatic and non-metastatic groups in patients with PTC, but not in FTC patients [146]. Conversely, another retrospective study from South Korea found that increased BMI was associated with the lymph node metastases of patients with PTC, and other invasive features including large tumor size, extra-thyroidal invasion, and multifocality, but these effects were independent of serum cholesterol levels [147]. Another case-control study form Italy did not reveal significant differences in serum cholesterol levels of DTC patients with suppressed thyrotropin (TSH) due to levo-thyroxine therapy compared to that of the euthyroid subjects [148].

4.2. LDL and thyroid cancer

As occurred with serum cholesterol, only few studies investigated the association between LDL-C and thyroid cancer risk. In the Chinese retrospective study reported above, LDL-C levels were also lower in the large cohort of women with thyroid cancer and those showing metastasis in the PTC group [146]. In line with these findings, we recently reported that patients bearing aggressive thyroid tumors presented an important decrease in both systemic serum LDL-C levels and APOB100 levels along with an upregulation of the *LDLR* expression in tumor tissue [149]. Noteworthy, LDL-C promoted proliferation and migration in anaplastic thyroid cells, but these effects were independent of changes in MAPK, PI3K, and mTOR signaling [149].

4.3. HDL and thyroid cancer

The serum lipid profile of Chinese patients with thyroid cancer reported lower HDL-C and APOA1 levels in women with thyroid cancer compared to the control group, and in metastatic compared to non-metastatic patients with PTC [146]. However, we reported that serum HDL-C levels were similar in patients with aggressive thyroid cancer compared with those presenting a benign thyroid carcinoma [149].

Since HDL-C may not be an accurate reflect of HDL function, a report evaluated one of the main antioxidant and anti-inflammatory HDL component, PON1. A small case-control study revealed that PON1 activity was significantly lower in patients with PTC compared to the control group, although HDL-C, lipid hydroperoxide, and total free sulfhydryl levels remained unchanged [150]. However, we did not found differences neither in the APOA1 levels nor in PON1 and PAF-AH activities between patients with the malignant thyroid tumors (PTC, PDTC, and FTC) and those patients with benign thyroid tumors **(Figure 2, panel A).** Additional long-term and larger scale studies are needed to clarify this issue.

It is noteworthy that we found that *SCARB1* gene expression was upregulated in thyroid carcinoma tissues of PTC and FTC compared to benign tumors, whereas *ABCA1* and *ABCG1* expression remained unchanged (**Figure 2, panel B**). Furthermore, the exogenous administration of HDL in anaplastic cells promoted cell proliferation along

with an upregulation of *SCARB1* expression when compared with the effects of HDL on thyroid follicular epithelial cells. HDL also enhanced cell migration in both cell lines (**Figure 2, panel C**). These data rather suggest a differential effect of HDL in thyroid tumorigenic cells; further, the role of SR-BI in thyroid carcinoma deserve further investigation.

4.4. Intracellular cholesterol metabolism and thyroid cancer

Little is known about the regulation of intracellular cholesterol metabolism in the thyroid carcinoma. As commented above, we found an upregulation of thyroid *LDLR* in tumor tissues, whereas *HMGCR* and *NR1H3*, which codifies *LXRα,* were strongly downregulated in malignant tumors, thus indicating a greater reliance on cholesterol uptake in more aggressive thyroid tumors [149]. We also reported that the tumors with worse prognosis showed higher levels of 27-HC which correlated with a of *CYP7B1* downregulation. Importantly, the overexpression of *CYP7B1* in anaplastic thyroid cell lines arrested growth and reduced cellular migration, indicating that the accumulation of 27-HC (NO SERIA AL REVÉS??) in the thyroid cells may be promoting the development and progression of epithelial thyroid cancer [149]. The identification of positive ER (α/β) in thyroid tumor samples could partly explain the 27-HC-mediated effects on cell proliferation [149].

Taken together, these results indicate that targeting LDL-C uptake and the synthesis of 27-HC may be a therapeutic strategy for controlling epithelial thyroid cancer (summarized in **Figure 1C)**.

5. Pancreatic cancer

Pancreatic cancer is a malignancy of the digestive system that has ranked the 11th most common cancer in the world [151]. The majority of cases occur in the exocrine component that produces digestive enzymes. Pancreatic adenocarcinoma accounts for 85% of all pancreatic cancers [152]. Worldwide incidence of pancreatic cancer correlates with increasing age and is more common in men than in women [103]. The disease is classified form early to late stages (I to IV) but most of the patients are asymptomatic until the disease develops to an advanced stage [153]. For this reason, pancreatic cancer has a very poor prognosis, and most patients will eventually have recurrence; only 25% of people survive 5 years after complete resection [154]. Because of its poor prognosis, pancreatic cancer is the seventh leading cause of mortality from all malignant tumors in Western Societies [103]. The lack of specific biomarkers for early diagnosis may also help explain the high mortality of these patients. Modifiable risk factors include smoking, alcohol, obesity, dietary factors, and exposure to toxic substances.

5.1. Cholesterol and pancreatic cancer

Two large Mendelian randomization studies that investigated the causal relevance of metabolic factors on pancreatic cancer did not found evidence for an association of genetically predicted serum cholesterol and pancreatic adenocarcinoma [155,156]. Furthermore, several large prospective studies reported null associations between serum total cholesterol and the risk of pancreatic cancer [157–159]. Data analysis of some large cohorts of Asian and Australia/New Zealand did not reveal any association between total serum cholesterol and mortality from pancreatic cancer [160]. These results were also confirmed in a large prospective cohort from UK [161]. However, two prospective analyses of US population and seven cohorts from Norway, Austria, and Sweden showed an inverse association between serum cholesterol levels and the risk of pancreatic cancer [162,163]. Noteworthy, a meta-analysis that included eight large studies from Asian and Europe revealed that serum cholesterol levels were not significantly associated with the risk of pancreatic cancer [164]. However, this meta-analysis showed a significant association of dietary cholesterol with the risk of pancreatic cancer in 6 studies conducted in North America [164].

The potential of dietary cholesterol was also analyzed in a meta-analysis of 19 studies conducted in Europe, US, and Asia, but the association between dietary cholesterol and pancreatic cancer risk was only significant in European studies [165]. However, in another meta-analysis of 16 studies, mainly from Europe and North America, demonstrated that cholesterol intake might increase the risk of pancreatic cancer, particularly in US and Canada [166]. These effects were also observed in a case-control study conducted in Japan [167]. Overall, these large studies found a general association between cholesterol intake and pancreatic cancer, but the association varied between geographical locations and their effects on serum cholesterol levels were rather limited in most studies. Early studies in experimental modelsdemonstrated that N-nitrosobis-induced pancreatic carcinogenesis in hamster was promoted by a cholesterol-containing diet [168], whereas cholesterol-free diets did not affect pancreatic neoplastic lesions [169].

5.2. LDL and pancreatic cancer

The large Mendelian randomization studies reported above revealed that the main trait associated with pancreatic adenocarcinoma was genetically predicted by body mass index [155,156], but only one study found that genetically higher levels of LDL-C were associated with pancreatic cancer, although LDL showed a BMI-mediated causal effect [156]. Furthermore, a long-term detailed prospective Swedish cohort analysis did not find evidence for an association between prostate cancer risk and LDL-C and neither with the main LDLR ligand gene, *APOB* [170].

OLR1 may also play a critical role in pancreatic cancer. A very recent study have demonstrated that *OLR1* expression was highly expressed in pancreatic cancer tissue compared with that of adjacent normal tissue [171]. Furthermore, inhibition of *OLR1* expression decreased the proliferation and metastasis of pancreatic cancer cells both *in vitro* and in a xenograft mouse model. OLR1 promoted metastasis of pancreatic cancer cells through increasing transcription of High mobility group AT-hook 2 (HMGA2) through c-Myc [171]. It should be noted that human pancreatic adenocarcinoma cells incubated with oxLDL and acetylated LDL, but not native LDL, enhanced their cytokine production when they were cultured with human monocytes. Furthermore,

anti-CD36 antibody inhibited this stimulatory effect [172]. These findings establish a potential role of modified LDL and their main receptors in pancreatic cancer development.

5.3. HDL and pancreatic cancer

The analyses of two large Mendelian randomization studies did not provide any evidence that genetically altered HDL-C were causally associated with an increased pancreatic cancer risk [155,156]. Similar results were reported in a large Finnish prospective analysis [157], and neither HDL-C was associated with pancreatic cancer risk in the Alpha-Tocopherol, Beta-Carotene Study (ATBC) of Finnish male smokers that investigated potentially modifiable factors for this cancer [173]. However, HDL-C was found inversely associated with pancreatic cancer risk in other studies. In four randomized controlled intervention studies of postmenopausal women from US, a modest but significant inverse association of HDL-C with pancreatic cancer was found; nevertheless, the inverse association dissapeared when women who lost significant weight were excluded [174]. Interestingly, serum HDL-C levels were significantly lower in pancreatic cancer postmenopausal women of a case-control study conducted in Greece. [175].

It is noteworthy that in several studies APOA1 levels was the main metabolic factor inversely associated with pancreatic cancer, as occurred in a case-control study of China, a prospective study of Sweden, and a retrospective study of Japan [170,176,177]. In line with these findings, both APOA1 and the second quantitatively most important HDL protein, APOA2, was found downregulated in proteomic serum analyses of pancreatic adenocarcinoma patients [178–180]. The mechanism responsible for the link between APOA1 and APOA2 and pancreatic cancer remains unclear. Reconstituted APOA2-containing HDL increased lipid uptake and cell proliferation in human pancreatic cancer cells and enhanced lipid uptake in xenograft tumors implanted in mice, likely by upregulating SR-BI [181]. Furthermore, serum PON1 levels were downregulated in a small case-control study conducted in patients with pancreatic cancer [182].

5.4. Intracellular cholesterol metabolism and pancreatic cancer

Beyond LDL-C levels, the use of a global transcriptomic microarray technology revealed that invasive genetically-engineered murine pancreatic adenocarcinoma samples showed a strongest upregulation of LDLR concomitant with an increased cholesterol uptake [183]. The authors also demonstrated that pancreatic cancer cell disruption of LDLR downregulated cholesterol uptake, impairing proliferative and tumorigenic capacities and inhibiting the ERK-dependent survival pathway [183]. Furthermore, elevated LDLR expression was correlated with an increased rate of relapse in patients with pancreatic adenocarcinoma [183]. In line with these findings, an independent study also showed that LDLR mRNA expression was associated with decreased patient survival in pancreatic adenocarcinoma [184], thereby emphasizing the significant contribution of LDL-C uptake to pancreatic cancer development.

The use of microarray technology also revealed that invasive genetically-engineered murine pancreatic adenocarcinoma samples showed a strongest upregulation of critical genes involved in *de novo* cholesterol synthesis, cholesterol storage and oxysterol/steroid synthesis, particularly in HMGCR, 24-dehydrocholesterol reductase, ACAT1, lipase A and 3-oxo-5α-steroid 4-dehydrogenase 1 genes [183]. Indeed, increased levels of cholesterol were also observed in human pancreatic adenocarcinoma cells [185]. Furthermore, these changes altered the ratio of cellular free/esterified cholesterol [183]. In line with these findings, a significant accumulation of cholesteryl esters mediated by ACAT1 was found in human pancreatic cancer specimens and cell lines [186]. More importantly, expression of ACAT1, detected by immunohistochemistry, showed a correlation with poor patient survival and, also, the blockage of cholesterol esterification either by an ACAT1 inhibitor or by downregulating ACAT1 expression suppressed tumor growth and metastasis in an orthotopic mouse model of pancreatic cancer [186]. Similar results were found in a xenograft mouse model of pancreatic adenocarcinoma treated with the ACAT1 inhibitor avasimibe and the chemotherapy agent gemcitabine, in part by downregulating Akt pathway [187]. Melittin, a Chinese traditional medicine for treating chronic inflammation, immunological diseases, and cancer, also inhibited tumor growth in pancreatic ductal adenocarcinoma xenograft mouse model by downregulating the main genes involved in cholesterol biosynthesis, and also enhanced the antitumoral effects of gemcitabine [188]. Other genes involved in cholesterol biosynthesis were associated

761 with radioresistance in pancreatic cancer cells [189]. Finally, caveolin-1, an active
762 component of caveolae affecting cholesterol signaling, plays a critical role in pancreas
763 cancer progression [190]. Caveolin-1 downregulation also resulted in a decrease
764 chemoresistant and metastatic phenotype of pancreatic cancer cells [191].
765
766 Taken together, these findings indicate that targeting metabolic pathways involved in
767 cholesterol uptake, biosynthesis, and storage may be a successful strategy for the
768 treatment of patients with pancreatic adenocarcinoma (summarized in **Figure 1D)**.
769

6. Ovarian cancer

Ovarian cancer has the highest mortality rate of all gynecological cancers worldwide [103]. About 90% of ovarian cancers are epithelial tumors, including serous tumor, endometrioid tumor, and mucinous cystadenocarcinoma [192]. The disease is often asymptomatic or shows non-specific symptoms being, in many cases, diagnosed at advanced stages [193]. More than one third of ovarian cancer patients present with malignant ascites at diagnosis [194]. Usual treatments include optimal debulking surgery followed by chemotherapy, mainly with platinum-based drugs [195]. Five-year cause-specific survival for all epithelial ovarian cancers is 47%; however, advanced-stage disease is a highly chemoresistant disease and the 5-year survival rate is only of 20% [192].

6.1. Cholesterol and ovarian cancer

A recent meta-analysis which included 12 studies regarding association of ovarian cancer risk with blood lipid level suggested that high cholesterol was associated with an increased ovarian cancer risk [196]. The same association was observed in two prospective studies that included cohorts from Austria, Norway, Sweden, and USA [197,198].

In contrast, reduced serum cholesterol levels were observed in ovarian cancer patients, compared to healthy women in several case-control and prospective studies [199–202] and in a recent meta-analysis which included 12 studies [203]. Compared with the patients in stage I-II, the patients in stage III-IV had lower levels of cholesterol [199]. Moreover, patients who were in complete remission of the cancer had higher cholesterol compared to diagnosis, whereas patients who died from their ovarian cancer presented a reduction in serum cholesterol [201]. The hypocholesterolemia observed in advanced ovarian cancer patients could be due to increased cholesterol uptake by the tumor.

Concerning cholesterol intake, a meta-analysis that included 7 studies found 1% greater risk of ovarian cancer per 50 mg/day increase in cholesterol intake [204]. A positive association between ovarian cancer risk and higher consumption of dietary cholesterol

was also observed in a case-control study from Canada [205], and in the prospective Nurses' Health Study (NHS), although NHS2 study did not find this association [206]. Another meta-analysis, as well as the European Prospective Investigation into Cancer and Nutrition, and Netherlands Cohort Study failed to find an association between cholesterol intake and ovarian cancer risk [207–209].

6.2. LDL and ovarian cancer

A Mendelian randomization analysis of 22 406 women with invasive epithelial ovarian cancer did not found any association between genetically variation ¿¿proxied?? in in controlling circulating LDL-C and risk of epithelial ovarian cancer [210]. Similarly, the AMORIS database did not find association between LDL or APOB levels and ovarian cancer risk [40]. However, LDL was suggested as a predictor of clinical outcome in a retrospective study from the U.S.A., since longer progression-free survival and overall disease-specific survival was found in patients with normal LDL levels compared to patients with elevated LDL [211]. On contrary, another retrospective study conducted in China found that elevated preoperative LDL was associated with an improved recurrence-free survival in women with ovarian cancer [212].

Discrepancies were also found concerning LDL-C levels in different ovarian cancer stages. Low LDL-C levels were observed in a small study conducted in Pakistan [200]. In another case-control study from Israel, elevated LDL-C levels were observed in early-stage ovarian and endometrial cancer patients compared to controls, but levels dropped at advanced stages of the disease [213]. In contrast, no differences in LDL-C levels were observed between low and high severity endothelial ovarian cancer patients in a retrospective study conducted in China [214].

When ovarian carcinoma cell lines CAOV3 and SKOV3 were treated with LDL, proliferation rates remained unchanged [215]. However, concentrations of oxLDL as small as 0.1 µg/mL stimulated proliferation in these cell lines, accompanied by an induction of the expression of the cytokine cardiotrophin 1, which has anti-apoptotic effects. These changes were counteracted when cells were treated with LXR agonists, concomitantly to oxLDL [215]. Interestingly, increased levels of oxLDL were observed

in ovarian cancer patients compared to control subjects [48]. These results rather indicate that oxLDL appears to have an important role in ovarian cancer development.

6.3. HDL and ovarian cancer

A large genome-wide analysis identified several loci involved in HDL transport (including CETP, APOA1, and ABCG1) associated with epithelial ovarian cancer in patients following first-line chemotherapy [216]. The role of HDL-C on ovarian cancer was also supported by the results of a large meta-analysis that reported low HDL-C levels in ovarian cancer patients [203]. And those of another meta-analysis that showed an association between high HDL-C levels and lower ovarian cancer risk [196]. The results of one of these studies also concluded that women with ovarian malignant tumors had both significant lower APOA1 and HDL-C levels, particularly in the small HDL3 fraction [217]. Other two retrospective studies also reported that low HDL-C levels were strongly associated with severity of epithelial ovarian cancer [199,214]. In line with these findings, HDL-C levels and PON1 activity were also lower in patients with newly diagnosed epithelial ovarian cancer and this was associated with histological grade of tumors and high lipid hydroperoxide levels [218].

Importantly, a prospective study also revealed that serum LCAT activity, mainly involved in the conversion of HDL3 to large HDL2, was lower in patients bearing indolent ovarian tumors; noteworthy, this activity together with other two serum biomarkers, were strongly associated with poor prognosis [219]. The use of experimental models provided conclusive evidence of the anti-tumorigenic effects of APOA1 in ovarian cancer since overexpression of human APOA1 increased HDL-C levels, reduced tumor development, and increased survival in mice bearing ovarian epithelial papillary serous adenocarcinoma cells [220]. Furthermore, human APOA1 incubation significantly inhibited proliferation of these adenocarcinoma cells [220].

6.4. Intracellular cholesterol metabolism and ovarian cancer

The genome-wide analyses reported above identified that genetic inhibition of HMGCR was significantly associated with lower odds of ovarian cancer [216]. In contrast, microarray data analysis showed that *SERBP2*, *HMGCR*, and *DHCR7* were strongly repressed in ovarian carcinomas compared to normal and benign tissues [221]. Also,

patients with ovarian tumors expressing high levels of *HMGCR* had a significantly favorable prognosis [222]. Other works also revealed potential divergent results in the association of enzymes controlling the mevalonate pathway and ovarian cancer. Ovarian cell carcinomas with functional mutations in AT-rich interactive domain-containing protein 1A, showed a downregulation in several enzymes of mevalonate pathway, including HMGCS and FDPS [223]. However, exposure to the ovarian microenvironment upregulated the expression of many genes involved mevalonate pathway in murine ovarian cancer cells, including *HMGCR*, *HMGCS*, and *FDPS* [224].

It should be noted that intracellular cholesterol levels were elevated in high grade serous ovarian cancer cells and malignant ascites.This feature modulated the sensitivity of ovarian cancer cells to chemoresitance [225,226]. Furthermore, platinum-resistant ovarian cancer cells also showed *LDLR* upregulation and this was associated with worse survival in ovarian cancer patients [226]. In line with these findings, *LDLR* was also upregulated in the microarray data analyses of ovarian carcinomas [221], thus indicating a greater reliance on cholesterol uptake in in the ovarian tumor cells. Cholesterol esters were also found to be increased in human ovarian carcinoma cell lines along with an upregulation of ACAT1 [227]. ACAT1 inhibition reduced cell proliferation, invasion, and viability in these ovarian cancer cells, mainly by increasing both caspase 3/7 activities and p53, and by reducing ROS production [227].

Gene expression and immunohystochemical analyses revealed that high expression of ABCA1 in primary tumors was strongly associated with reduced survival in two cohorts of serous ovarian cancer patients [228]. *ABCA1* downregulation also inhibited ovarian cancer cell growth and migration *in vitro* [228]. EN OTROS TUMORES AUMENTAR ABCA1 ERA POSITIVO, LO QUE CUADRABA CON UNA MENOR TENDENCIA A ACUMULAR COLESTEROL. EN OVARIO ES LO CONTRARIO ¿PORQUÉ? Importantly, a very recent report found that ovarian cancer cells injected in mice, stimulated ABCA1-mediated cholesterol efflux in tumor associated macrophages, depleting lipid rafts and increasing IL-4 signaling, thereby inducing PI3K activity and mTOR-mediated Akt phosphorylation [229]. Ovarian cancer cells might, thus, uptake cholesterol from HDL effluxed on tumor-associated macrophages and these cells were reprogrammed toward a tumor-promoting phenotype via STAT6 [229]. In contrat, higher *APOA1* mRNA levels in prechemotherapy serous ovarian cancer effusions were

associated with longer overall survival [230]. However, the potential of APOA1 to regulate cholesterol efflux in the tumor microenvironment deserve further investigation.

As occurred with breast cancer patients, high expression of *CYP27A1* was associated with a significant decrease in overall survival in early stage ovarian cancer patients, while high expression of CYP7B1 was associated with lower overall survival [231]. Furthermore, exogenous 27-HC appeared to impact the peritoneal spread of tumors.tumors failed to thrive in mice lacking CYP27A1 and orthotopically grafted with ovarian cancer cells [231]. Finally, 25-HC also induced proliferative effects in ovarian cancer cells by modulating ERα and Cyclin D1 protein levels [232].

¿¿Overall, these results indicate that targeting cholesterol uptake and efflux, intracellular cholesterol storage and conversion to HC could be a good strategy for the treatment of ovarian cancer patients (summarized in **Figure 1E)**.??

7. Adrenal and testicular cancer

Adrenal and testicular cells require large amounts of cholesterol for the optimal steroid hormone production. These major steroidogenic organs synthesize cholesterol *de novo* under the influence of the tropic hormone, while the adrenal preferentially use cholesterol from LDL and HDL thought LDLR and SR-BI, respectively [233].

The two major types of adrenal cortex tumors are the benign adrenocortical adenoma , which is extremely common, and the rare and malignant adrenocortical carcinoma [234]. Only 15% of adrenocortical adenomas are "functional", thereby producing glucocorticoids, mineralocorticoids, and sex steroids. Sometimes, these tumors are termed incidentalomas because they are found by accident. However, adrenocortical ¿carcinomas? are mainly functional. Functional tumors result in endocrine disorders such as Cushing's syndrome, hyperaldosteronism, female virilization, or male feminization. Although functional adrenal incidentalomas were early associated with high LDL-C [235], several later studies found no association with lipoprotein cholesterol changes [236,237].

Both human LDL- and HDL-C were used for steroid production by primary adrenocortical cells obtained from adenomas [238]. These findings were also found in adrenocortical carcinoma cells, mainly by the action of LDLR and SR-BI [239,240]. In the latter report, the tumor tissue of the female patient expressed high levels of LDLR and a severe reduction in LDL-C and HDL-C. More importantly, her serum cholesterol levels were normalized few days after tumor removal [240]. In line with these findings, the transcriptome analyses of adrenocortical adenomas revealed a major association of *HMGR*, *SQLE*, *DHCR24*, *SCARB1*, and *LDLR* with cortisol secretion [241] and, also cortisol-producing adenomas showed a higher content of cholesterol along an upregulation of *LDLR*, *DCHR24*, and *HMGCR* and a downregulation of *ABCA1* [242]. Overall, these results emphasize the role of LDL, HDL, and cholesterol synthesized *de novo* on adrenocortical cancer cell production of steroids. However their effects on carcinogenic pathways remain largely unknown.

Testicular cancer is a common cancer in middle-aged men. Chemotherapy has achieved a higher survival rate even in patients with metastasis [243]. A large population-based

cohort Swedish study, with a follow-up of 25 years, found a highly significant positive association between serum cholesterol and the risk of developing testicular cancer; this was particularly relevant with cholesterol levels higher than 7 mM [244]. Early studies demonstrated that the use of LDL under acute hormonal stimulation had little effect on the amount of steroid synthesized in cultured Leydig tumor cells and these cells rather enhanced demand of cholesterol by increasing *de novo* synthesis [245,246]. However, LDL appears to play a critical role by providing cholesterol substrate to the tumor cells under prolonged hormonal stimulation [245]. It has also been reported that ACAT 1 inhibition results in cholesterol accumulation in the Leidyg tumor cells. Furthermore, it should be noted that a high prevalence of metabolic abnormalities is present in testicular cancer patients treated with chemotherapy, including higher LDL-C and lower HDL-C [247]. This indicate that testicular cancer survivors should adopt healthy lifestyle and measures to control their lipid levels. Clearly, more studies are needed to clarify the role of cholesterol on testicular carcinogenic pathways.

8. Therapeutic strategies

8.1. LDL and cholesterol-lowering based therapies

Because of the vital and prooncogenic functions of cholesterol in endocrine-related cancers, impeding active cholesterol metabolism is considered to be a feasible anti-carcinogenesis strategy. Statins are the most common LDL-C-lowering drugs that reduce the incidence of cardiovascular events. For this reason, statins have been the most widely evaluated cholesterol-metabolism-targeting drugs in clinical studies for patients with cancer and, particularly in breast cancer [1]. Fewer studies have addressed the potential of other cholesterol-lowering agents such as ezetimibe and PCSK9 inhibitors on cancer development.

8.1.1. Statins

In general, statins are safe at standard doses, showing only mild adverse effects on the muscle and liver that vary depending on the exact statin used, as well as the dosage and combination with other drugs [248]. Statins may exert their anti-tumor effects in different ways. The inhibition of HMGCR is considered the main molecular mechanism underlying most of the anti-tumor effects of statins [249,250]. However, the use of the mevalonate pathway as therapeutic target is difficult, since influences a large number of cellular processes. The inhibition of intracellular cholesterol synthesis can be counteracted by an upregulation in LDLR expression thus adquiring more cholesterol from LDL and promoting tumor growth [46,149,183]. By controlling the mevalonate pathway, it is however possible to alter cholesterol synthesis and prenylation patterns, thereby affecting the function of proteins and oncoproteins that regulate proliferation, migration, invasion, cell cycle, and cell fate, and apoptosis [251,252]. Notably, although statins are well-known hypocholesterolemiant drugs, they might also target different pathways [253,254].Therefore, other anti-tumoral statin effects also include anti-inflammatory properties and immunomodulation, such as restoring tumor immune surveillance mechanisms, either by increasing the immunogenicity of cancer cells or by directly engaging the immune system response against them [250,255].

Up to date, several clinical studies exist and have suggested benefits of statin usage on patient survival for endocrine-related cancers. However, other studies have found no

effect of statins, or even a less favorable outcomes. A summary of the main clinical trials evaluating the association between statins use and endocrine-related cancer risk is shown in Table 1. Overall, discrepancies among results derived from meta-analyses of observational case studies exist. We could explain the conflicting results if we take into account the different nature of of these clinical studies, the heterogeneity in patient samples and tumor characteristics, as well as the consistent number of confounding variables and bias this .

1008 **Table 1.** Clinical trials evaluating the association between statins use and cancer risk

Tumor type	Reference	Year	Study design	Participants	Main findings
All cancers	Jeong *et al.* [256]	2020	Meta-analysis	1 173 269	Although there was a preventive effect of statin on cancer mortality in some cancer types, the evidence supporting the use of statins to reduce cancer mortality or survival was low.
	Liu *et al.* [257]	2017	Meta-analysis	197 048	Significant protective effects of lipophilic statin use, but not hydrophilic statins, against cancer-specific mortality.
	Emberson *et al.* [258]	2012	Meta-analysis	175 000	A median of 5 years of statin therapy had no effect on the incidence of, or mortality from any type of cancer (including pancreas, prostate and breast cancer).
	Baigent *et al.* [259]	2005	Meta-analysis	90 056	There was no evidence that statins increased the incidence of cancer overall.
	Manthravadi *et al.* [260]	2016	Meta-analysis	75 684	Lipophilic statin use was associated with improved recurrence-free survival.
	Rossebø *et al.* [261]	2008	Prospective	1873	Cancer occurred more frequently in patients with aortic stenosis treated with simvastatin and ezetimibe.
	Jacobs *et al.* [262]	2011	Retrospective	133255	Long-term use of statins did not increase nor decrease overall cancer risk, including pancreatic, prostate and breast cancers
	Nielsen *et al.* [263]	2012	Case-control	Total: 295 925 Cases: 18 721 Controls: 277 204	Reduced cancer-related mortality among statin users as compared with those who had never used statins was observed for each of 13 cancer types (including prostate, breast and pancreatic cancers).
Breast cancer	Ference *et al.* [264]	2019	Mendelian randomization	654 783	Genetic inhibition of *HMGCR* did not affect breast cancer risk.
	Undela *et al.* [265]	2012	Meta-analysis	>2.4 million	Statin use and long-term statin use did not significantly affect breast cancer risk.
	Bonovas *et al.* [266]	2005	Meta-analysis	327 238	Statin use did not significantly affect breast cancer risk.

Wu *et al.* [267]	2015	Meta-analysis	144 830	There was a significant negative association between prediagnosis statin use and breast cancer mortality and for disease-specific revisar: ¿esto parece contrario? survival. There was also a significant inverse association between postdiagnosis statin use and breast cancer disease ¿esto parece lo contrario? -specific survival. No significant association was detected between statin use and breast cancer risk.
Mansourian *et al.* [268]	2016	Meta-analysis	124 669	Significant reduction in breast cancer recurrence and death among statin users.
Islam *et al.* [269]	2017	Meta-analysis	121 399	There was no association between statin use and breast cancer risk.
Dale *et al.* [270]	2006	Meta-analysis	86 936	Statins did not reduce the incidence of breast cancer.
Murtola *et al.* [271]	2014	Prospective	31 236	Both postdiagnostic and prediagnostic statin uses were associated with a lowered risk of breast cancer death.
Ahern *et al.* [272]	2011	Prospective	18 769	Significant reduction in breast cancer recurrence among patients using simvastatin after 10 y of follow up.
Borgquist *et al.* [273]	2017	Prospective	8010	Initiation of cholesterol-lowering medication in postmenopausal women with early stage cancer?, esto no es de lo que estamos hablanco: “hormone receptor-positive invasive breast cancer during endocrine therapy was related to improved disease-free survival, breast cancer-free interval and distant recurrence-free interval.”
Cauley *et al.* [274]	2003	Prospective	7528	Older women who used statins had a reduced risk of breast cancer compared with nonusers.
Brewer *et al.* [275]	2013	Prospective	723	Hydrophilic statins were associated with significantly improved progression-free survival compared with no statin in breast cancer patients.
Anothaisintawee *et al.* [276]	2016	Retrospective	15 718	Use of lipophilic statins, but not hydrophilic statins, could significantly reduce the risk of breast cancer
Mc Menamin	2016	Retrospective	15 140	There was no evidence of an association between statin use and

	et al. [277]				breast cancer-specific death.
	Smith *et al.* [278]	2017	Retrospective	6314	Prediagnostic statin use was associated with a decrease in breast cancer-specific mortality. This reduction was greatest in statin users with ER-positive tumors.
	Shaitelman *et al.* [279]	2017	Retrospective	869	Statin use was significantly associated with overall survival in triple-negative breast cancer.
	Chae *et al.* [280]	2011	Retrospective	703	Significant reduction in breast cancer recurrence among patients who used statins. No association was found regarding overall survival.
	Sakellakis *et al.* [281]	2016	Retrospective	610	Statins may be linked to a favorable outcome in early breast cancer patients, especially in younger age groups.
	Schairer *et al.* [282]	2018	Case-control	Total: 228 973 Cases: 30 004 Controls: 198 969	Statin use did not significantly affect breast cancer risk.
	McDougall *et al.* [283]	2013	Case-control	Total: 2886 Cases: 916 Controls: 902	Current users of statins for >10 y had increased risk of invasive ductal carcinoma and invasive lobular carcinoma compared with never users of statins.
Prostate cancer	Hutchinson et al. [284]	2017	Meta-analysis	774 316	Statin use in patients with prostate cancer receiving radiation therapy did not translate into an overall survival benefit for patients
	Platz *et al.* [285]	2006	Prospective	34 989	The use of statin drugs was not associated with risk of prostate cancer overall but was associated with a reduced risk of advanced (especially metastatic or fatal) prostate cancer.
	Larsen *et al.* [286]	2017	Retrospective	31 790	Postdiagnosis statin use was associated with reduced mortality from prostate cancer.
	Hamilton *et al.* [287]	2010	Case-control	Total: 1319 Cases: 236 Controls: 1083	Statin use was associated with a dose-dependent reduction in the risk of biochemical recurrence of prostate cancer, suggesting that statins may slow prostate cancer progression after radical prostatectomy.

Pancreatic cancer	Bonovas *et al*. [288]	2008	Meta-analysis	914 601	Statins do not reduce the risk of pancreatic cancer when taken at doses for managing hypercholesterolemia
	Cui *et al.* [289]	2012	Meta-analysis	7807	An inverse association between statin use and pancreatic cancer risk was found
	Huang *et al.* [290]	2017	Retrospective	2142	Statin use was associated with lower mortality risk.
	Lee *et al.* [121]	2016	Retrospective	1761	The use of simvastatin and atorvastatin was associated with longer survival in patients with nonmetastatic pancreatic adenocarcinoma
	Chagpar *et al.* [292]	2011	Retrospective	518	Preoperative use of statins was found to be a predictor of increased early postoperative mortality in patients with resected pancreatic cancer.
	Jeon *et al.* [293]	2014	Retrospective	263	Hydrophilic statin use was associated with longer survival in pancreatic patient with metabolic syndrome.
	Nakai *et al.* [294]	2013	Retrospective	250	Statin use was associated with better survival in diabetic patients with pancreatic cancer.
	Khurana *et al.* [295]	2007	Case-control	483733 Total, 163467 cases, 320266 controls.	Statins seem to be protective against the development of pancreatic cancer, and the magnitude of the effect correlates with the duration of statin use.
	Bradley *et al.* [296]	2010	Case-control	9095 Total, 1141 cases, 7954 controls	Statin use was not associated with the risk of exocrine pancreatic cancer
	Walker *et al.* [297]	2015	Case-control	1405 Total, 536 cases and 869 controls	Risk reduction of prostate cancer was found and it appeared to be sex-specific and more pronounced in long-term users.
	Chiu *et al.* [298]	2011	Case-control	950 Total, 190 cases, 760 controls.	No beneficial association between usage of statin and pancreatic cancer was observed.
	Carey *et al.*	2013	Case-control	756 Total, 252	Statins reduce the odds of pancreatic cancer in male smokers.

	[299]			cases, 504 controls	
Ovarian cancer	Majidi *et al.* [300]	2020	Meta-analysis	22 521	The analysis suggests improved survival in statin users compared to non-users.
	Li *et al.* [301]	2018	Meta-analysis	19 904	Post-diagnosis statin use can improve the survival of patients with ovarian cancer. Increased intensity of statin use was significantly associated with improved overall survival.
	Liu *et al.* [302]	2014	Meta-analysis	12 904	Statin use was inversely associated with ovarian cancer risk. The association was stronger for long-term statin use (>5 years)
	Harding *et al.* [303]	2019	Retrospective	2195	Statin use following a diagnosis with ovarian cancer was associated with a lower risk of cancer death.
	Urpilainen *et al.* [304]	2018	Retrospective	244 322	Pre-diagnostic use of statins was observed to be associated with improved prognosis and decreased mortality from ovarian cancer compared with no such use
	Desai *et al*. [305]	2018	Retrospective	126 253	In time-dependent models, statins were associated with an increased risk of ovarian cancer, largely attributed to the effect of the hydrophilic statin pravastatin.
	Couttenier *et al.* [306]	2017	Retrospective	5416	Evidence of a protective effect of statin use on ovarian cancer-specific and all-cause mortality exists. Simvastatin and rosuvastatin in particular appeared to have the strongest protective association.
	Verdoodt *et al*. [307]	2017	Retrospective	4419	No strong evidence of an association between post-diagnostic statin use and reduced mortality in ovarian cancer patients was found. Reduced mortality with statin use was observed in sub-cohorts of new users of statins and of patients not using low-dose aspirin.
	Chen *et al.* [308]	2016	Retrospective	60	Statin use was not associated with improved overall survival in patients with advanced-stage ovarian cancer undergoing surgery and chemotherapy.
	Habis *et al*.	2014	Retrospective	442	Statin use among patients with non-serous papillary ovarian

[309]				cancer was associated with improvement in both progression-free survival and disease-specific survival
Wang *et el*. [310]	2019	Case-control	Total: 1 999 362 Cases: 19 849 Controls: 1 979 513	Statin use did not lower the risk of ovarian cancer. The long-term use of statins (>5 years) was not associated with a reduction in the risk of ovarian cancer.
Akinwunmi *et al.* [311]	2019	Case-control	Total: 4140 Cases: 2040 Controls: 2100	Statins were found to lower the risk for both serous and non-serous epithelial ovarian cancer and especially mucinous epithelial ovarian cancer.
Baandrup *et al*. [312]	2015	Case-control	Total: 62 809 Cases: 4103 Controls: 58 706	A neutral association between ever use of statins and epithelial ovarian cancer risk was found, with no apparent risk variation according to duration, intensity or type of statin use.

Due to side effects of statins, increasing doses in cancer patients is unadvisable. An alternative strategy to overcome this situation is to combine statin therapy with other drugs. Accumulating evidence indicates that targeting cholesterol metabolism sensitizes endocrine-related cancer cells to other anti-tumor therapies. Accordingly, a synergistic effect has been observed when statins are combined with other chemotherapeutic drugs. For instance, in breast cancer cells positive for Erb-b2 tyrosine kinase receptor , suppression of cholesterol biosynthesis by inhibitors such as lovastatin can trigger ErbB2 internalization and degradation. In this scenario, adding ErbB2 inhibitors represses tumor growth [313]. In prostate cancer cells, a combination therapy of enzalutamide and simvastatin has been shown to have a significant synergistic effect on tumor suppression [314]. In other cancer cells, cholesterol-metabolism-blockade therapy causes feedback responses that decrease drug efficacy. Therefore, inhibiting feedback responses with another therapy might enhance anti-tumor efficacy. For example, a treatment combining aspirin or metformin with fluvastatin has been found to almost completely abrogate the colonization capability of breast cancer cells [315]. In another recent study, statin treatment has been found to significantly decrease levels of the mevalonate-pathway product coenzyme Q in cancer cells, thus leading to excessive oxidative stress [316]. Upregulating antioxidant pathways synergizes with statins to produce a robust antitumor response [316]. Despite these positive results, definitive evidence of these combination therapeutic strategies on endocrine cancer will require human clinical trials.

8.1.2. Ezetimibe and PCSK9 inhibitors

Other LDL-C lowering drugs other tha statinsshould also be taken into account. Ezetimibe, which significantly reduces the absorption of cholesterol from the intestine, was first hypothesized to increase the incidence of cancer when added to statin therapy for enhancing LDL-C reduction [261]. Nevertheless, larger trials with statistically independent evidence, found no adverse effect on cancer when added to statin therapy [317] la refer 318 dice que no hya diferencias en el riesgo de cancer de tratados con eze+simva: [318]. In contrast, ezetimibe was an effective inhibitor of tumor angiogenesis in the progression of prostate cancer cells implanted in mice fed a high fat high cholesterol diet [319]. However, it should be noted that the predominant lipoprotein in mice is HDL and they show significant metabolic lipoprotein differences when compared with that of human [320].

On the other side, drugs inhibiting PCSK9 lead to increased hepatic LDLR abundance, reducing effectively LDL-C, which may be seen as a strategy to limit the exogenous lipids to support the proliferation of tumors. It was recently reported that LDL-C-raising genetic variants of PCSK9 were associated with a higher risk of breast cancer, while LDL-lowering variants mimicking PCSK9 inhibitors were found to have a significant lower risk of ER-positive breast cancer [35]. Works performed on mice revealed that PCSK9 inhibition not only exerts no harmful effects but also could somewhat improve breast cancer behavior in an experimental model of breast cancer, suggesting safety and efficacy of PCSK9 inhibitors in conditions other than cardiovascular disease such as cancer [321]. However, from a clinical perspective, there is no evidence that PCSK9 inhibition might influence the course of endocrine-related cancers, whether beneficially or deleteriously [322].

8.2. HDL-C based therapies

Some HDL-based strategies have emerged with the aim to prevent cancer development. The potential of some HDL and APO mimetics and some specific LXR agonists are reviewed in two reports of this Special Issue. Interestingly, the effects of the most effective current drugs for elevation of HDL-C levels, the CETP inhibitors, and other HDL cholesterol-raising drugs such as fibrates and niacin, have been evaluated in experimental models and large clinical trials, including some relevant data on endocrine-related cancer.

Despite CETP inhibitors increase plasma HDL-C levels substantially, drug development for most CETP inhibitors (i.e., torcetrapib, evacetrapib, dalcetrapib) was stopped because of futility [323,324] or adverse cardiovascular side effects [325]. Patients receiving torcetrapib showed significant side effects on blood pressure and adverse cardiovascular outcomes; furthermore, a higher number of patients in the torcetrapib group died from cancer (including breast and pancreatic cancer), although the mechanism underlying this excess of deaths remains unclear [325]. The only exception was anacetrapib, which reduced cardiovascular disease events on top of statin therapy in a large trial with patients with atherosclerotic vascular disease without any variation in the incidence of fatal or non-fatal cancer, including breast cancer [326].

Fibrates are activators of PPAR-α, leading to significant reduction of triglyceride concentration, but also up-regulating APOA1 and APOA2 expression and ultimately increasing plasma HDL-C levels. Results regarding fibrates and HDL-C levels on endocrine-related cancer risk are controversial. A previous work found increased cancer-related deaths following the use of clofibrate for the primary prevention of ischemic heart disease [327], however, this excess of mortality was not related with endocrine cancers [327]. Also, experimental works with rats and mice found increased hepatic carcinogenesis after fibrate use [328], but fenofibrate considerably inhibited the growth of the breast tumors in mice [329]. Several large clinical trials found no effect of fibrates on cancer incidence and cancer-related deaths, independently of the fibrate used and cancer type [330–333]. Furthermore, some large and long-follow up observational studies revealed that gemfibrozil had no significant effects in cancer mortality, including prostate cancer [334–336]. Moreover, bezafibrate treatment was associated with reduced risk of cancer, including prostate cancer, among patients with coronary artery disease, however, this association was not sensitive to adjustment for on-trial lipid levels [337]. Overall, there is not enough evidence suggesting that the increased HDL-C levels following fibrate treatment might have an impact on any cancer-related outcomes; thus, their use with anticancer purposes cannot be considered in clinical practice.

Niacin increases HDL-C by 20-25% and reduces triglycerides and LDL-C by 25-30% and 20%, respectively [338]. Data on cancer-related outcomes do not suggest significant beneficial effects of niacin in endocrine cancers. In that sense, cancer deaths in the Coronary Drug Project were similar between treated and untreated patients, although the number of cases reported was low [339]. Moreover, in a large study with adults with vascular disease, the use of niacin in combination with laropiprant did not influence the overall incidence of cancer, including breast cancer [340].

In this context, an innovative area of research in which HDL-like particles are used to vehiculate anticancer drugs and molecules to cancer cells is producing interesting results [341], however, further preclinical and clinical trials are necessary to verify the efficacy in terms of endocrine cancer incidence and progression and safety of therapeutic increase of HDL-C.

In conclusion, the effect of these hypolipidemiant drugs in human cancer prevention and treatment remains controversial and more carefully designed studies are needed before a definite conclusion regarding endocrine cancer risk and recurrence can be made.

9. Concluding remarks

Although the endocrine-related tumors show different specific molecular signatures, they all require a high demand of cholesterol for the tumor growth and survival due, at least in part, to the increased hormone and steroid production by these cells. Although several large clinical trials indicate a positive association between plasma cholesterol levels and the risk for some endocrine cancers, not all the studies revealed an association and, even some of them revealed an inverse relationship with these cancers. Some of these studies pointed to a direct association between LDL-C levels and breast cancer, but this association was not found in other endocrine cancers. Beyond LDL-C levels, LDLR may be essential for the progression of endocrine-related cancers by maintaining the cholesterol distribution of tumor cells. Furthermore, both LDLR and OLR1 may modulate cellular signaling pathways involved in tumorigenesis. SR-BI-mediated cholesterol uptake may also enhance cell proliferation and play a critical role in cancer cells expressing high levels of this protein, such as those of breast, prostate, and ovarian cancer. However, HDL also exhibits antioxidant and anti-inflammatory properties that could protect against oxidative stress-mediated proliferation in some endocrine cancer cells. These divergent HDL actions may differentially affect endocrine cancers depending of their cholesterol needs and the role of inflammatory and oxidative processes in tumor development. The excess of intracellullar unesterified cholesterol may also be converted into 27-HC, which can promote tumorigenic processes in breast end epithelial thyroid cancer. Deregulation of genes involved in cholesterol synthesis has also been reported in all endocrine-related cancer cells but this is highly dependent of tumor cell type and both an upregulation and downregulation of mevalonate pathway have been reported. Although some large clinical trials indicated that statins may reduce the incidence of breast, prostate, pancreatic and ovarian cancer, these findings were not reproduced in all studies.

Collectively, these studies strongly indicate that cholesterol homeostasis deregulation is a key contributing factor to endocrine-related cancer development. Therapeutic targeting of lipoprotein-mediated cholesterol uptake and cholesterol storage pathways might constitute a potentially effective approach to prevent or delay progression endocrine-related cancers

Conflict of interest statement

The authors declare that there are no conflicts of interest.

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Bibliography

[1] B. Huang, B. Song, C. Xu, Cholesterol metabolism in cancer: mechanisms and therapeutic opportunities, Nat Metab. 2 (2020) 132–141. https://doi.org/10.1038/s42255-020-0174-0.

[2] X. Ding, W. Zhang, S. Li, H. Yang, The role of cholesterol metabolism in cancer, Am J Cancer Res. 9 (2019) 219–227.

[3] A. Chimento, I. Casaburi, P. Avena, F. Trotta, A. De Luca, V. Rago, V. Pezzi, R. Sirianni, Cholesterol and Its Metabolites in Tumor Growth: Therapeutic Potential of Statins in Cancer Treatment, Front Endocrinol (Lausanne). 9 (2018) 807. https://doi.org/10.3389/fendo.2018.00807.

[4] R. Lloyd, R. Osamura, G. Klöppel, J. Rosai, WHO Classification of Tumours of Endocrine Organs, 4th edition, 2017.

[5] T. Sudhop, D. Lütjohann, A. Kodal, M. Igel, D.L. Tribble, S. Shah, I. Perevozskaya, K. von Bergmann, Inhibition of intestinal cholesterol absorption by ezetimibe in humans, Circulation. 106 (2002) 1943–1948. https://doi.org/10.1161/01.cir.0000034044.95911.dc.

[6] M.Y.M. van der Wulp, H.J. Verkade, A.K. Groen, Regulation of cholesterol homeostasis, Mol. Cell. Endocrinol. 368 (2013) 1–16. https://doi.org/10.1016/j.mce.2012.06.007.

[7] M.S. Brown, A. Radhakrishnan, J.L. Goldstein, Retrospective on Cholesterol Homeostasis: The Central Role of Scap, Annu. Rev. Biochem. 87 (2018) 783–807. https://doi.org/10.1146/annurev-biochem-062917-011852.

[8] E. Ikonen, Cellular cholesterol trafficking and compartmentalization, Nat. Rev. Mol. Cell Biol. 9 (2008) 125–138. https://doi.org/10.1038/nrm2336.

[9] A. Rigotti, H.E. Miettinen, M. Krieger, The role of the high-density lipoprotein receptor SR-BI in the lipid metabolism of endocrine and other tissues, Endocr. Rev. 24 (2003) 357–387. https://doi.org/10.1210/er.2001-0037.

[10] L. Zhang, K. Reue, L.G. Fong, S.G. Young, P. Tontonoz, Feedback regulation of cholesterol uptake by the LXR-IDOL-LDLR axis, Arterioscler. Thromb. Vasc. Biol. 32 (2012) 2541–2546. https://doi.org/10.1161/ATVBAHA.112.250571.

[11] A. Kloudova, F.P. Guengerich, P. Soucek, The Role of Oxysterols in Human Cancer, Trends Endocrinol. Metab. 28 (2017) 485–496. https://doi.org/10.1016/j.tem.2017.03.002.

[12] K. Georgila, D. Vyrla, E. Drakos, Apolipoprotein A-I (ApoA-I), Immunity, Inflammation and Cancer, Cancers. 11 (2019) 1097. https://doi.org/10.3390/cancers11081097.

[13] T. Bacchetti, G. Ferretti, A. Sahebkar, The role of paraoxonase in cancer, Semin. Cancer Biol. 56 (2019) 72–86. https://doi.org/10.1016/j.semcancer.2017.11.013.

[14] Global Burden of Disease Cancer Collaboration, C. Fitzmaurice, T.F. Akinyemiju, F.H. Al Lami, T. Alam, R. Alizadeh-Navaei, C. Allen, U. Alsharif, N. Alvis-Guzman, E. Amini, B.O. Anderson, O. Aremu, A. Artaman, S.W. Asgedom, R. Assadi, T.M. Atey, L. Avila-Burgos, A. Awasthi, H.O. Ba Saleem, A. Barac, J.R. Bennett, I.M. Bensenor, N. Bhakta, H. Brenner, L. Cahuana-Hurtado, C.A. Castañeda-Orjuela, F. Catalá-López, J.-Y.J. Choi, D.J. Christopher, S.-C. Chung, M.P. Curado, L. Dandona, R. Dandona, J. das Neves, S. Dey, S.D. Dharmaratne, D.T. Doku, T.R. Driscoll, M. Dubey, H. Ebrahimi, D. Edessa, Z. El-Khatib, A.Y. Endries, F. Fischer, L.M. Force, K.J. Foreman, S.W. Gebrehiwot, S.V. Gopalani, G. Grosso, R. Gupta, B. Gyawali, R.R. Hamadeh, S. Hamidi, J. Harvey, H.Y. Hassen, R.J. Hay, S.I. Hay, B. Heibati, M.K. Hiluf, N. Horita, H.D. Hosgood, O.S. Ilesanmi,

K. Innos, F. Islami, M.B. Jakovljevic, S.C. Johnson, J.B. Jonas, A. Kasaeian, T.D. Kassa, Y.S. Khader, E.A. Khan, G. Khan, Y.-H. Khang, M.H. Khosravi, J. Khubchandani, J.A. Kopec, G.A. Kumar, M. Kutz, D.P. Lad, A. Lafranconi, Q. Lan, Y. Legesse, J. Leigh, S. Linn, R. Lunevicius, A. Majeed, R. Malekzadeh, D.C. Malta, L.G. Mantovani, B.J. McMahon, T. Meier, Y.A. Melaku, M. Melku, P. Memiah, W. Mendoza, T.J. Meretoja, H.B. Mezgebe, T.R. Miller, S. Mohammed, A.H. Mokdad, M. Moosazadeh, P. Moraga, S.M. Mousavi, V. Nangia, C.T. Nguyen, V.M. Nong, F.A. Ogbo, A.T. Olagunju, M. Pa, E.-K. Park, T. Patel, D.M. Pereira, F. Pishgar, M.J. Postma, F. Pourmalek, M. Qorbani, A. Rafay, S. Rawaf, D.L. Rawaf, G. Roshandel, S. Safiri, H. Salimzadeh, J.R. Sanabria, M.M. Santric Milicevic, B. Sartorius, M. Satpathy, S.G. Sepanlou, K.A. Shackelford, M.A. Shaikh, M. Sharif-Alhoseini, J. She, M.-J. Shin, I. Shiue, M.G. Shrime, A.H. Sinke, M. Sisay, A. Sligar, M.B. Sufiyan, B.L. Sykes, R. Tabarés-Seisdedos, G.A. Tessema, R. Topor-Madry, T.T. Tran, B.X. Tran, K.N. Ukwaja, V.V. Vlassov, S.E. Vollset, E. Weiderpass, H.C. Williams, N.B. Yimer, N. Yonemoto, M.Z. Younis, C.J.L. Murray, M. Naghavi, Global, Regional, and National Cancer Incidence, Mortality, Years of Life Lost, Years Lived With Disability, and Disability-Adjusted Life-Years for 29 Cancer Groups, 1990 to 2016: A Systematic Analysis for the Global Burden of Disease Study, JAMA Oncol. 4 (2018) 1553–1568. https://doi.org/10.1001/jamaoncol.2018.2706.

[15] D. Vuong, P.T. Simpson, B. Green, M.C. Cummings, S.R. Lakhani, Molecular classification of breast cancer, Virchows Arch. 465 (2014) 1–14. https://doi.org/10.1007/s00428-014-1593-7.

[16] A.R. Cervino, M. Burei, L. Mansi, L. Evangelista, Molecular pathways and molecular imaging in breast cancer: an update, Nucl. Med. Biol. 40 (2013) 581–591. https://doi.org/10.1016/j.nucmedbio.2013.03.002.

[17] K.M. Cornejo, D. Kandil, A. Khan, E.F. Cosar, Theranostic and molecular classification of breast cancer, Arch. Pathol. Lab. Med. 138 (2014) 44–56. https://doi.org/10.5858/arpa.2012-0442-RA.

[18] C.M. Kitahara, A. Berrington de González, N.D. Freedman, R. Huxley, Y. Mok, S.H. Jee, J.M. Samet, Total cholesterol and cancer risk in a large prospective study in Korea, J. Clin. Oncol. 29 (2011) 1592–1598. https://doi.org/10.1200/JCO.2010.31.5200.

[19] M. His, L. Zelek, M. Deschasaux, C. Pouchieu, E. Kesse-Guyot, S. Hercberg, P. Galan, P. Latino-Martel, J. Blacher, M. Touvier, Prospective associations between serum biomarkers of lipid metabolism and overall, breast and prostate cancer risk, Eur. J. Epidemiol. 29 (2014) 119–132. https://doi.org/10.1007/s10654-014-9884-5.

[20] L.J. Martin, O. Melnichouk, E. Huszti, P.W. Connelly, C.V. Greenberg, S. Minkin, N.F. Boyd, Serum Lipids, Lipoproteins, and Risk of Breast Cancer: A Nested Case-Control Study Using Multiple Time Points, JNCI J Natl Cancer Inst. 107 (2015) djv032. https://doi.org/10.1093/jnci/djv032.

[21] H. Ni, H. Liu, R. Gao, Serum Lipids and Breast Cancer Risk: A Meta-Analysis of Prospective Cohort Studies, Plos One. 10 (2015) e0142669. https://doi.org/10.1371/journal.pone.0142669.

[22] J.L.F. Bosco, J.R. Palmer, D.A. Boggs, E.E. Hatch, L. Rosenberg, Cardiometabolic factors and breast cancer risk in U.S. black women, Breast Cancer Res. Treat. 134 (2012) 1247–1256. https://doi.org/10.1007/s10549-012-2131-4.

[23] M. Ha, J. Sung, Y.-M. Song, Serum total cholesterol and the risk of breast cancer in postmenopausal Korean women, Cancer Causes Control. 20 (2009) 1055–1060. https://doi.org/10.1007/s10552-009-9301-7.

[24] A.H. Eliassen, G.A. Colditz, B. Rosner, W.C. Willett, S.E. Hankinson, Serum lipids, lipid-lowering drugs, and the risk of breast cancer, Arch. Intern. Med. 165 (2005) 2264–2271. https://doi.org/10.1001/archinte.165.19.2264.
[25] E.R. Nelson, C. Chang, D.P. McDonnell, Cholesterol and breast cancer pathophysiology, Trends Endocrinol. Metab. 25 (2014) 649–655. https://doi.org/10.1016/j.tem.2014.10.001.
[26] J. Hu, C. La Vecchia, M. de Groh, E. Negri, H. Morrison, L. Mery, Canadian Cancer Registries Epidemiology Research Group, Dietary cholesterol intake and cancer, Ann. Oncol. 23 (2012) 491–500. https://doi.org/10.1093/annonc/mdr155.
[27] C. Li, L. Yang, D. Zhang, W. Jiang, Systematic review and meta-analysis suggest that dietary cholesterol intake increases risk of breast cancer, Nutrition Research. 36 (2016) 627–635. https://doi.org/10.1016/j.nutres.2016.04.009.
[28] G. Llaverias, C. Danilo, I. Mercier, K. Daumer, F. Capozza, T.M. Williams, F. Sotgia, M.P. Lisanti, P.G. Frank, Role of cholesterol in the development and progression of breast cancer, Am. J. Pathol. 178 (2011) 402–412. https://doi.org/10.1016/j.ajpath.2010.11.005.
[29] C.T. Guy, R.D. Cardiff, W.J. Muller, Induction of mammary tumors by expression of polyomavirus middle T oncogene: a transgenic mouse model for metastatic disease, Mol. Cell. Biol. 12 (1992) 954–961.
[30] K. Pelton, C.M. Coticchia, A.S. Curatolo, C.P. Schaffner, D. Zurakowski, K.R. Solomon, M.A. Moses, Hypercholesterolemia induces angiogenesis and accelerates growth of breast tumors in vivo, Am. J. Pathol. 184 (2014) 2099–2110. https://doi.org/10.1016/j.ajpath.2014.03.006.
[31] N. Alikhani, R.D. Ferguson, R. Novosyadlyy, E.J. Gallagher, E.J. Scheinman, S. Yakar, D. LeRoith, Mammary tumor growth and pulmonary metastasis are enhanced in a hyperlipidemic mouse model, Oncogene. 32 (2013) 961–967. https://doi.org/10.1038/onc.2012.113.
[32] E.R. Nelson, S.E. Wardell, J.S. Jasper, S. Park, S. Suchindran, M.K. Howe, N.J. Carver, R.V. Pillai, P.M. Sullivan, V. Sondhi, M. Umetani, J. Geradts, D.P. McDonnell, 27-Hydroxycholesterol links hypercholesterolemia and breast cancer pathophysiology, Science. 342 (2013) 1094–1098. https://doi.org/10.1126/science.1241908.
[33] C. Rodrigues dos Santos, G. Domingues, I. Matias, J. Matos, I. Fonseca, J.M. de Almeida, S. Dias, LDL-cholesterol signaling induces breast cancer proliferation and invasion, Lipids Health Dis. 13 (2014) 16. https://doi.org/10.1186/1476-511X-13-16.
[34] C. Rodrigues dos Santos, I. Fonseca, S. Dias, J.C. Mendes de Almeida, Plasma level of LDL-cholesterol at diagnosis is a predictor factor of breast tumor progression, BMC Cancer. 14 (2014) 132. https://doi.org/10.1186/1471-2407-14-132.
[35] C. Nowak, J. Ärnlöv, A Mendelian randomization study of the effects of blood lipids on breast cancer risk, Nat Commun. 9 (2018) 3957. https://doi.org/10.1038/s41467-018-06467-9.
[36] A. Beeghly-Fadiel, N.K. Khankari, R.J. Delahanty, X.-O. Shu, Y. Lu, M.K. Schmidt, M.K. Bolla, K. Michailidou, Q. Wang, J. Dennis, D. Yannoukakos, A.M. Dunning, P.D.P. Pharoah, G. Chenevix-Trench, R.L. Milne, D.J. Hunter, H. Per, P. Kraft, J. Simard, D.F. Easton, W. Zheng, A Mendelian randomization analysis of circulating lipid traits and breast cancer risk, Int J Epidemiol. (2019). https://doi.org/10.1093/ije/dyz242.

[37] M. Touvier, P. Fassier, M. His, T. Norat, D.S.M. Chan, J. Blacher, S. Hercberg, P. Galan, N. Druesne-Pecollo, P. Latino-Martel, Cholesterol and breast cancer risk: a systematic review and meta-analysis of prospective studies, Br. J. Nutr. 114 (2015) 347–357. https://doi.org/10.1017/S000711451500183X.
[38] P.D. Chandler, Y. Song, J. Lin, S. Zhang, H.D. Sesso, S. Mora, E.L. Giovannucci, K.E. Rexrode, M.V. Moorthy, C. Li, P.M. Ridker, I.-M. Lee, J.E. Manson, J.E. Buring, L. Wang, Lipid biomarkers and long-term risk of cancer in the Women's Health Study, Am J Clin Nutr. 103 (2016) 1397–1407. https://doi.org/10.3945/ajcn.115.124321.
[39] S. Borgquist, T. Butt, P. Almgren, D. Shiffman, T. Stocks, M. Orho-Melander, J. Manjer, O. Melander, Apo-lipoproteins, lipids and risk of cancer, Int. J. Cancer. (2016). https://doi.org/10.1002/ijc.30013.
[40] J.C. Melvin, D. Seth, L. Holmberg, H. Garmo, N. Hammar, I. Jungner, G. Walldius, M. Lambe, A. Wigertz, M. Van Hemelrijck, Lipid profiles and risk of breast and ovarian cancer in the Swedish AMORIS study, Cancer Epidemiol. Biomarkers Prev. 21 (2012) 1381–1384. https://doi.org/10.1158/1055-9965.EPI-12-0188.
[41] A.A. Llanos, K.H. Makambi, C.A. Tucker, S.F. Wallington, P.G. Shields, L.L. Adams-Campbell, Cholesterol, lipoproteins, and breast cancer risk in African American women, Ethn Dis. 22 (2012) 281–287.
[42] C.-W. Lu, Y.-H. Lo, C.-H. Chen, C.-Y. Lin, C.-H. Tsai, P.-J. Chen, Y.-F. Yang, C.-H. Wang, C.-H. Tan, M.-F. Hou, S.-S.F. Yuan, VLDL and LDL, but not HDL, promote breast cancer cell proliferation, metastasis and angiogenesis, Cancer Lett. 388 (2017) 130–138. https://doi.org/10.1016/j.canlet.2016.11.033.
[43] C.J. Antalis, T. Arnold, T. Rasool, B. Lee, K.K. Buhman, R.A. Siddiqui, High ACAT1 expression in estrogen receptor negative basal-like breast cancer cells is associated with LDL-induced proliferation, Breast Cancer Res. Treat. 122 (2010) 661–670. https://doi.org/10.1007/s10549-009-0594-8.
[44] M. Rotheneder, G.M. Kostner, Effects of low- and high-density lipoproteins on the proliferation of human breast cancer cells in vitro: differences between hormone-dependent and hormone-independent cell lines, Int. J. Cancer. 43 (1989) 875–879. https://doi.org/10.1002/ijc.2910430523.
[45] C.J. Antalis, A. Uchida, K.K. Buhman, R.A. Siddiqui, Migration of MDA-MB-231 breast cancer cells depends on the availability of exogenous lipids and cholesterol esterification, Clin. Exp. Metastasis. 28 (2011) 733–741. https://doi.org/10.1007/s10585-011-9405-9.
[46] D. de Gonzalo-Calvo, L. López-Vilaró, L. Nasarre, M. Perez-Olabarria, T. Vázquez, D. Escuin, L. Badimon, A. Barnadas, E. Lerma, V. Llorente-Cortés, Intratumor cholesteryl ester accumulation is associated with human breast cancer proliferation and aggressive potential: a molecular and clinicopathological study, BMC Cancer. 15 (2015) 460. https://doi.org/10.1186/s12885-015-1469-5.
[47] S.-H. Oh, S.-Y. Choi, H.-J. Choi, H.-M. Ryu, Y.-J. Kim, H.-Y. Jung, J.-H. Cho, C.-D. Kim, S.-H. Park, T.-H. Kwon, Y.-L. Kim, The emerging role of xanthine oxidase inhibition for suppression of breast cancer cell migration and metastasis associated with hypercholesterolemia, FASEB J. 33 (2019) 7301–7314. https://doi.org/10.1096/fj.201802415RR.
[48] I. Delimaris, E. Faviou, G. Antonakos, E. Stathopoulou, A. Zachari, A. Dionyssiou-Asteriou, Oxidized LDL, serum oxidizability and serum lipid levels in patients with breast or ovarian cancer, Clinical Biochemistry. 40 (2007) 1129–1134. https://doi.org/10.1016/j.clinbiochem.2007.06.007.

[49] S. Pucci, C. Polidoro, C. Greggi, F. Amati, E. Morini, M. Murdocca, M. Biancolella, A. Orlandi, F. Sangiuolo, G. Novelli, Pro-oncogenic action of LOX-1 and its splice variant LOX-1Δ4 in breast cancer phenotypes, Cell Death Dis. 10 (2019) 53. https://doi.org/10.1038/s41419-018-1279-1.
[50] M. Khaidakov, S. Mitra, B.-Y. Kang, X. Wang, S. Kadlubar, G. Novelli, V. Raj, M. Winters, W.C. Carter, J.L. Mehta, Oxidized LDL receptor 1 (OLR1) as a possible link between obesity, dyslipidemia and cancer, PLoS ONE. 6 (2011) e20277. https://doi.org/10.1371/journal.pone.0020277.
[51] M. Liang, P. Zhang, J. Fu, Up-regulation of LOX-1 expression by TNF-α promotes trans-endothelial migration of MDA-MB-231 breast cancer cells, Cancer Letters. 258 (2007) 31–37. https://doi.org/10.1016/j.canlet.2007.08.003.
[52] B. Wang, H. Zhao, L. Zhao, Y. Zhang, Q. Wan, Y. Shen, X. Bu, M. Wan, C. Shen, Up-regulation of OLR1 expression by TBC1D3 through activation of TNFα/NF-κB pathway promotes the migration of human breast cancer cells, Cancer Lett. 408 (2017) 60–70. https://doi.org/10.1016/j.canlet.2017.08.021.
[53] M. Khaidakov, J.L. Mehta, Oxidized LDL triggers pro-oncogenic signaling in human breast mammary epithelial cells partly via stimulation of MiR-21, PLoS ONE. 7 (2012) e46973. https://doi.org/10.1371/journal.pone.0046973.
[54] H.A. Hirsch, D. Iliopoulos, A. Joshi, Y. Zhang, S.A. Jaeger, M. Bulyk, P.N. Tsichlis, X. Shirley Liu, K. Struhl, A transcriptional signature and common gene networks link cancer with lipid metabolism and diverse human diseases, Cancer Cell. 17 (2010) 348–361. https://doi.org/10.1016/j.ccr.2010.01.022.
[55] X. Li, H. Tang, J. Wang, X. Xie, P. Liu, Y. Kong, F. Ye, Z. Shuang, Z. Xie, X. Xie, The effect of preoperative serum triglycerides and high-density lipoprotein-cholesterol levels on the prognosis of breast cancer, Breast. 32 (2017) 1–6. https://doi.org/10.1016/j.breast.2016.11.024.
[56] A.M. Kucharska-Newton, W.D. Rosamond, P.J. Mink, A.J. Alberg, E. Shahar, A.R. Folsom, HDL-cholesterol and incidence of breast cancer in the ARIC cohort study, Ann Epidemiol. 18 (2008) 671–677. https://doi.org/10.1016/j.annepidem.2008.06.006.
[57] Y. Kim, S.K. Park, W. Han, D.-H. Kim, Y.-C. Hong, E.H. Ha, S.-H. Ahn, D.-Y. Noh, D. Kang, K.-Y. Yoo, Serum high-density lipoprotein cholesterol and breast cancer risk by menopausal status, body mass index, and hormonal receptor in Korea, Cancer Epidemiol. Biomarkers Prev. 18 (2009) 508–515. https://doi.org/10.1158/1055-9965.EPI-08-0133.
[58] A.-S. Furberg, M.B. Veierød, T. Wilsgaard, L. Bernstein, I. Thune, Serum high-density lipoprotein cholesterol, metabolic profile, and breast cancer risk, J. Natl. Cancer Inst. 96 (2004) 1152–1160. https://doi.org/10.1093/jnci/djh216.
[59] M. His, L. Dartois, G. Fagherazzi, A. Boutten, T. Dupré, S. Mesrine, M.-C. Boutron-Ruault, F. Clavel-Chapelon, L. Dossus, Associations between serum lipids and breast cancer incidence and survival in the E3N prospective cohort study, Cancer Causes Control. 28 (2017) 77–88. https://doi.org/10.1007/s10552-016-0832-4.
[60] D. Gospodarowicz, G.M. Lui, R. Gonzalez, High-density lipoproteins and the proliferation of human tumor cells maintained on extracellular matrix-coated dishes and exposed to defined medium, Cancer Res. 42 (1982) 3704–3713.
[61] C. Danilo, J.L. Gutierrez-Pajares, M.A. Mainieri, I. Mercier, M.P. Lisanti, P.G. Frank, Scavenger receptor class B type I regulates cellular cholesterol metabolism and cell signaling associated with breast cancer development, Breast Cancer Res. 15 (2013) R87. https://doi.org/10.1186/bcr3483.

[62] H. Balci, H. Genc, C. Papila, G. Can, B. Papila, H. Yanardag, H. Uzun, Serum lipid hydroperoxide levels and paraoxonase activity in patients with lung, breast, and colorectal cancer, J. Clin. Lab. Anal. 26 (2012) 155–160. https://doi.org/10.1002/jcla.21503.
[63] M.O. Kaya, S. Sinan, Ö.Ö. Güler, O. Arslan, Is there a relation between genetic susceptibility with cancer? A study about paraoxanase (PON1) enzyme activity in breast cancer cases, Journal of Enzyme Inhibition and Medicinal Chemistry. 31 (2016) 1349–1355. https://doi.org/10.3109/14756366.2015.1134523.
[64] Y. Okuturlar, M. Gunaldi, H. Kocoglu, M. Hursitoglu, A. Gedikbasi, D. Acarer, O. Harmankaya, A. Kumbasar, Serum paraoxonase and arylesterase can be useful markers to predict neoadjuvant chemotherapy requirement in patients with breast cancer, J Cancer Res Ther. 14 (2018) S362–S367. https://doi.org/10.4103/0973-1482.235355.
[65] C. Antognelli, C. Del Buono, V. Ludovini, S. Gori, V.N. Talesa, L. Crinò, F. Barberini, A. Rulli, CYP17, GSTP1, PON1 and GLO1 gene polymorphisms as risk factors for breast cancer: an Italian case-control study, BMC Cancer. 9 (2009) 115. https://doi.org/10.1186/1471-2407-9-115.
[66] M. Saadat, Paraoxonase 1 genetic polymorphisms and susceptibility to breast cancer: a meta-analysis, Cancer Epidemiol. 36 (2012) e101-103. https://doi.org/10.1016/j.canep.2011.10.015.
[67] B. Mackness, P.N. Durrington, M.I. Mackness, Human Serum Paraoxonase, General Pharmacology: The Vascular System. 31 (1998) 329–336. https://doi.org/10.1016/S0306-3623(98)00028-7.
[68] J. Wu, M. Fang, X. Zhou, B. Zhu, Z. Yang, Paraoxonase 1 gene polymorphisms are associated with an increased risk of breast cancer in a population of Chinese women, Oncotarget. 8 (2017) 25362–25371. https://doi.org/10.18632/oncotarget.15911.
[69] P. Liu, Q. Wang, Y. Cui, J. Wang, A meta-analysis of the relationship between paraoxonase 1 polymorphisms and cancer, Free Radic. Res. 53 (2019) 1045–1050. https://doi.org/10.1080/10715762.2019.1645956.
[70] Y. Wen, Z. Huang, X. Zhang, B. Gao, Y. He, Correlation between PON1 gene polymorphisms and breast cancer risk: a Meta-analysis, Int J Clin Exp Med. 8 (2015) 20343–20348.
[71] V.L. Stevens, C. Rodriguez, A.L. Pavluck, M.J. Thun, E.E. Calle, Association of polymorphisms in the paraoxonase 1 gene with breast cancer incidence in the CPS-II Nutrition Cohort, Cancer Epidemiol. Biomarkers Prev. 15 (2006) 1226–1228. https://doi.org/10.1158/1055-9965.EPI-05-0930.
[72] A. Farmohammadi, A. Momeni, B. Bahmani, H. Ghorbani, R. Ramzanpour, Association of PON1-L55M Genetic Variation and Breast Cancer Risk: A Case-Control Trial, Asian Pac. J. Cancer Prev. 21 (2020) 255–258. https://doi.org/10.31557/APJCP.2020.21.1.255.
[73] H.-L. Huang, T. Stasyk, S. Morandell, H. Dieplinger, G. Falkensammer, A. Griesmacher, M. Mogg, M. Schreiber, I. Feuerstein, C.W. Huck, G. Stecher, G.K. Bonn, L.A. Huber, Biomarker discovery in breast cancer serum using 2-D differential gel electrophoresis/ MALDI-TOF/TOF and data validation by routine clinical assays, Electrophoresis. 27 (2006) 1641–1650. https://doi.org/10.1002/elps.200500857.
[74] S.-J. Chang, M.-F. Hou, S.-M. Tsai, S.-H. Wu, L.A. Hou, H. Ma, T.-Y. Shann, S.-H. Wu, L.-Y. Tsai, The association between lipid profiles and breast cancer

among Taiwanese women, Clin. Chem. Lab. Med. 45 (2007) 1219–1223. https://doi.org/10.1515/CCLM.2007.263.
[75] L. Cedó, A. García-León, L. Baila-Rueda, D. Santos, V. Grijalva, M.R. Martínez-Cignoni, J.M. Carbó, J. Metso, L. López-Vilaró, A. Zorzano, A.F. Valledor, A. Cenarro, M. Jauhiainen, E. Lerma, A.M. Fogelman, S.T. Reddy, J.C. Escolà-Gil, F. Blanco-Vaca, ApoA-I mimetic administration, but not increased apoA-I-containing HDL, inhibits tumour growth in a mouse model of inherited breast cancer, Sci Rep. 6 (2016) 36387. https://doi.org/10.1038/srep36387.
[76] L. Cedó, S.T. Reddy, E. Mato, F. Blanco-Vaca, J.C. Escolà-Gil, HDL and LDL: Potential New Players in Breast Cancer Development, J Clin Med. 8 (2019). https://doi.org/10.3390/jcm8060853.
[77] C. Ben Hassen, J.L. Gutierrez-Pajares, C. Guimaraes, R. Guibon, M. Pinault, G. Fromont, P.G. Frank, Apolipoprotein-mediated regulation of lipid metabolism induces distinctive effects in different types of breast cancer cells, Breast Cancer Research. 22 (2020) 38. https://doi.org/10.1186/s13058-020-01276-9.
[78] P. Boyle, M. Boniol, A. Koechlin, C. Robertson, F. Valentini, K. Coppens, L.-L. Fairley, M. Boniol, T. Zheng, Y. Zhang, M. Pasterk, M. Smans, M.P. Curado, P. Mullie, S. Gandini, M. Bota, G.B. Bolli, J. Rosenstock, P. Autier, Diabetes and breast cancer risk: a meta-analysis, Br. J. Cancer. 107 (2012) 1608–1617. https://doi.org/10.1038/bjc.2012.414.
[79] P.J. Hardefeldt, S. Edirimanne, G.D. Eslick, Diabetes increases the risk of breast cancer: a meta-analysis, Endocr. Relat. Cancer. 19 (2012) 793–803. https://doi.org/10.1530/ERC-12-0242.
[80] A. Kontush, M.J. Chapman, Why is HDL functionally deficient in type 2 diabetes?, Curr. Diab. Rep. 8 (2008) 51–59. https://doi.org/10.1007/s11892-008-0010-5.
[81] B. Pan, H. Ren, Y. Ma, D. Liu, B. Yu, L. Ji, L. Pan, J. Li, L. Yang, X. Lv, X. Shen, B. Chen, Y. Zhang, B. Willard, Y. He, L. Zheng, High-density lipoprotein of patients with type 2 diabetes mellitus elevates the capability of promoting migration and invasion of breast cancer cells, Int. J. Cancer. 131 (2012) 70–82. https://doi.org/10.1002/ijc.26341.
[82] B. Pan, H. Ren, Y. He, X. Lv, Y. Ma, J. Li, L. Huang, B. Yu, J. Kong, C. Niu, Y. Zhang, W. Sun, L. Zheng, HDL of patients with type 2 diabetes mellitus elevates the capability of promoting breast cancer metastasis, Clin. Cancer Res. 18 (2012) 1246–1256. https://doi.org/10.1158/1078-0432.CCR-11-0817.
[83] X. Huang, D. He, J. Ming, Y. He, C. Zhou, H. Ren, X. He, C. Wang, J. Jin, L. Ji, B. Willard, B. Pan, L. Zheng, High-density lipoprotein of patients with breast cancer complicated with type 2 diabetes mellitus promotes cancer cells adhesion to vascular endothelium via ICAM-1 and VCAM-1 upregulation, Breast Cancer Res. Treat. 155 (2016) 441–455. https://doi.org/10.1007/s10549-016-3696-0.
[84] L.A. Pires, R. Hegg, F.R. Freitas, E.R. Tavares, C.P. Almeida, E.C. Baracat, R.C. Maranhão, Effect of neoadjuvant chemotherapy on low-density lipoprotein (LDL) receptor and LDL receptor-related protein 1 (LRP-1) receptor in locally advanced breast cancer, Braz. J. Med. Biol. Res. 45 (2012) 557–564.
[85] W.M. Cao, K. Murao, H. Imachi, X. Yu, H. Abe, A. Yamauchi, M. Niimi, A. Miyauchi, N.C.W. Wong, T. Ishida, A mutant high-density lipoprotein receptor inhibits proliferation of human breast cancer cells, Cancer Res. 64 (2004) 1515–1521.
[86] B. Jamalzei, F.S. Karami Tehrani, M. Atri, Evaluation of LDL receptor and Scavenger Receptor, Class B, Type 1 in the malignant and benign breast tumors:

The correlation with the expression of miR-199a-5p, miR-199b-5p and miR-455-5p, Gene. 749 (2020) 144720. https://doi.org/10.1016/j.gene.2020.144720.
[87] E.J. Gallagher, Z. Zelenko, B.A. Neel, I.M. Antoniou, L. Rajan, N. Kase, D. LeRoith, Elevated tumor LDLR expression accelerates LDL cholesterol-mediated breast cancer growth in mouse models of hyperlipidemia, Oncogene. 36 (2017) 6462–6471. https://doi.org/10.1038/onc.2017.247.
[88] B. Yuan, C. Wu, X. Wang, D. Wang, H. Liu, L. Guo, X.-A. Li, J. Han, H. Feng, High scavenger receptor class B type I expression is related to tumor aggressiveness and poor prognosis in breast cancer, Tumour Biol. 37 (2016) 3581–3588. https://doi.org/10.1007/s13277-015-4141-4.
[89] J. Li, J. Wang, M. Li, L. Yin, X.-A. Li, T.-G. Zhang, Up-regulated expression of scavenger receptor class B type 1 (SR-B1) is associated with malignant behaviors and poor prognosis of breast cancer, Pathol. Res. Pract. 212 (2016) 555–559. https://doi.org/10.1016/j.prp.2016.03.011.
[90] S. Schimanski, P.J. Wild, O. Treeck, F. Horn, A. Sigruener, C. Rudolph, H. Blaszyk, M. Klinkhammer-Schalke, O. Ortmann, A. Hartmann, G. Schmitz, Expression of the lipid transporters ABCA3 and ABCA1 is diminished in human breast cancer tissue, Horm. Metab. Res. 42 (2010) 102–109. https://doi.org/10.1055/s-0029-1241859.
[91] B. Smith, H. Land, Anticancer activity of the cholesterol exporter ABCA1 gene, Cell Rep. 2 (2012) 580–590. https://doi.org/10.1016/j.celrep.2012.08.011.
[92] H. Pan, Y. Zheng, Q. Pan, H. Chen, F. Chen, J. Wu, D. Di, Expression of LXR-β, ABCA1 and ABCG1 in human triple-negative breast cancer tissues, Oncol. Rep. 42 (2019) 1869–1877. https://doi.org/10.3892/or.2019.7279.
[93] L.-L. Vedin, S.A. Lewandowski, P. Parini, J.-A. Gustafsson, K.R. Steffensen, The oxysterol receptor LXR inhibits proliferation of human breast cancer cells, Carcinogenesis. 30 (2009) 575–579. https://doi.org/10.1093/carcin/bgp029.
[94] S. Ehmsen, M.H. Pedersen, G. Wang, M.G. Terp, A. Arslanagic, B.L. Hood, T.P. Conrads, R. Leth-Larsen, H.J. Ditzel, Increased Cholesterol Biosynthesis Is a Key Characteristic of Breast Cancer Stem Cells Influencing Patient Outcome, Cell Rep. 27 (2019) 3927-3938.e6. https://doi.org/10.1016/j.celrep.2019.05.104.
[95] D.W. Russell, Oxysterol biosynthetic enzymes, Biochimica et Biophysica Acta (BBA) - Molecular and Cell Biology of Lipids. 1529 (2000) 126–135. https://doi.org/10.1016/S1388-1981(00)00142-6.
[96] Q. Wu, T. Ishikawa, R. Sirianni, H. Tang, J.G. McDonald, I.S. Yuhanna, B. Thompson, L. Girard, C. Mineo, R.A. Brekken, M. Umetani, D.M. Euhus, Y. Xie, P.W. Shaul, 27-Hydroxycholesterol promotes cell-autonomous, ER-positive breast cancer growth, Cell Rep. 5 (2013) 637–645. https://doi.org/10.1016/j.celrep.2013.10.006.
[97] S. Raza, J.E. Ohm, A. Dhasarathy, J. Schommer, C. Roche, K.D.P. Hammer, O. Ghribi, The cholesterol metabolite 27-hydroxycholesterol regulates p53 activity and increases cell proliferation via MDM2 in breast cancer cells, Mol. Cell. Biochem. 410 (2015) 187–195. https://doi.org/10.1007/s11010-015-2551-7.
[98] L.-M. Ma, Z.-R. Liang, K.-R. Zhou, H. Zhou, L.-H. Qu, 27-Hydroxycholesterol increases Myc protein stability via suppressing PP2A, SCP1 and FBW7 transcription in MCF-7 breast cancer cells, Biochem. Biophys. Res. Commun. 480 (2016) 328–333. https://doi.org/10.1016/j.bbrc.2016.10.038.
[99] D. Zhu, Z. Shen, J. Liu, J. Chen, Y. Liu, C. Hu, Z. Li, Y. Li, The ROS-mediated activation of STAT-3/VEGF signaling is involved in the 27-hydroxycholesterol-

induced angiogenesis in human breast cancer cells, Toxicol. Lett. 264 (2016) 79–86. https://doi.org/10.1016/j.toxlet.2016.11.006.
[100] C.G. Torres, M.E. Ramírez, P. Cruz, M.J. Epuñan, L.E. Valladares, W.D. Sierralta, 27-hydroxycholesterol induces the transition of MCF7 cells into a mesenchymal phenotype, Oncol. Rep. 26 (2011) 389–397. https://doi.org/10.3892/or.2011.1284.
[101] Z. Shen, D. Zhu, J. Liu, J. Chen, Y. Liu, C. Hu, Z. Li, Y. Li, 27-Hydroxycholesterol induces invasion and migration of breast cancer cells by increasing MMP9 and generating EMT through activation of STAT-3, Environ. Toxicol. Pharmacol. 51 (2017) 1–8. https://doi.org/10.1016/j.etap.2017.02.001.
[102] S.-Z. Shi, E.-J. Lee, Y.-J. Lin, L. Chen, H.-Y. Zheng, X.-Q. He, J.-Y. Peng, S.K. Noonepalle, A.Y. Shull, F.C. Pei, L.-B. Deng, X.-L. Tian, K.-Y. Deng, H. Shi, H.-B. Xin, Recruitment of monocytes and epigenetic silencing of intratumoral CYP7B1 primarily contribute to the accumulation of 27-hydroxycholesterol in breast cancer, Am J Cancer Res. 9 (2019) 2194–2208.
[103] F. Bray, J. Ferlay, I. Soerjomataram, R.L. Siegel, L.A. Torre, A. Jemal, Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries, CA Cancer J Clin. 68 (2018) 394–424. https://doi.org/10.3322/caac.21492.
[104] X. Filella, E. Fernández-Galan, R. Fernández Bonifacio, L. Foj, Emerging biomarkers in the diagnosis of prostate cancer, Pharmgenomics Pers Med. 11 (2018) 83–94. https://doi.org/10.2147/PGPM.S136026.
[105] J.I. Epstein, W.C. Allsbrook, M.B. Amin, L.L. Egevad, ISUP Grading Committee, The 2005 International Society of Urological Pathology (ISUP) Consensus Conference on Gleason Grading of Prostatic Carcinoma, Am. J. Surg. Pathol. 29 (2005) 1228–1242. https://doi.org/10.1097/01.pas.0000173646.99337.b1.
[106] E.A. Platz, C. Till, P.J. Goodman, H.L. Parnes, W.D. Figg, D. Albanes, M.L. Neuhouser, E.A. Klein, I.M. Thompson, A.R. Kristal, Men with low serum cholesterol have a lower risk of high-grade prostate cancer in the placebo arm of the prostate cancer prevention trial, Cancer Epidemiol. Biomarkers Prev. 18 (2009) 2807–2813. https://doi.org/10.1158/1055-9965.EPI-09-0472.
[107] T.J. Murtola, T.V.J. Kasurinen, K. Talala, K. Taari, T.L.J. Tammela, A. Auvinen, Serum cholesterol and prostate cancer risk in the Finnish randomized study of screening for prostate cancer, Prostate Cancer Prostatic Dis. 22 (2019) 66–76. https://doi.org/10.1038/s41391-018-0087-0.
[108] L. YuPeng, Z. YuXue, L. PengFei, C. Cheng, Z. YaShuang, L. DaPeng, D. Chen, Cholesterol Levels in Blood and the Risk of Prostate Cancer: A Meta-analysis of 14 Prospective Studies, Cancer Epidemiol. Biomarkers Prev. 24 (2015) 1086–1093. https://doi.org/10.1158/1055-9965.EPI-14-1329.
[109] S. Cheng, Q. Zheng, G. Ding, G. Li, Influence of serum total cholesterol, LDL, HDL, and triglyceride on prostate cancer recurrence after radical prostatectomy, Cancer Manag Res. 11 (2019) 6651–6661. https://doi.org/10.2147/CMAR.S204947.
[110] M. Van Hemelrijck, H. Garmo, L. Holmberg, G. Walldius, I. Jungner, N. Hammar, M. Lambe, Prostate cancer risk in the Swedish AMORIS study: the interplay among triglycerides, total cholesterol, and glucose, Cancer. 117 (2011) 2086–2095. https://doi.org/10.1002/cncr.25758.
[111] J. Jamnagerwalla, L.E. Howard, E.H. Allott, A.C. Vidal, D.M. Moreira, R. Castro-Santamaria, G.L. Andriole, M.R. Freeman, S.J. Freedland, Serum cholesterol and risk of high-grade prostate cancer: results from the REDUCE study, Prostate

Cancer Prostatic Dis. 21 (2018) 252–259. https://doi.org/10.1038/s41391-017-0030-9.
[112] P. Rawla, Epidemiology of Prostate Cancer, World J Oncol. 10 (2019) 63–89. https://doi.org/10.14740/wjon1191.
[113] K.M. Di Sebastiano, M. Mourtzakis, The role of dietary fat throughout the prostate cancer trajectory, Nutrients. 6 (2014) 6095–6109. https://doi.org/10.3390/nu6126095.
[114] E.A. Mostaghel, K.R. Solomon, K. Pelton, M.R. Freeman, R.B. Montgomery, Impact of circulating cholesterol levels on growth and intratumoral androgen concentration of prostate tumors, PLoS ONE. 7 (2012) e30062. https://doi.org/10.1371/journal.pone.0030062.
[115] A.J.C. Pommier, J. Dufour, G. Alves, E. Viennois, H. De Boussac, A. Trousson, D.H. Volle, F. Caira, P. Val, P. Arnaud, J.-M.A. Lobaccaro, S. Baron, Liver x receptors protect from development of prostatic intra-epithelial neoplasia in mice, PLoS Genet. 9 (2013) e1003483. https://doi.org/10.1371/journal.pgen.1003483.
[116] S. Narita, T. Nara, H. Sato, A. Koizumi, M. Huang, T. Inoue, T. Habuchi, Research Evidence on High-Fat Diet-Induced Prostate Cancer Development and Progression, J Clin Med. 8 (2019). https://doi.org/10.3390/jcm8050597.
[117] E. Bidoli, R. Talamini, C. Bosetti, E. Negri, D. Maruzzi, M. Montella, S. Franceschi, C. La Vecchia, Macronutrients, fatty acids, cholesterol and prostate cancer risk, Ann. Oncol. 16 (2005) 152–157. https://doi.org/10.1093/annonc/mdi010.
[118] E.J. Jacobs, V.L. Stevens, C.C. Newton, S.M. Gapstur, Plasma total, LDL, and HDL cholesterol and risk of aggressive prostate cancer in the Cancer Prevention Study II Nutrition Cohort, Cancer Causes Control. 23 (2012) 1289–1296. https://doi.org/10.1007/s10552-012-0006-y.
[119] D.E.G. Kok, J.G.H. van Roermund, K.K.H. Aben, M. den Heijer, D.W. Swinkels, E. Kampman, L. a. L.M. Kiemeney, Blood lipid levels and prostate cancer risk; a cohort study, Prostate Cancer Prostatic Dis. 14 (2011) 340–345. https://doi.org/10.1038/pcan.2011.30.
[120] C.J. Bull, C. Bonilla, J.M.P. Holly, C.M. Perks, N. Davies, P. Haycock, O.H.Y. Yu, J.B. Richards, R. Eeles, D. Easton, Z. Kote-Jarai, A. Amin Al Olama, S. Benlloch, K. Muir, G.G. Giles, R.J. MacInnis, F. Wiklund, H. Gronberg, C.A. Haiman, J. Schleutker, B.G. Nordestgaard, R.C. Travis, D. Neal, N. Pashayan, K.-T. Khaw, J.L. Stanford, W.J. Blot, S. Thibodeau, C. Maier, A.S. Kibel, C. Cybulski, L. Cannon-Albright, H. Brenner, J. Park, R. Kaneva, J. Batra, M.R. Teixeira, A. Micheal, H. Pandha, G.D. Smith, S.J. Lewis, R.M. Martin, PRACTICAL consortium, Blood lipids and prostate cancer: a Mendelian randomization analysis, Cancer Med. 5 (2016) 1125–1136. https://doi.org/10.1002/cam4.695.
[121] T.J. Murtola, H. Syvälä, P. Pennanen, M. Bläuer, T. Solakivi, T. Ylikomi, T.L.J. Tammela, The importance of LDL and cholesterol metabolism for prostate epithelial cell growth, PLoS ONE. 7 (2012) e39445. https://doi.org/10.1371/journal.pone.0039445.
[122] S. Yue, J. Li, S.-Y. Lee, H.J. Lee, T. Shao, B. Song, L. Cheng, T.A. Masterson, X. Liu, T.L. Ratliff, J.-X. Cheng, Cholesteryl ester accumulation induced by PTEN loss and PI3K/AKT activation underlies human prostate cancer aggressiveness, Cell Metab. 19 (2014) 393–406. https://doi.org/10.1016/j.cmet.2014.01.019.
[123] F. Wan, X. Qin, G. Zhang, X. Lu, Y. Zhu, H. Zhang, B. Dai, G. Shi, D. Ye, Oxidized low-density lipoprotein is associated with advanced-stage prostate cancer, Tumour Biol. 36 (2015) 3573–3582. https://doi.org/10.1007/s13277-014-2994-6.

[124] G.A. Asare, E. Owusu-Boateng, B. Asiedu, B.Y. Amoah, E. Essendoh, R.Y. Otoo, Oxidised low-density lipoprotein, a possible distinguishing lipid profile biomolecule between prostate cancer and benign prostatic hyperplasia, Andrologia. 51 (2019) e13321. https://doi.org/10.1111/and.13321.
[125] I. González-Chavarría, E. Fernandez, N. Gutierrez, E.E. González-Horta, F. Sandoval, P. Cifuentes, C. Castillo, R. Cerro, O. Sanchez, J.R. Toledo, LOX-1 activation by oxLDL triggers an epithelial mesenchymal transition and promotes tumorigenic potential in prostate cancer cells, Cancer Lett. 414 (2018) 34–43. https://doi.org/10.1016/j.canlet.2017.10.035.
[126] K. Kotani, Y. Sekine, S. Ishikawa, I.Z. Ikpot, K. Suzuki, A.T. Remaley, High-density lipoprotein and prostate cancer: an overview, J Epidemiol. 23 (2013) 313–319. https://doi.org/10.2188/jea.je20130006.
[127] M. Ruscica, M. Botta, N. Ferri, E. Giorgio, C. Macchi, G. Franceschini, P. Magni, L. Calabresi, M. Gomaraschi, High Density Lipoproteins Inhibit Oxidative Stress-Induced Prostate Cancer Cell Proliferation, Sci Rep. 8 (2018) 2236. https://doi.org/10.1038/s41598-018-19568-8.
[128] Y. Sekine, S.J. Demosky, J.A. Stonik, Y. Furuya, H. Koike, K. Suzuki, A.T. Remaley, High-density lipoprotein induces proliferation and migration of human prostate androgen-independent cancer cells by an ABCA1-dependent mechanism, Mol. Cancer Res. 8 (2010) 1284–1294. https://doi.org/10.1158/1541-7786.MCR-10-0008.
[129] Y. Sekine, K. Suzuki, A.T. Remaley, HDL and sphingosine-1-phosphate activate stat3 in prostate cancer DU145 cells via ERK1/2 and S1P receptors, and promote cell migration and invasion, Prostate. 71 (2011) 690–699. https://doi.org/10.1002/pros.21285.
[130] G. Singh, S. Sankanagoudar, P. Dogra, N.C. Chandra, Interlink between cholesterol & cell cycle in prostate carcinoma, Indian J. Med. Res. 146 (2017) S38–S44. https://doi.org/10.4103/ijmr.IJMR_1639_15.
[131] K.H. Stopsack, T.A. Gerke, O. Andrén, S.-O. Andersson, E.L. Giovannucci, L.A. Mucci, J.R. Rider, Cholesterol uptake and regulation in high-grade and lethal prostate cancers, Carcinogenesis. 38 (2017) 806–811. https://doi.org/10.1093/carcin/bgx058.
[132] S. Jiang, X. Wang, D. Song, X. Liu, Y. Gu, Z. Xu, X. Wang, X. Zhang, Q. Ye, Z. Tong, B. Yan, J. Yu, Y. Chen, M. Sun, Y. Wang, S. Gao, Cholesterol Induces Epithelial-to-Mesenchymal Transition of Prostate Cancer Cells by Suppressing Degradation of EGFR through APMAP, Cancer Res. 79 (2019) 3063–3075. https://doi.org/10.1158/0008-5472.CAN-18-3295.
[133] J.V. Swinnen, K. Brusselmans, G. Verhoeven, Increased lipogenesis in cancer cells: new players, novel targets, Curr Opin Clin Nutr Metab Care. 9 (2006) 358–365. https://doi.org/10.1097/01.mco.0000232894.28674.30.
[134] H.-J. Jin, J. Kim, J. Yu, Androgen receptor genomic regulation, Transl Androl Urol. 2 (2013) 157–177. https://doi.org/10.3978/j.issn.2223-4683.2013.09.01.
[135] H.V. Heemers, G. Verhoeven, J.V. Swinnen, Androgen activation of the sterol regulatory element-binding protein pathway: Current insights, Mol. Endocrinol. 20 (2006) 2265–2277. https://doi.org/10.1210/me.2005-0479.
[136] L. Bonaccorsi, P. Luciani, G. Nesi, E. Mannucci, C. Deledda, F. Dichiara, M. Paglierani, F. Rosati, L. Masieri, S. Serni, M. Carini, L. Proietti-Pannunzi, S. Monti, G. Forti, G. Danza, M. Serio, A. Peri, Androgen receptor regulation of the seladin-1/DHCR24 gene: altered expression in prostate cancer, Lab. Invest. 88 (2008) 1049–1056. https://doi.org/10.1038/labinvest.2008.80.

[137] J. Fukuchi, R.A. Hiipakka, J.M. Kokontis, S. Hsu, A.L. Ko, M.L. Fitzgerald, S. Liao, Androgenic suppression of ATP-binding cassette transporter A1 expression in LNCaP human prostate cancer cells, Cancer Res. 64 (2004) 7682–7685. https://doi.org/10.1158/0008-5472.CAN-04-2647.
[138] D. Schörghofer, K. Kinslechner, A. Preitschopf, B. Schütz, C. Röhrl, M. Hengstschläger, H. Stangl, M. Mikula, The HDL receptor SR-BI is associated with human prostate cancer progression and plays a possible role in establishing androgen independence, Reprod. Biol. Endocrinol. 13 (2015) 88. https://doi.org/10.1186/s12958-015-0087-z.
[139] J. Fukuchi, J.M. Kokontis, R.A. Hiipakka, C.-P. Chuu, S. Liao, Antiproliferative effect of liver X receptor agonists on LNCaP human prostate cancer cells, Cancer Res. 64 (2004) 7686–7689. https://doi.org/10.1158/0008-5472.CAN-04-2332.
[140] S. Varambally, S.M. Dhanasekaran, M. Zhou, T.R. Barrette, C. Kumar-Sinha, M.G. Sanda, D. Ghosh, K.J. Pienta, R.G.A.B. Sewalt, A.P. Otte, M.A. Rubin, A.M. Chinnaiyan, The polycomb group protein EZH2 is involved in progression of prostate cancer, Nature. 419 (2002) 624–629. https://doi.org/10.1038/nature01075.
[141] C.-Y. Lin, C. Huo, L.-K. Kuo, R.A. Hiipakka, R.B. Jones, H.-P. Lin, Y. Hung, L.-C. Su, J.-C. Tseng, Y.-Y. Kuo, Y.-L. Wang, Y. Fukui, Y.-H. Kao, J.M. Kokontis, C.-C. Yeh, L. Chen, S.-D. Yang, H.-H. Fu, Y.-W. Chen, K.K.C. Tsai, J.-Y. Chang, C.-P. Chuu, Cholestane-3β, 5α, 6β-triol suppresses proliferation, migration, and invasion of human prostate cancer cells, PLoS ONE. 8 (2013) e65734. https://doi.org/10.1371/journal.pone.0065734.
[142] S. Raza, M. Meyer, J. Schommer, K.D.P. Hammer, B. Guo, O. Ghribi, 27-Hydroxycholesterol stimulates cell proliferation and resistance to docetaxel-induced apoptosis in prostate epithelial cells, Med. Oncol. 33 (2016) 12. https://doi.org/10.1007/s12032-015-0725-5.
[143] M. Olsson, O. Gustafsson, C. Skogastierna, A. Tolf, B.D. Rietz, R. Morfin, A. Rane, L. Ekström, Regulation and expression of human CYP7B1 in prostate: overexpression of CYP7B1 during progression of prostatic adenocarcinoma, Prostate. 67 (2007) 1439–1446. https://doi.org/10.1002/pros.20630.
[144] G. Pellegriti, F. Frasca, C. Regalbuto, S. Squatrito, R. Vigneri, Worldwide increasing incidence of thyroid cancer: update on epidemiology and risk factors, J Cancer Epidemiol. 2013 (2013) 965212. https://doi.org/10.1155/2013/965212.
[145] C.M. Kitahara, J.A. Sosa, The changing incidence of thyroid cancer, Nat Rev Endocrinol. 12 (2016) 646–653. https://doi.org/10.1038/nrendo.2016.110.
[146] D. Li, L. Zhou, C. Ma, W. Chen, Y. Zhang, S. Yu, D. Wang, Y. Zou, J. Wu, L. Qiu, Comparative analysis of the serum proteome profiles of thyroid cancer: An initial focus on the lipid profile, Oncol Lett. 18 (2019) 3349–3357. https://doi.org/10.3892/ol.2019.10655.
[147] H.J. Kim, N.K. Kim, J.H. Choi, S.Y. Sohn, S.W. Kim, S.-M. Jin, H.W. Jang, S. Suh, Y.-K. Min, J.H. Chung, S.W. Kim, Associations between body mass index and clinico-pathological characteristics of papillary thyroid cancer, Clin. Endocrinol. (Oxf). 78 (2013) 134–140. https://doi.org/10.1111/j.1365-2265.2012.04506.x.
[148] M. Giusti, L. Mortara, R. Degrandi, F. Cecoli, M. Mussap, G. Rodriguez, D. Ferone, F. Minuto, Metabolic and cardiovascular risk in patients with a history of differentiated thyroid carcinoma: A case-controlled cohort study, Thyroid Res. 1 (2008) 2. https://doi.org/10.1186/1756-6614-1-2.
[149] G. Revilla, M. de P. Pons, L. Baila-Rueda, A. García-León, D. Santos, A. Cenarro, M. Magalhaes, R.M. Blanco, A. Moral, J. Ignacio Pérez, G. Sabé, C. González, V. Fuste, E. Lerma, M.D.S. Faria, A. de Leiva, R. Corcoy, J. Carles

Escolà-Gil, E. Mato, Cholesterol and 27-hydroxycholesterol promote thyroid carcinoma aggressiveness, Sci Rep. 9 (2019) 10260. https://doi.org/10.1038/s41598-019-46727-2.
[150] H. Korkmaz, S. Tabur, M. Özkaya, N. Aksoy, H. Yildiz, E. Akarsu, Paraoxonase and arylesterase activities in patients with papillary thyroid cancer, Scandinavian Journal of Clinical and Laboratory Investigation. 75 (2015) 259–264. https://doi.org/10.3109/00365513.2014.1003597.
[151] B. Stewart, C. Wild, World Cancer Report 2014, n.d. https://publications.iarc.fr/Non-Series-Publications/World-Cancer-Reports/World-Cancer-Report-2014 (accessed June 2, 2020).
[152] D.P. Ryan, T.S. Hong, N. Bardeesy, Pancreatic adenocarcinoma, N. Engl. J. Med. 371 (2014) 1039–1049. https://doi.org/10.1056/NEJMra1404198.
[153] G. Bond-Smith, N. Banga, T.M. Hammond, C.J. Imber, Pancreatic adenocarcinoma, BMJ. 344 (2012) e2476. https://doi.org/10.1136/bmj.e2476.
[154] T. Kamisawa, L.D. Wood, T. Itoi, K. Takaori, Pancreatic cancer, Lancet. 388 (2016) 73–85. https://doi.org/10.1016/S0140-6736(16)00141-0.
[155] R. Carreras-Torres, M. Johansson, V. Gaborieau, P.C. Haycock, K.H. Wade, C.L. Relton, R.M. Martin, G. Davey Smith, P. Brennan, The Role of Obesity, Type 2 Diabetes, and Metabolic Factors in Pancreatic Cancer: A Mendelian Randomization Study, J. Natl. Cancer Inst. 109 (2017). https://doi.org/10.1093/jnci/djx012.
[156] Y. Lu, M. Gentiluomo, J. Lorenzo-Bermejo, L. Morelli, O. Obazee, D. Campa, F. Canzian, Mendelian randomisation study of the effects of known and putative risk factors on pancreatic cancer, J. Med. Genet. (2020). https://doi.org/10.1136/jmedgenet-2019-106200.
[157] R.Z. Stolzenberg-Solomon, P. Pietinen, P.R. Taylor, J. Virtamo, D. Albanes, A prospective study of medical conditions, anthropometry, physical activity, and pancreatic cancer in male smokers (Finland), Cancer Causes Control. 13 (2002) 417–426. https://doi.org/10.1023/a:1015729615148.
[158] A. Berrington de Gonzalez, J.E. Yun, S.-Y. Lee, A.P. Klein, S.H. Jee, Pancreatic cancer and factors associated with the insulin resistance syndrome in the Korean cancer prevention study, Cancer Epidemiol. Biomarkers Prev. 17 (2008) 359–364. https://doi.org/10.1158/1055-9965.EPI-07-0507.
[159] D. Johansen, T. Stocks, H. Jonsson, B. Lindkvist, T. Björge, H. Concin, M. Almquist, C. Häggström, A. Engeland, H. Ulmer, G. Hallmans, R. Selmer, G. Nagel, S. Tretli, P. Stattin, J. Manjer, Metabolic factors and the risk of pancreatic cancer: a prospective analysis of almost 580,000 men and women in the Metabolic Syndrome and Cancer Project, Cancer Epidemiol. Biomarkers Prev. 19 (2010) 2307–2317. https://doi.org/10.1158/1055-9965.EPI-10-0234.
[160] A. Ansary-Moghaddam, R. Huxley, F. Barzi, C. Lawes, T. Ohkubo, X. Fang, S.H. Jee, M. Woodward, Asia Pacific Cohort Studies Collaboration, The effect of modifiable risk factors on pancreatic cancer mortality in populations of the Asia-Pacific region, Cancer Epidemiol. Biomarkers Prev. 15 (2006) 2435–2440. https://doi.org/10.1158/1055-9965.EPI-06-0368.
[161] G.D. Batty, M. Kivimaki, D. Morrison, R. Huxley, G.D. Smith, R. Clarke, M.G. Marmot, M.J. Shipley, Risk factors for pancreatic cancer mortality: extended follow-up of the original Whitehall Study, Cancer Epidemiol. Biomarkers Prev. 18 (2009) 673–675. https://doi.org/10.1158/1055-9965.EPI-08-1032.
[162] A. Schatzkin, R.N. Hoover, P.R. Taylor, R.G. Ziegler, C.L. Carter, D. Albanes, D.B. Larson, L.M. Licitra, Site-specific analysis of total serum cholesterol and

incident cancer in the National Health and Nutrition Examination Survey I Epidemiologic Follow-up Study, Cancer Res. 48 (1988) 452–458.
[163] S. Strohmaier, M. Edlinger, J. Manjer, T. Stocks, T. Bjørge, W. Borena, C. Häggström, A. Engeland, G. Nagel, M. Almquist, R. Selmer, S. Tretli, H. Concin, G. Hallmans, H. Jonsson, P. Stattin, H. Ulmer, Total serum cholesterol and cancer incidence in the Metabolic syndrome and Cancer Project (Me-Can), PLoS ONE. 8 (2013) e54242. https://doi.org/10.1371/journal.pone.0054242.
[164] J. Wang, W.-J. Wang, L. Zhai, D.-F. Zhang, Association of cholesterol with risk of pancreatic cancer: a meta-analysis, World J. Gastroenterol. 21 (2015) 3711–3719. https://doi.org/10.3748/wjg.v21.i12.3711.
[165] X. Chen, T. Zhou, M. Chen, Meta analysis of the association of cholesterol with pancreatic carcinoma risk, J BUON. 20 (2015) 109–113.
[166] H. Chen, S. Qin, M. Wang, T. Zhang, S. Zhang, Association between cholesterol intake and pancreatic cancer risk: evidence from a meta-analysis, Sci Rep. 5 (2015) 8243. https://doi.org/10.1038/srep08243.
[167] Y. Lin, A. Tamakoshi, T. Hayakawa, S. Naruse, M. Kitagawa, Y. Ohno, Nutritional factors and risk of pancreatic cancer: a population-based case-control study based on direct interview in Japan, J. Gastroenterol. 40 (2005) 297–301. https://doi.org/10.1007/s00535-004-1537-0.
[168] T. Ogawa, T. Makino, K. Kosahara, A. Koga, F. Nakayama, Promoting effects of both dietary cholesterol and cholestyramine on pancreatic carcinogenesis initiated by N-nitrosobis(2-oxopropyl)amine in Syrian golden hamsters, Carcinogenesis. 13 (1992) 2047–2052. https://doi.org/10.1093/carcin/13.11.2047.
[169] T. Ogawa, T. Makino, N. Hirose, M. Sugano, Lack of influence of low blood cholesterol levels on pancreatic carcinogenesis after initiation with N-nitrosobis(2-oxopropyl)amine in Syrian golden hamsters, Carcinogenesis. 15 (1994) 1663–1666. https://doi.org/10.1093/carcin/15.8.1663.
[170] M. Van Hemelrijck, G. Walldius, I. Jungner, N. Hammar, H. Garmo, E. Binda, A. Hayday, M. Lambe, L. Holmberg, Low levels of apolipoprotein A-I and HDL are associated with risk of prostate cancer in the Swedish AMORIS study, Cancer Causes Control. 22 (2011) 1011–1019. https://doi.org/10.1007/s10552-011-9774-z.
[171] G. Yang, G. Xiong, M. Feng, F. Zhao, J. Qiu, Y. Liu, Z. Cao, H. Wang, J. Yang, L. You, L. Zheng, T. Zhang, Y. Zhao, OLR1 Promotes Pancreatic Cancer Metastasis via Increased c-Myc Expression and Transcription of HMGA2, Mol. Cancer Res. 18 (2020) 685–697. https://doi.org/10.1158/1541-7786.MCR-19-0718.
[172] B. Mytar, M. Woloszyn, A. Macura-Biegun, B. Hajto, I. Ruggiero, B. Piekarska, M. Zembala, Involvement of pattern recognition receptors in the induction of cytokines and reactive oxygen intermediates production by human monocytes/macrophages stimulated with tumour cells, Anticancer Res. 24 (2004) 2287–2293.
[173] C.L. Meinhold, A. Berrington de Gonzalez, D. Albanes, S.J. Weinstein, P.R. Taylor, J. Virtamo, R.Z. Stolzenberg-Solomon, Predictors of fasting serum insulin and glucose and the risk of pancreatic cancer in smokers, Cancer Causes Control. 20 (2009) 681–690. https://doi.org/10.1007/s10552-008-9281-z.
[174] G.C. Kabat, M.Y. Kim, R.T. Chlebowski, M.Z. Vitolins, S. Wassertheil-Smoller, T.E. Rohan, Serum lipids and risk of obesity-related cancers in postmenopausal women, Cancer Causes Control. 29 (2018) 13–24. https://doi.org/10.1007/s10552-017-0991-y.

[175] V. Michalaki, G. Koutroulis, K. Syrigos, C. Piperi, A. Kalofoutis, Evaluation of serum lipids and high-density lipoprotein subfractions (HDL2, HDL3) in postmenopausal patients with breast cancer, Mol. Cell. Biochem. 268 (2005) 19–24.
[176] Q. Wu, G. Chen, W.-M. Wu, L. Zhou, L. You, T.-P. Zhang, Y.-P. Zhao, Metabolic syndrome components and risk factors for pancreatic adenocarcinoma: a case-control study in China, Digestion. 86 (2012) 294–301. https://doi.org/10.1159/000341397.
[177] K. Kashiwagi, T. Seino, S. Fukuhara, K. Minami, M. Horibe, E. Iwasaki, H. Takaishi, K. Itoh, Y. Sugino, N. Inoue, Y. Iwao, T. Kanai, Pancreatic Fat Content Detected by Computed Tomography and Its Significant Relationship With Intraductal Papillary Mucinous Neoplasm, Pancreas. 47 (2018) 1087–1092. https://doi.org/10.1097/MPA.0000000000001103.
[178] A. Xue, C.J. Scarlett, L. Chung, G. Butturini, A. Scarpa, R. Gandy, S.R. Wilson, R.C. Baxter, R.C. Smith, Discovery of serum biomarkers for pancreatic adenocarcinoma using proteomic analysis, Br. J. Cancer. 103 (2010) 391–400. https://doi.org/10.1038/sj.bjc.6605764.
[179] K. Honda, T. Okusaka, K. Felix, S. Nakamori, N. Sata, H. Nagai, T. Ioka, A. Tsuchida, T. Shimahara, M. Shimahara, Y. Yasunami, H. Kuwabara, T. Sakuma, Y. Otsuka, N. Ota, M. Shitashige, T. Kosuge, M.W. Büchler, T. Yamada, Altered plasma apolipoprotein modifications in patients with pancreatic cancer: protein characterization and multi-institutional validation, PLoS ONE. 7 (2012) e46908. https://doi.org/10.1371/journal.pone.0046908.
[180] C. Lin, W.-C. Wu, G.-C. Zhao, D.-S. Wang, W.-H. Lou, D.-Y. Jin, ITRAQ-based quantitative proteomics reveals apolipoprotein A-I and transferrin as potential serum markers in CA19-9 negative pancreatic ductal adenocarcinoma, Medicine (Baltimore). 95 (2016) e4527. https://doi.org/10.1097/MD.0000000000004527.
[181] S.M. Julovi, A. Xue, T.N. Thanh LE, A.J. Gill, J.C. Bulanadi, M. Patel, L.J. Waddington, K.-A. Rye, M.J. Moghaddam, R.C. Smith, Apolipoprotein A-II Plus Lipid Emulsion Enhance Cell Growth via SR-B1 and Target Pancreatic Cancer In Vitro and In Vivo, PLoS ONE. 11 (2016) e0151475. https://doi.org/10.1371/journal.pone.0151475.
[182] M.N. Akçay, M.F. Polat, I. Yilmaz, G. Akçay, Serum paraoxonase levels in pancreatic cancer, Hepatogastroenterology. 50 Suppl 2 (2003) ccxxv–ccxxvii.
[183] F. Guillaumond, G. Bidaut, M. Ouaissi, S. Servais, V. Gouirand, O. Olivares, S. Lac, L. Borge, J. Roques, O. Gayet, M. Pinault, C. Guimaraes, J. Nigri, C. Loncle, M.-N. Lavaut, S. Garcia, A. Tailleux, B. Staels, E. Calvo, R. Tomasini, J.L. Iovanna, S. Vasseur, Cholesterol uptake disruption, in association with chemotherapy, is a promising combined metabolic therapy for pancreatic adenocarcinoma, Proc. Natl. Acad. Sci. U.S.A. 112 (2015) 2473–2478. https://doi.org/10.1073/pnas.1421601112.
[184] S.L. Gonias, N. Karimi-Mostowfi, S.S. Murray, E. Mantuano, A.S. Gilder, Expression of LDL receptor-related proteins (LRPs) in common solid malignancies correlates with patient survival, PLoS ONE. 12 (2017) e0186649. https://doi.org/10.1371/journal.pone.0186649.
[185] M. Watanabe, S. Sheriff, K.B. Lewis, J. Cho, S.L. Tinch, A. Balasubramaniam, M.A. Kennedy, Metabolic Profiling Comparison of Human Pancreatic Ductal Epithelial Cells and Three Pancreatic Cancer Cell Lines using NMR Based Metabonomics, J Mol Biomark Diagn. 3 (2012). https://doi.org/10.4172/2155-9929.S3-002.

[186] J. Li, D. Gu, S.S.-Y. Lee, B. Song, S. Bandyopadhyay, S. Chen, S.F. Konieczny, T.L. Ratliff, X. Liu, J. Xie, J.-X. Cheng, Abrogating cholesterol esterification suppresses growth and metastasis of pancreatic cancer, Oncogene. 35 (2016) 6378–6388. https://doi.org/10.1038/onc.2016.168.
[187] J. Li, X. Qu, J. Tian, J.-T. Zhang, J.-X. Cheng, Cholesterol esterification inhibition and gemcitabine synergistically suppress pancreatic ductal adenocarcinoma proliferation, PLoS ONE. 13 (2018) e0193318. https://doi.org/10.1371/journal.pone.0193318.
[188] X. Wang, J. Xie, X. Lu, H. Li, C. Wen, Z. Huo, J. Xie, M. Shi, X. Tang, H. Chen, C. Peng, Y. Fang, X. Deng, B. Shen, Melittin inhibits tumor growth and decreases resistance to gemcitabine by downregulating cholesterol pathway gene CLU in pancreatic ductal adenocarcinoma, Cancer Lett. 399 (2017) 1–9. https://doi.org/10.1016/j.canlet.2017.04.012.
[189] J.J. Souchek, M.J. Baine, C. Lin, S. Rachagani, S. Gupta, S. Kaur, K. Lester, D. Zheng, S. Chen, L. Smith, A. Lazenby, S.L. Johansson, M. Jain, S.K. Batra, Unbiased analysis of pancreatic cancer radiation resistance reveals cholesterol biosynthesis as a novel target for radiosensitisation, Br. J. Cancer. 111 (2014) 1139–1149. https://doi.org/10.1038/bjc.2014.385.
[190] C.P. Tanase, S. Dima, M. Mihai, E. Raducan, M.I. Nicolescu, L. Albulescu, B. Voiculescu, T. Dumitrascu, L.M. Cruceru, M. Leabu, I. Popescu, M.E. Hinescu, Caveolin-1 overexpression correlates with tumour progression markers in pancreatic ductal adenocarcinoma, J. Mol. Histol. 40 (2009) 23–29. https://doi.org/10.1007/s10735-008-9209-7.
[191] V.K. Gupta, N.S. Sharma, K. Kesh, P. Dauer, A. Nomura, B. Giri, V. Dudeja, S. Banerjee, S. Bhattacharya, A. Saluja, S. Banerjee, Metastasis and chemoresistance in CD133 expressing pancreatic cancer cells are dependent on their lipid raft integrity, Cancer Lett. 439 (2018) 101–112. https://doi.org/10.1016/j.canlet.2018.09.028.
[192] L.A. Torre, B. Trabert, C.E. DeSantis, K.D. Miller, G. Samimi, C.D. Runowicz, M.M. Gaudet, A. Jemal, R.L. Siegel, Ovarian cancer statistics, 2018, CA Cancer J Clin. 68 (2018) 284–296. https://doi.org/10.3322/caac.21456.
[193] E. Lengyel, Ovarian cancer development and metastasis, Am. J. Pathol. 177 (2010) 1053–1064. https://doi.org/10.2353/ajpath.2010.100105.
[194] E. Kipps, D.S.P. Tan, S.B. Kaye, Meeting the challenge of ascites in ovarian cancer: new avenues for therapy and research, Nat. Rev. Cancer. 13 (2013) 273–282. https://doi.org/10.1038/nrc3432.
[195] D. Luvero, A. Milani, J.A. Ledermann, Treatment options in recurrent ovarian cancer: latest evidence and clinical potential, Ther Adv Med Oncol. 6 (2014) 229–239. https://doi.org/10.1177/1758834014544121.
[196] D. Zhang, Y. Xi, Y. Feng, Ovarian cancer risk in relation to blood lipid levels and hyperlipidemia: a systematic review and meta-analysis of observational epidemiologic studies, Eur. J. Cancer Prev. (2020). https://doi.org/10.1097/CEJ.0000000000000597.
[197] T. Bjørge, A. Lukanova, S. Tretli, J. Manjer, H. Ulmer, T. Stocks, R. Selmer, G. Nagel, M. Almquist, H. Concin, G. Hallmans, H. Jonsson, C. Häggström, P. Stattin, A. Engeland, Metabolic risk factors and ovarian cancer in the Metabolic Syndrome and Cancer project, Int J Epidemiol. 40 (2011) 1667–1677. https://doi.org/10.1093/ije/dyr130.

[198] K.J. Helzlsouer, A.J. Alberg, E.P. Norkus, J.S. Morris, S.C. Hoffman, G.W. Comstock, Prospective study of serum micronutrients and ovarian cancer, J. Natl. Cancer Inst. 88 (1996) 32–37. https://doi.org/10.1093/jnci/88.1.32.
[199] G. Li, K. Zhang, F. Gong, H. Jin, A study on changes and clinical significance of blood glucose, blood lipid and inflammation in patients with ovarian cancer, J BUON. 24 (2019) 2322–2326.
[200] M.I. Qadir, S.A. Malik, Plasma lipid profile in gynecologic cancers, Eur. J. Gynaecol. Oncol. 29 (2008) 158–161.
[201] E.H. Avall-Lundqvist, C.O. Peterson, Serum cholesterol and apolipoprotein B levels may reflect disease activity in ovarian cancer patients, Acta Oncol. 35 (1996) 1007–1010. https://doi.org/10.3109/02841869609100719.
[202] H. Gadomska, J. Janecki, L. Marianowski, G. Nowicka, Lipids in serum of patients with malignant ovarian neoplasms, Int J Gynaecol Obstet. 57 (1997) 287–293. https://doi.org/10.1016/s0020-7292(97)00071-4.
[203] J.U. Onwuka, A.P. Okekunle, O.M. Olutola, O.M. Akpa, R. Feng, Lipid profile and risk of ovarian tumours: a meta-analysis, BMC Cancer. 20 (2020) 200. https://doi.org/10.1186/s12885-020-6679-9.
[204] A. Sadeghi, S. Shab-Bidar, M. Parohan, K. Djafarian, Dietary Fat Intake and Risk of Ovarian Cancer: A Systematic Review and Dose-Response Meta-Analysis of Observational Studies, Nutr Cancer. 71 (2019) 939–953. https://doi.org/10.1080/01635581.2019.1595049.
[205] S.Y. Pan, A.-M. Ugnat, Y. Mao, S.W. Wen, K.C. Johnson, Canadian Cancer Registries Epidemiology Research Group, A case-control study of diet and the risk of ovarian cancer, Cancer Epidemiol. Biomarkers Prev. 13 (2004) 1521–1527.
[206] M.S. Rice, E.M. Poole, W.C. Willett, S.S. Tworoger, Adult dietary fat intake and ovarian cancer risk, Int. J. Cancer. 146 (2020) 2756–2772. https://doi.org/10.1002/ijc.32635.
[207] J.M. Genkinger, D.J. Hunter, D. Spiegelman, K.E. Anderson, W.L. Beeson, J.E. Buring, G.A. Colditz, G.E. Fraser, J.L. Freudenheim, R.A. Goldbohm, S.E. Hankinson, K.L. Koenig, S.C. Larsson, M. Leitzmann, M.L. McCullough, A.B. Miller, C. Rodriguez, T.E. Rohan, J.A. Ross, A. Schatzkin, L.J. Schouten, E. Smit, W.C. Willett, A. Wolk, A. Zeleniuch-Jacquotte, S.M. Zhang, S.A. Smith-Warner, A pooled analysis of 12 cohort studies of dietary fat, cholesterol and egg intake and ovarian cancer, Cancer Causes Control. 17 (2006) 273–285. https://doi.org/10.1007/s10552-005-0455-7.
[208] M.A. Merritt, E. Riboli, E. Weiderpass, K.K. Tsilidis, K. Overvad, A. Tjønneland, L. Hansen, L. Dossus, G. Fagherazzi, L. Baglietto, R.T. Fortner, J. Ose, A. Steffen, H. Boeing, A. Trichopoulou, D. Trichopoulos, P. Lagiou, G. Masala, S. Sieri, A. Mattiello, R. Tumino, C. Sacerdote, H.B.A. Bueno-de-Mesquita, N.C. Onland-Moret, P.H. Peeters, A. Hjartåker, I.T. Gram, J.R. Quirós, M. Obón-Santacana, E. Molina-Montes, J.M. Huerta Castaño, E. Ardanaz, S. Chamosa, E. Sonestedt, A. Idahl, E. Lundin, K.-T. Khaw, N. Wareham, R.C. Travis, S. Rinaldi, I. Romieu, V. Chajes, M.J. Gunter, Dietary fat intake and risk of epithelial ovarian cancer in the European Prospective Investigation into Cancer and Nutrition, Cancer Epidemiol. 38 (2014) 528–537. https://doi.org/10.1016/j.canep.2014.07.011.
[209] M.A. Merritt, I. Tzoulaki, P.A. van den Brandt, L.J. Schouten, K.K. Tsilidis, E. Weiderpass, C.J. Patel, A. Tjønneland, L. Hansen, K. Overvad, M. His, L. Dartois, M.-C. Boutron-Ruault, R.T. Fortner, R. Kaaks, K. Aleksandrova, H. Boeing, A. Trichopoulou, P. Lagiou, C. Bamia, D. Palli, V. Krogh, R. Tumino, F. Ricceri, A. Mattiello, H.B. Bueno-de-Mesquita, N.C. Onland-Moret, P.H. Peeters, G. Skeie, M.

Jareid, J.R. Quirós, M. Obón-Santacana, M.-J. Sánchez, S. Chamosa, J.M. Huerta, A. Barricarte, J.A. Dias, E. Sonestedt, A. Idahl, E. Lundin, N.J. Wareham, K.-T. Khaw, R.C. Travis, P. Ferrari, E. Riboli, M.J. Gunter, Nutrient-wide association study of 57 foods/nutrients and epithelial ovarian cancer in the European Prospective Investigation into Cancer and Nutrition study and the Netherlands Cohort Study, Am. J. Clin. Nutr. 103 (2016) 161–167. https://doi.org/10.3945/ajcn.115.118588.

[210] J. Yarmolinsky, C.J. Bull, E.E. Vincent, J. Robinson, A. Walther, G.D. Smith, S.J. Lewis, C.L. Relton, R.M. Martin, Association Between Genetically Proxied Inhibition of HMG-CoA Reductase and Epithelial Ovarian Cancer, JAMA. 323 (2020) 646–655. https://doi.org/10.1001/jama.2020.0150.

[211] A.J. Li, R.G. Elmore, I.Y. Chen, B.Y. Karlan, Serum low-density lipoprotein levels correlate with survival in advanced stage epithelial ovarian cancers, Gynecol. Oncol. 116 (2010) 78–81. https://doi.org/10.1016/j.ygyno.2009.09.027.

[212] F. Zhu, X. Xu, B. Shi, L. Zeng, L. Wang, X. Wu, H. Zhu, The positive predictive value of low-density lipoprotein for recurrence-free survival in ovarian cancer, Int J Gynaecol Obstet. 143 (2018) 232–238. https://doi.org/10.1002/ijgo.12645.

[213] D. Yam, H. Ben-Hur, A. Fink, R. Dgani, A. Shani, A. Eliraz, V. Insler, E.M. Berry, Insulin and glucose status, tissue and plasma lipids in patients with tumours of the ovary or endometrium: possible dietary implications, Br. J. Cancer. 70 (1994) 1186–1187. https://doi.org/10.1038/bjc.1994.470.

[214] Y. Zhang, J. Wu, J.-Y. Liang, X. Huang, L. Xia, D.-W. Ma, X.-Y. Xu, P.-P. Wu, Association of serum lipids and severity of epithelial ovarian cancer: an observational cohort study of 349 Chinese patients, J Biomed Res. 32 (2018) 336–342. https://doi.org/10.7555/JBR.32.20170096.

[215] D.R. Scoles, X. Xu, H. Wang, H. Tran, B. Taylor-Harding, A. Li, B.Y. Karlan, Liver X receptor agonist inhibits proliferation of ovarian carcinoma cells stimulated by oxidized low density lipoprotein, Gynecol. Oncol. 116 (2010) 109–116. https://doi.org/10.1016/j.ygyno.2009.09.034.

[216] S.E. Johnatty, J.P. Tyrer, S. Kar, J. Beesley, Y. Lu, B. Gao, P.A. Fasching, A. Hein, A.B. Ekici, M.W. Beckmann, D. Lambrechts, E. Van Nieuwenhuysen, I. Vergote, S. Lambrechts, M.A. Rossing, J.A. Doherty, J. Chang-Claude, F. Modugno, R.B. Ness, K.B. Moysich, D.A. Levine, L.A. Kiemeney, L.F.A.G. Massuger, J. Gronwald, J. Lubiński, A. Jakubowska, C. Cybulski, L. Brinton, J. Lissowska, N. Wentzensen, H. Song, V. Rhenius, I. Campbell, D. Eccles, W. Sieh, A.S. Whittemore, V. McGuire, J.H. Rothstein, R. Sutphen, H. Anton-Culver, A. Ziogas, S.A. Gayther, A. Gentry-Maharaj, U. Menon, S.J. Ramus, C.L. Pearce, M.C. Pike, D.O. Stram, A.H. Wu, J. Kupryjanczyk, A. Dansonka-Mieszkowska, I.K. Rzepecka, B. Spiewankiewicz, M.T. Goodman, L.R. Wilkens, M.E. Carney, P.J. Thompson, F. Heitz, A. du Bois, I. Schwaab, P. Harter, J. Pisterer, P. Hillemanns, AGO Study Group, B.Y. Karlan, C. Walsh, J. Lester, S. Orsulic, S.J. Winham, M. Earp, M.C. Larson, Z.C. Fogarty, E. Høgdall, A. Jensen, S.K. Kjaer, B.L. Fridley, J.M. Cunningham, R.A. Vierkant, J.M. Schildkraut, E.S. Iversen, K.L. Terry, D.W. Cramer, E.V. Bandera, I. Orlow, T. Pejovic, Y. Bean, C. Høgdall, L. Lundvall, I. McNeish, J. Paul, K. Carty, N. Siddiqui, R. Glasspool, T. Sellers, C. Kennedy, Y.-E. Chiew, A. Berchuck, S. MacGregor, P.D.P. Pharoah, E.L. Goode, A. deFazio, P.M. Webb, G. Chenevix-Trench, Australian Ovarian Cancer Study Group, Genome-wide Analysis Identifies Novel Loci Associated with Ovarian Cancer Outcomes: Findings from the Ovarian Cancer Association Consortium, Clin.

Cancer Res. 21 (2015) 5264–5276. https://doi.org/10.1158/1078-0432.CCR-15-0632.
[217] H. Gadomska, B. Grzechocińska, J. Janecki, G. Nowicka, M. Powolny, L. Marianowski, Serum lipids concentration in women with benign and malignant ovarian tumours, Eur. J. Obstet. Gynecol. Reprod. Biol. 120 (2005) 87–90. https://doi.org/10.1016/j.ejogrb.2004.02.045.
[218] H. Camuzcuoglu, D.T. Arioz, H. Toy, S. Kurt, H. Celik, O. Erel, Serum paraoxonase and arylesterase activities in patients with epithelial ovarian cancer, Gynecol. Oncol. 112 (2009) 481–485. https://doi.org/10.1016/j.ygyno.2008.10.031.
[219] M.R. Russell, C. Graham, A. D'Amato, A. Gentry-Maharaj, A. Ryan, J.K. Kalsi, C. Ainley, A.D. Whetton, U. Menon, I. Jacobs, R.L.J. Graham, A combined biomarker panel shows improved sensitivity for the early detection of ovarian cancer allowing the identification of the most aggressive type II tumours, Br. J. Cancer. 117 (2017) 666–674. https://doi.org/10.1038/bjc.2017.199.
[220] F. Su, K.R. Kozak, S. Imaizumi, F. Gao, M.W. Amneus, V. Grijalva, C. Ng, A. Wagner, G. Hough, G. Farias-Eisner, G.M. Anantharamaiah, B.J. Van Lenten, M. Navab, A.M. Fogelman, S.T. Reddy, R. Farias-Eisner, Apolipoprotein A-I (apoA-I) and apoA-I mimetic peptides inhibit tumor development in a mouse model of ovarian cancer, Proc. Natl. Acad. Sci. U.S.A. 107 (2010) 19997–20002. https://doi.org/10.1073/pnas.1009010107.
[221] G. Pampalakis, A.-L. Politi, A. Papanastasiou, G. Sotiropoulou, Distinct cholesterogenic and lipidogenic gene expression patterns in ovarian cancer - a new pool of biomarkers, Genes Cancer. 6 (2015) 472–479. https://doi.org/10.18632/genesandcancer.87.
[222] D.J. Brennan, J. Brändstedt, E. Rexhepaj, M. Foley, F. Pontén, M. Uhlén, W.M. Gallagher, D.P. O'Connor, C. O'Herlihy, K. Jirstrom, Tumour-specific HMG-CoAR is an independent predictor of recurrence free survival in epithelial ovarian cancer, BMC Cancer. 10 (2010) 125. https://doi.org/10.1186/1471-2407-10-125.
[223] A.R. Goldman, B.G. Bitler, Z. Schug, J.R. Conejo-Garcia, R. Zhang, D.W. Speicher, The Primary Effect on the Proteome of ARID1A-mutated Ovarian Clear Cell Carcinoma is Downregulation of the Mevalonate Pathway at the Post-transcriptional Level, Mol. Cell Proteomics. 15 (2016) 3348–3360. https://doi.org/10.1074/mcp.M116.062539.
[224] J.B. Greenaway, C. Virtanen, K. Osz, T. Revay, D. Hardy, T. Shepherd, G. DiMattia, J. Petrik, Ovarian tumour growth is characterized by mevalonate pathway gene signature in an orthotopic, syngeneic model of epithelial ovarian cancer, Oncotarget. 7 (2016) 47343–47365. https://doi.org/10.18632/oncotarget.10121.
[225] S. Kim, M. Lee, D.N. Dhanasekaran, Y.S. Song, Activation of LXRα/β by cholesterol in malignant ascites promotes chemoresistance in ovarian cancer, BMC Cancer. 18 (2018) 1232. https://doi.org/10.1186/s12885-018-5152-5.
[226] D. Criscuolo, R. Avolio, G. Calice, C. Laezza, S. Paladino, G. Navarra, F. Maddalena, F. Crispo, C. Pagano, M. Bifulco, M. Landriscina, D.S. Matassa, F. Esposito, Cholesterol Homeostasis Modulates Platinum Sensitivity in Human Ovarian Cancer, Cells. 9 (2020). https://doi.org/10.3390/cells9040828.
[227] V.N. Ayyagari, X. Wang, P.L. Diaz-Sylvester, K. Groesch, L. Brard, Assessment of acyl-CoA cholesterol acyltransferase (ACAT-1) role in ovarian cancer progression-An in vitro study, PLoS ONE. 15 (2020) e0228024. https://doi.org/10.1371/journal.pone.0228024.
[228] E.L. Hedditch, B. Gao, A.J. Russell, Y. Lu, C. Emmanuel, J. Beesley, S.E. Johnatty, X. Chen, P. Harnett, J. George, Australian Ovarian Cancer Study Group,

R.T. Williams, C. Flemming, D. Lambrechts, E. Despierre, S. Lambrechts, I. Vergote, B. Karlan, J. Lester, S. Orsulic, C. Walsh, P. Fasching, M.W. Beckmann, A.B. Ekici, A. Hein, K. Matsuo, S. Hosono, T. Nakanishi, Y. Yatabe, T. Pejovic, Y. Bean, F. Heitz, P. Harter, A. du Bois, I. Schwaab, E. Hogdall, S.K. Kjaer, A. Jensen, C. Hogdall, L. Lundvall, S.A. Engelholm, B. Brown, J. Flanagan, M.D. Metcalf, N. Siddiqui, T. Sellers, B. Fridley, J. Cunningham, J. Schildkraut, E. Iversen, R.P. Weber, A. Berchuck, E. Goode, D.D. Bowtell, G. Chenevix-Trench, A. deFazio, M.D. Norris, S. MacGregor, M. Haber, M.J. Henderson, ABCA transporter gene expression and poor outcome in epithelial ovarian cancer, J. Natl. Cancer Inst. 106 (2014). https://doi.org/10.1093/jnci/dju149.

[229] P. Goossens, J. Rodriguez-Vita, A. Etzerodt, M. Masse, O. Rastoin, V. Gouirand, T. Ulas, O. Papantonopoulou, M. Van Eck, N. Auphan-Anezin, M. Bebien, C. Verthuy, T.P. Vu Manh, M. Turner, M. Dalod, J.L. Schultze, T. Lawrence, Membrane Cholesterol Efflux Drives Tumor-Associated Macrophage Reprogramming and Tumor Progression, Cell Metab. 29 (2019) 1376-1389.e4. https://doi.org/10.1016/j.cmet.2019.02.016.

[230] H. Tuft Stavnes, D.A. Nymoen, T.E. Hetland Falkenthal, J. Kærn, C.G. Tropé, B. Davidson, APOA1 mRNA expression in ovarian serous carcinoma effusions is a marker of longer survival, Am. J. Clin. Pathol. 142 (2014) 51–57. https://doi.org/10.1309/AJCPD8NBSHXRXQL7.

[231] S. He, L. Ma, A.E. Baek, A. Vardanyan, V. Vembar, J.J. Chen, A.T. Nelson, J.E. Burdette, E.R. Nelson, Host CYP27A1 expression is essential for ovarian cancer progression, Endocr. Relat. Cancer. 26 (2019) 659–675. https://doi.org/10.1530/ERC-18-0572.

[232] R. Lappano, A.G. Recchia, E.M. De Francesco, T. Angelone, M.C. Cerra, D. Picard, M. Maggiolini, The cholesterol metabolite 25-hydroxycholesterol activates estrogen receptor α-mediated signaling in cancer cells and in cardiomyocytes, PLoS ONE. 6 (2011) e16631. https://doi.org/10.1371/journal.pone.0016631.

[233] J. Hu, Z. Zhang, W.-J. Shen, S. Azhar, Cellular cholesterol delivery, intracellular processing and utilization for biosynthesis of steroid hormones, Nutrition & Metabolism. 7 (2010) 47. https://doi.org/10.1186/1743-7075-7-47.

[234] A.K. Lam, Update on Adrenal Tumours in 2017 World Health Organization (WHO) of Endocrine Tumours, Endocr Pathol. 28 (2017) 213–227. https://doi.org/10.1007/s12022-017-9484-5.

[235] R. Rossi, L. Tauchmanova, A. Luciano, M. Di Martino, C. Battista, L. Del Viscovo, V. Nuzzo, G. Lombardi, Subclinical Cushing's syndrome in patients with adrenal incidentaloma: clinical and biochemical features, J. Clin. Endocrinol. Metab. 85 (2000) 1440–1448. https://doi.org/10.1210/jcem.85.4.6515.

[236] M. Terzolo, A. Pia, A. Alì, G. Osella, G. Reimondo, S. Bovio, F. Daffara, M. Procopio, P. Paccotti, G. Borretta, A. Angeli, Adrenal Incidentaloma: A New Cause of the Metabolic Syndrome?, J Clin Endocrinol Metab. 87 (2002) 998–1003. https://doi.org/10.1210/jcem.87.3.8277.

[237] G. Mintziori, T. Georgiou, P. Anagnostis, F. Adamidou, Z. Efstathiadou, A. Panagiotou, M. Kita, Could Lipid Profile be Used as a Marker of Autonomous Cortisol Secretion in Patients with Adrenal Incidentalomas?, Horm Metab Res. 50 (2018) 551–555. https://doi.org/10.1055/a-0630-1397.

[238] M. Higashijima, K. Kato, H. Nawata, H. Ibayashi, Studies on lipoprotein and adrenal steroidogenesis: II. Utilization of low density lipoprotein- and high density lipoprotein-cholesterol for steroid production in functioning human adrenocortical

adenoma cells in culture, Endocrinol. Jpn. 34 (1987) 647–657. https://doi.org/10.1507/endocrj1954.34.647.
[239] G. Martin, A. Pilon, C. Albert, M. Vallé, D.W. Hum, J.C. Fruchart, J. Najib, V. Clavey, B. Staels, Comparison of expression and regulation of the high-density lipoprotein receptor SR-BI and the low-density lipoprotein receptor in human adrenocortical carcinoma NCI-H295 cells, Eur. J. Biochem. 261 (1999) 481–491. https://doi.org/10.1046/j.1432-1327.1999.00296.x.
[240] T. Nakagawa, Y. Ueyama, S. Nozaki, S. Yamashita, M. Menju, T. Funahashi, K. Kameda-Takemura, M. Kubo, K. Tokunaga, T. Tanaka, Marked hypocholesterolemia in a case with adrenal adenoma--enhanced catabolism of low density lipoprotein (LDL) via the LDL receptors of tumor cells, J. Clin. Endocrinol. Metab. 80 (1995) 92–96. https://doi.org/10.1210/jcem.80.1.7829645.
[241] H. Wilmot Roussel, D. Vezzosi, M. Rizk-Rabin, O. Barreau, B. Ragazzon, F. René-Corail, A. de Reynies, J. Bertherat, G. Assié, Identification of Gene Expression Profiles Associated With Cortisol Secretion in Adrenocortical Adenomas, J Clin Endocrinol Metab. 98 (2013) E1109–E1121. https://doi.org/10.1210/jc.2012-4237.
[242] E. London, C.A. Wassif, A. Horvath, C. Tatsi, A. Angelousi, A.S. Karageorgiadis, F.D. Porter, C.A. Stratakis, Cholesterol Biosynthesis and Trafficking in Cortisol-Producing Lesions of the Adrenal Cortex, J. Clin. Endocrinol. Metab. 100 (2015) 3660–3667. https://doi.org/10.1210/jc.2015-2212.
[243] N.H. Hanna, L.H. Einhorn, Testicular cancer--discoveries and updates, N. Engl. J. Med. 371 (2014) 2005–2016. https://doi.org/10.1056/NEJMra1407550.
[244] A.-B. Wiréhn, S. Törnberg, J. Carstensen, Serum cholesterol and testicular cancer incidence in 45,000 men followed for 25 years, Br. J. Cancer. 92 (2005) 1785–1786. https://doi.org/10.1038/sj.bjc.6602539.
[245] D.A. Freeman, M. Ascoli, Studies on the source of cholesterol used for steroid biosynthesis in cultured Leydig tumor cells, J. Biol. Chem. 257 (1982) 14231–14238.
[246] D.A. Freeman, M. Ascoli, The low-density lipoprotein pathway of cultured Leydig tumor cells. Utilization of low-density lipoprotein-derived cholesterol for steroidogenesis, Biochim. Biophys. Acta. 754 (1983) 72–81. https://doi.org/10.1016/0005-2760(83)90083-8.
[247] M.A. Zaid, W.G. Gathirua-Mwangi, C. Fung, P.O. Monahan, O. El-Charif, A.M. Williams, D.R. Feldman, R.J. Hamilton, D.J. Vaughn, C.J. Beard, R. Cook, S.K. Althouse, S. Ardeshir-Rouhani-Fard, P.C. Dinh, H.D. Sesso, L.H. Einhorn, S.D. Fossa, L.B. Travis, Platinum Study Group, Clinical and Genetic Risk Factors for Adverse Metabolic Outcomes in North American Testicular Cancer Survivors, J Natl Compr Canc Netw. 16 (2018) 257–265. https://doi.org/10.6004/jnccn.2017.7046.
[248] J. Armitage, The safety of statins in clinical practice, Lancet. 370 (2007) 1781–1790. https://doi.org/10.1016/S0140-6736(07)60716-8.
[249] J.L. Goldstein, M.S. Brown, Regulation of the mevalonate pathway, Nature. 343 (1990) 425–430. https://doi.org/10.1038/343425a0.
[250] S. Pisanti, P. Picardi, E. Ciaglia, A. D'Alessandro, M. Bifulco, Novel prospects of statins as therapeutic agents in cancer, Pharmacol. Res. 88 (2014) 84–98. https://doi.org/10.1016/j.phrs.2014.06.013.
[251] M. Afzali, M. Vatankhah, S.N. Ostad, Investigation of simvastatin-induced apoptosis and cell cycle arrest in cancer stem cells of MCF-7, J Cancer Res Ther. 12 (2016) 725–730. https://doi.org/10.4103/0973-1482.146127.

[252] T. Alarcon Martinez, N.D. Zeybek, S. Müftüoğlu, Evaluation of the Cytotoxic and Autophagic Effects of Atorvastatin on MCF-7 Breast Cancer Cells, Balkan Med J. 35 (2018) 256–262. https://doi.org/10.4274/balkanmedj.2017.0604.
[253] M. Malik, J. Britten, M. Borahay, J. Segars, W.H. Catherino, Simvastatin, at clinically relevant concentrations, affects human uterine leiomyoma growth and extracellular matrix production, Fertil. Steril. 110 (2018) 1398-1407.e1. https://doi.org/10.1016/j.fertnstert.2018.07.024.
[254] C.F. Christie, D. Fang, E.G. Hunt, M.E. Morris, A. Rovini, K.A. Heslop, G.C. Beeson, C.C. Beeson, E.N. Maldonado, Statin-dependent modulation of mitochondrial metabolism in cancer cells is independent of cholesterol content, FASEB J. 33 (2019) 8186–8201. https://doi.org/10.1096/fj.201802723R.
[255] G. Gruenbacher, M. Thurnher, Mevalonate metabolism in cancer, Cancer Lett. 356 (2015) 192–196. https://doi.org/10.1016/j.canlet.2014.01.013.
[256] G.H. Jeong, K.H. Lee, J.Y. Kim, M. Eisenhut, A. Kronbichler, H.J. van der Vliet, J.I. Shin, G. Gamerith, Statin and Cancer Mortality and Survival: An Umbrella Systematic Review and Meta-Analysis, J Clin Med. 9 (2020). https://doi.org/10.3390/jcm9020326.
[257] B. Liu, Z. Yi, X. Guan, Y.-X. Zeng, F. Ma, The relationship between statins and breast cancer prognosis varies by statin type and exposure time: a meta-analysis, Breast Cancer Res. Treat. 164 (2017) 1–11. https://doi.org/10.1007/s10549-017-4246-0.
[258] Cholesterol Treatment Trialists' (CTT) Collaboration, J.R. Emberson, P.M. Kearney, L. Blackwell, C. Newman, C. Reith, N. Bhala, L. Holland, R. Peto, A. Keech, R. Collins, J. Simes, C. Baigent, Lack of effect of lowering LDL cholesterol on cancer: meta-analysis of individual data from 175,000 people in 27 randomised trials of statin therapy, PLoS ONE. 7 (2012) e29849. https://doi.org/10.1371/journal.pone.0029849.
[259] C. Baigent, A. Keech, P.M. Kearney, L. Blackwell, G. Buck, C. Pollicino, A. Kirby, T. Sourjina, R. Peto, R. Collins, R. Simes, Cholesterol Treatment Trialists' (CTT) Collaborators, Efficacy and safety of cholesterol-lowering treatment: prospective meta-analysis of data from 90,056 participants in 14 randomised trials of statins, Lancet. 366 (2005) 1267–1278. https://doi.org/10.1016/S0140-6736(05)67394-1.
[260] S. Manthravadi, A. Shrestha, S. Madhusudhana, Impact of statin use on cancer recurrence and mortality in breast cancer: A systematic review and meta-analysis: Breast cancer: A systematic review and meta-analysis, International Journal of Cancer. 139 (2016) 1281–1288. https://doi.org/10.1002/ijc.30185.
[261] A.B. Rossebø, T.R. Pedersen, K. Boman, P. Brudi, J.B. Chambers, K. Egstrup, E. Gerdts, C. Gohlke-Bärwolf, I. Holme, Y.A. Kesäniemi, W. Malbecq, C.A. Nienaber, S. Ray, T. Skjaerpe, K. Wachtell, R. Willenheimer, SEAS Investigators, Intensive lipid lowering with simvastatin and ezetimibe in aortic stenosis, N. Engl. J. Med. 359 (2008) 1343–1356. https://doi.org/10.1056/NEJMoa0804602.
[262] E.J. Jacobs, C.C. Newton, M.J. Thun, S.M. Gapstur, Long-term use of cholesterol-lowering drugs and cancer incidence in a large United States cohort, Cancer Res. 71 (2011) 1763–1771. https://doi.org/10.1158/0008-5472.CAN-10-2953.
[263] S.F. Nielsen, B.G. Nordestgaard, S.E. Bojesen, Statin use and reduced cancer-related mortality, N. Engl. J. Med. 367 (2012) 1792–1802. https://doi.org/10.1056/NEJMoa1201735.

[264] B.A. Ference, K.K. Ray, A.L. Catapano, T.B. Ference, S. Burgess, D.R. Neff, C. Oliver-Williams, A.M. Wood, A.S. Butterworth, E. Di Angelantonio, J. Danesh, J.J.P. Kastelein, S.J. Nicholls, Mendelian Randomization Study of ACLY and Cardiovascular Disease, N. Engl. J. Med. 380 (2019) 1033–1042. https://doi.org/10.1056/NEJMoa1806747.
[265] K. Undela, V. Srikanth, D. Bansal, Statin use and risk of breast cancer: a meta-analysis of observational studies, Breast Cancer Res. Treat. 135 (2012) 261–269. https://doi.org/10.1007/s10549-012-2154-x.
[266] S. Bonovas, K. Filioussi, N. Tsavaris, N.M. Sitaras, Use of statins and breast cancer: a meta-analysis of seven randomized clinical trials and nine observational studies, J. Clin. Oncol. 23 (2005) 8606–8612. https://doi.org/10.1200/JCO.2005.02.7045.
[267] Q.-J. Wu, C. Tu, Y.-Y. Li, J. Zhu, K.-Q. Qian, W.-J. Li, L. Wu, Statin use and breast cancer survival and risk: a systematic review and meta-analysis, Oncotarget. 6 (2015) 42988–43004. https://doi.org/10.18632/oncotarget.5557.
[268] M. Mansourian, S. Haghjooy-Javanmard, A. Eshraghi, G. Vaseghi, A. Hayatshahi, J. Thomas, Statins Use and Risk of Breast Cancer Recurrence and Death: A Systematic Review and Meta-Analysis of Observational Studies, J Pharm Pharm Sci. 19 (2016) 72–81. https://doi.org/10.18433/J3202B.
[269] M.M. Islam, H.-C. Yang, P.-A. Nguyen, T.N. Poly, C.-W. Huang, S. Kekade, A.M. Khalfan, T. Debnath, Y.-C.J. Li, S.S. Abdul, Exploring association between statin use and breast cancer risk: an updated meta-analysis, Arch. Gynecol. Obstet. 296 (2017) 1043–1053. https://doi.org/10.1007/s00404-017-4533-3.
[270] K.M. Dale, C.I. Coleman, N.N. Henyan, J. Kluger, C.M. White, Statins and cancer risk: a meta-analysis, JAMA. 295 (2006) 74–80. https://doi.org/10.1001/jama.295.1.74.
[271] T.J. Murtola, K. Visvanathan, M. Artama, H. Vainio, E. Pukkala, Statin use and breast cancer survival: a nationwide cohort study from Finland, PLoS ONE. 9 (2014) e110231. https://doi.org/10.1371/journal.pone.0110231.
[272] T.P. Ahern, L. Pedersen, M. Tarp, D.P. Cronin-Fenton, J.P. Garne, R.A. Silliman, H.T. Sørensen, T.L. Lash, Statin prescriptions and breast cancer recurrence risk: a Danish nationwide prospective cohort study, J. Natl. Cancer Inst. 103 (2011) 1461–1468. https://doi.org/10.1093/jnci/djr291.
[273] S. Borgquist, A. Giobbie-Hurder, T.P. Ahern, J.E. Garber, M. Colleoni, I. Láng, M. Debled, B. Ejlertsen, R. von Moos, I. Smith, A.S. Coates, A. Goldhirsch, M. Rabaglio, K.N. Price, R.D. Gelber, M.M. Regan, B. Thürlimann, Cholesterol, Cholesterol-Lowering Medication Use, and Breast Cancer Outcome in the BIG 1-98 Study, J. Clin. Oncol. 35 (2017) 1179–1188. https://doi.org/10.1200/JCO.2016.70.3116.
[274] J.A. Cauley, J.M. Zmuda, L.-Y. Lui, T.A. Hillier, R.B. Ness, K.L. Stone, S.R. Cummings, D.C. Bauer, Lipid-lowering drug use and breast cancer in older women: a prospective study, J Womens Health (Larchmt). 12 (2003) 749–756. https://doi.org/10.1089/154099903322447710.
[275] T.M. Brewer, H. Masuda, D.D. Liu, Y. Shen, P. Liu, T. Iwamoto, K. Kai, C.M. Barnett, W.A. Woodward, J.M. Reuben, P. Yang, G.N. Hortobagyi, N.T. Ueno, Statin use in primary inflammatory breast cancer: a cohort study, Br. J. Cancer. 109 (2013) 318–324. https://doi.org/10.1038/bjc.2013.342.
[276] T. Anothaisintawee, U. Udomsubpayakul, M. McEvoy, P. Lerdsitthichai, J. Attia, A. Thakkinstian, Effect of Lipophilic and Hydrophilic Statins on Breast

Cancer Risk in Thai Women: A Cross-sectional Study, J Cancer. 7 (2016) 1163–1168. https://doi.org/10.7150/jca.14941.
[277] Ú.C. Mc Menamin, L.J. Murray, C.M. Hughes, C.R. Cardwell, Statin use and breast cancer survival: a nationwide cohort study in Scotland, BMC Cancer. 16 (2016) 600. https://doi.org/10.1186/s12885-016-2651-0.
[278] A. Smith, L. Murphy, L. Zgaga, T.I. Barron, K. Bennett, Pre-diagnostic statin use, lymph node status and mortality in women with stages I-III breast cancer, Br. J. Cancer. 117 (2017) 588–596. https://doi.org/10.1038/bjc.2017.227.
[279] S.F. Shaitelman, M.C. Stauder, P. Allen, S. Reddy, S. Lakoski, B. Atkinson, J. Reddy, D. Amaya, W. Guerra, N. Ueno, A. Caudle, W. Tereffe, W.A. Woodward, Impact of Statin Use on Outcomes in Triple Negative Breast Cancer, J Cancer. 8 (2017) 2026–2032. https://doi.org/10.7150/jca.18743.
[280] Y.K. Chae, M.E. Valsecchi, J. Kim, A.L. Bianchi, D. Khemasuwan, A. Desai, W. Tester, Reduced risk of breast cancer recurrence in patients using ACE inhibitors, ARBs, and/or statins, Cancer Invest. 29 (2011) 585–593. https://doi.org/10.3109/07357907.2011.616252.
[281] M. Sakellakis, K. Akinosoglou, A. Kostaki, D. Spyropoulou, A. Koutras, Statins and risk of breast cancer recurrence, Breast Cancer (Dove Med Press). 8 (2016) 199–205. https://doi.org/10.2147/BCTT.S116694.
[282] C. Schairer, D.M. Freedman, S.M. Gadalla, R.M. Pfeiffer, Lipid-lowering drugs, dyslipidemia, and breast cancer risk in a Medicare population, Breast Cancer Res. Treat. 169 (2018) 607–614. https://doi.org/10.1007/s10549-018-4680-7.
[283] J.A. McDougall, K.E. Malone, J.R. Daling, K.L. Cushing-Haugen, P.L. Porter, C.I. Li, Long-Term Statin Use and Risk of Ductal and Lobular Breast Cancer among Women 55 to 74 Years of Age, Cancer Epidemiology Biomarkers & Prevention. 22 (2013) 1529–1537. https://doi.org/10.1158/1055-9965.epi-13-0414.
[284] J. Hutchinson, L. Marignol, Clinical Potential of Statins in Prostate Cancer Radiation Therapy, Anticancer Res. 37 (2017) 5363–5372. https://doi.org/10.21873/anticanres.11962.
[285] E.A. Platz, M.F. Leitzmann, K. Visvanathan, E.B. Rimm, M.J. Stampfer, W.C. Willett, E. Giovannucci, Statin drugs and risk of advanced prostate cancer, J. Natl. Cancer Inst. 98 (2006) 1819–1825. https://doi.org/10.1093/jnci/djj499.
[286] S.B. Larsen, C. Dehlendorff, C. Skriver, S.O. Dalton, C.G. Jespersen, M. Borre, K. Brasso, M. Nørgaard, C. Johansen, H.T. Sørensen, J. Hallas, S. Friis, Postdiagnosis Statin Use and Mortality in Danish Patients With Prostate Cancer, J. Clin. Oncol. 35 (2017) 3290–3297. https://doi.org/10.1200/JCO.2016.71.8981.
[287] R.J. Hamilton, L.L. Banez, W.J. Aronson, M.K. Terris, E.A. Platz, C.J. Kane, J.C. Presti, C.L. Amling, S.J. Freedland, Statin medication use and the risk of biochemical recurrence after radical prostatectomy: results from the Shared Equal Access Regional Cancer Hospital (SEARCH) Database, Cancer. 116 (2010) 3389–3398. https://doi.org/10.1002/cncr.25308.
[288] S. Bonovas, K. Filioussi, N.M. Sitaras, Statins are not associated with a reduced risk of pancreatic cancer at the population level, when taken at low doses for managing hypercholesterolemia: evidence from a meta-analysis of 12 studies, Am. J. Gastroenterol. 103 (2008) 2646–2651. https://doi.org/10.1111/j.1572-0241.2008.02051.x.
[289] X. Cui, Y. Xie, M. Chen, J. Li, X. Liao, J. Shen, M. Shi, W. Li, H. Zheng, B. Jiang, Statin use and risk of pancreatic cancer: a meta-analysis, Cancer Causes Control. 23 (2012) 1099–1111. https://doi.org/10.1007/s10552-012-9979-9.

[290] B.Z. Huang, J.I. Chang, E. Li, A.H. Xiang, B.U. Wu, Influence of Statins and Cholesterol on Mortality Among Patients With Pancreatic Cancer, J. Natl. Cancer Inst. 109 (2017). https://doi.org/10.1093/jnci/djw275.
[291] H.S. Lee, S.H. Lee, H.J. Lee, M.J. Chung, J.Y. Park, S.W. Park, S.Y. Song, S. Bang, Statin Use and Its Impact on Survival in Pancreatic Cancer Patients, Medicine (Baltimore). 95 (2016) e3607. https://doi.org/10.1097/MD.0000000000003607.
[292] R.B. Chagpar, R.C.G. Martin, S.A. Ahmad, H.J. Kim, C. Rupp, S. Weber, A. Ebelhar, J. Gilbert, A. Brinkman, E. Winslow, C.S. Cho, D. Kooby, C.K. Chu, C.A. Staley, K.M. McMasters, C.R. Scoggins, Medically managed hypercholesterolemia and insulin-dependent diabetes mellitus preoperatively predicts poor survival after surgery for pancreatic cancer, J. Gastrointest. Surg. 15 (2011) 551–557. https://doi.org/10.1007/s11605-011-1448-3.
[293] C.Y. Jeon, S.J. Pandol, M.T. Goodman, Survival time in pancreatic cancer patients with metabolic syndrome varies by use of insulin and statins, Cancer Res. 74 (2014) 2173–2173. https://doi.org/10.1158/1538-7445.AM2014-2173.
[294] Y. Nakai, H. Isayama, T. Sasaki, S. Mizuno, N. Sasahira, H. Kogure, K. Kawakubo, N. Yamamoto, K. Hirano, H. Ijichi, K. Tateishi, M. Tada, K. Koike, Clinical outcomes of chemotherapy for diabetic and nondiabetic patients with pancreatic cancer: better prognosis with statin use in diabetic patients, Pancreas. 42 (2013) 202–208. https://doi.org/10.1097/MPA.0b013e31825de678.
[295] V. Khurana, A. Sheth, G. Caldito, J.S. Barkin, Statins reduce the risk of pancreatic cancer in humans: a case-control study of half a million veterans, Pancreas. 34 (2007) 260–265. https://doi.org/10.1097/MPA.0b013e318030e963.
[296] M.C. Bradley, C.M. Hughes, M.M. Cantwell, L.J. Murray, Statins and pancreatic cancer risk: a nested case-control study, Cancer Causes Control. 21 (2010) 2093–2100. https://doi.org/10.1007/s10552-010-9628-0.
[297] E.J. Walker, A.H. Ko, E.A. Holly, P.M. Bracci, Statin use and risk of pancreatic cancer: results from a large, clinic-based case-control study, Cancer. 121 (2015) 1287–1294. https://doi.org/10.1002/cncr.29256.
[298] H.-F. Chiu, C.-C. Chang, S.-C. Ho, T.-N. Wu, C.-Y. Yang, Statin use and the risk of pancreatic cancer: a population-based case-control study, Pancreas. 40 (2011) 669–672. https://doi.org/10.1097/MPA.0b013e31821fd5cd.
[299] F.J. Carey, M.W. Little, T.F.G. Pugh, R. Ndokera, H. Ing, A. Clark, A. Dennison, M.S. Metcalfe, R.J. Robinson, A.R. Hart, The differential effects of statins on the risk of developing pancreatic cancer: a case-control study in two centres in the United Kingdom, Dig. Dis. Sci. 58 (2013) 3308–3312. https://doi.org/10.1007/s10620-013-2778-7.
[300] A. Majidi, R. Na, S. Dixon-Suen, S.J. Jordan, P.M. Webb, Common medications and survival in women with ovarian cancer: A systematic review and meta-analysis, Gynecol. Oncol. 157 (2020) 678–685. https://doi.org/10.1016/j.ygyno.2020.03.028.
[301] X. Li, J. Zhou, Impact of postdiagnostic statin use on ovarian cancer mortality: A systematic review and meta-analysis of observational studies, Br J Clin Pharmacol. 84 (2018) 1109–1120. https://doi.org/10.1111/bcp.13559.
[302] Y. Liu, A. Qin, T. Li, X. Qin, S. Li, Effect of statin on risk of gynecologic cancers: a meta-analysis of observational studies and randomized controlled trials, Gynecol. Oncol. 133 (2014) 647–655. https://doi.org/10.1016/j.ygyno.2014.04.007.
[303] B.N. Harding, J.A. Delaney, R.R. Urban, N.S. Weiss, Use of Statin Medications Following Diagnosis in Relation to Survival among Women with Ovarian Cancer, Cancer Epidemiol. Biomarkers Prev. 28 (2019) 1127–1133. https://doi.org/10.1158/1055-9965.EPI-18-1194.

[304] E. Urpilainen, M. Marttila, A. Hautakoski, M. Arffman, R. Sund, P. Ilanne-Parikka, R. Arima, J. Kangaskokko, U. Puistola, M. Hinkula, E. Läärä, Prognosis of ovarian cancer in women with type 2 diabetes using metformin and other forms of antidiabetic medication or statins: a retrospective cohort study, BMC Cancer. 18 (2018) 767. https://doi.org/10.1186/s12885-018-4676-z.
[305] P. Desai, R. Wallace, M.L. Anderson, B.V. Howard, R.M. Ray, C. Wu, M. Safford, L.W. Martin, T. Rohan, J.E. Manson, M.S. Simon, An analysis of the association between statin use and risk of endometrial and ovarian cancers in the Women's Health Initiative, Gynecol. Oncol. 148 (2018) 540–546. https://doi.org/10.1016/j.ygyno.2018.01.006.
[306] A. Couttenier, O. Lacroix, E. Vaes, C.R. Cardwell, H. De Schutter, A. Robert, Statin use is associated with improved survival in ovarian cancer: A retrospective population-based study, PLoS ONE. 12 (2017) e0189233. https://doi.org/10.1371/journal.pone.0189233.
[307] F. Verdoodt, M. Kjaer Hansen, S.K. Kjaer, A. Pottegård, S. Friis, C. Dehlendorff, Statin use and mortality among ovarian cancer patients: A population-based cohort study, Int. J. Cancer. 141 (2017) 279–286. https://doi.org/10.1002/ijc.30738.
[308] H.-Y. Chen, Q. Wang, Q.-H. Xu, L. Yan, X.-F. Gao, Y.-H. Lu, L. Wang, Statin as a Combined Therapy for Advanced-Stage Ovarian Cancer: A Propensity Score Matched Analysis, Biomed Res Int. 2016 (2016) 9125238. https://doi.org/10.1155/2016/9125238.
[309] M. Habis, K. Wroblewski, M. Bradaric, N. Ismail, S.D. Yamada, L. Litchfield, E. Lengyel, I.L. Romero, Statin therapy is associated with improved survival in patients with non-serous-papillary epithelial ovarian cancer: a retrospective cohort analysis, PLoS ONE. 9 (2014) e104521. https://doi.org/10.1371/journal.pone.0104521.
[310] Y. Wang, F. Ren, Z. Song, P. Chen, S. Liu, L. Ouyang, Statin use and the risk of ovarian and endometrial cancers: a meta-analysis, BMC Cancer. 19 (2019) 730. https://doi.org/10.1186/s12885-019-5954-0.
[311] B. Akinwunmi, A.F. Vitonis, L. Titus, K.L. Terry, D.W. Cramer, Statin therapy and association with ovarian cancer risk in the New England Case Control (NEC) study, Int. J. Cancer. 144 (2019) 991–1000. https://doi.org/10.1002/ijc.31758.
[312] L. Baandrup, C. Dehlendorff, S. Friis, J.H. Olsen, S.K. Kjær, Statin use and risk for ovarian cancer: a Danish nationwide case-control study, Br. J. Cancer. 112 (2015) 157–161. https://doi.org/10.1038/bjc.2014.574.
[313] J. Zhang, Q. Li, Y. Wu, D. Wang, L. Xu, Y. Zhang, S. Wang, T. Wang, F. Liu, M.Y. Zaky, S. Hou, S. Liu, K. Zou, H. Lei, L. Zou, Y. Zhang, H. Liu, Cholesterol content in cell membrane maintains surface levels of ErbB2 and confers a therapeutic vulnerability in ErbB2-positive breast cancer, Cell Commun. Signal. 17 (2019) 15. https://doi.org/10.1186/s12964-019-0328-4.
[314] Y. Kong, L. Cheng, F. Mao, Z. Zhang, Y. Zhang, E. Farah, J. Bosler, Y. Bai, N. Ahmad, S. Kuang, L. Li, X. Liu, Inhibition of cholesterol biosynthesis overcomes enzalutamide resistance in castration-resistant prostate cancer (CRPC), J. Biol. Chem. 293 (2018) 14328–14341. https://doi.org/10.1074/jbc.RA118.004442.
[315] A. Bhardwaj, H. Singh, C.M. Trinidad, C.T. Albarracin, K.K. Hunt, I. Bedrosian, The isomiR-140-3p-regulated mevalonic acid pathway as a potential target for prevention of triple negative breast cancer, Breast Cancer Res. 20 (2018) 150. https://doi.org/10.1186/s13058-018-1074-z.

[316] G.H. McGregor, A.D. Campbell, S.K. Fey, S. Tumanov, D. Sumpton, G.R. Blanco, G. Mackay, C. Nixon, A. Vazquez, O.J. Sansom, J.J. Kamphorst, Targeting the Metabolic Response to Statin-Mediated Oxidative Stress Produces a Synergistic Antitumor Response, Cancer Res. 80 (2020) 175–188. https://doi.org/10.1158/0008-5472.CAN-19-0644.
[317] R. Peto, J. Emberson, M. Landray, C. Baigent, R. Collins, R. Clare, R. Califf, Analyses of cancer data from three ezetimibe trials, N. Engl. J. Med. 359 (2008) 1357–1366. https://doi.org/10.1056/NEJMsa0806603.
[318] A. Green, D.R. Ramey, M. Emneus, M. Iachina, K. Stavem, K. Bolin, R. McNally, M. Busch-Sørensen, R. Willenheimer, K. Egstrup, Y.A. Kesäniemi, S. Ray, N. Basta, C. Kent, T.R. Pedersen, Incidence of cancer and mortality in patients from the Simvastatin and Ezetimibe in Aortic Stenosis (SEAS) trial, Am. J. Cardiol. 114 (2014) 1518–1522. https://doi.org/10.1016/j.amjcard.2014.08.016.
[319] K.R. Solomon, K. Pelton, K. Boucher, J. Joo, C. Tully, D. Zurakowski, C.P. Schaffner, J. Kim, M.R. Freeman, Ezetimibe is an inhibitor of tumor angiogenesis, Am. J. Pathol. 174 (2009) 1017–1026. https://doi.org/10.2353/ajpath.2009.080551.
[320] M. Lee-Rueckert, J.C. Escola-Gil, P.T. Kovanen, HDL functionality in reverse cholesterol transport – Challenges in translating data emerging from mouse models to human disease, Biochim. Biophys. Acta. (2016). https://doi.org/10.1016/j.bbalip.2016.03.004.
[321] A.A. Momtazi-Borojeni, M.E. Nik, M.R. Jaafari, M. Banach, A. Sahebkar, Effects of immunization against PCSK9 in an experimental model of breast cancer, Arch Med Sci. 15 (2019) 570–579. https://doi.org/10.5114/aoms.2019.84734.
[322] R.M. Stoekenbroek, G. Lambert, B. Cariou, G.K. Hovingh, Inhibiting PCSK9 - biology beyond LDL control, Nat Rev Endocrinol. 15 (2018) 52–62. https://doi.org/10.1038/s41574-018-0110-5.
[323] A.M. Lincoff, S.J. Nicholls, J.S. Riesmeyer, P.J. Barter, H.B. Brewer, K.A.A. Fox, C.M. Gibson, C. Granger, V. Menon, G. Montalescot, D. Rader, A.R. Tall, E. McErlean, K. Wolski, G. Ruotolo, B. Vangerow, G. Weerakkody, S.G. Goodman, D. Conde, D.K. McGuire, J.C. Nicolau, J.L. Leiva-Pons, Y. Pesant, W. Li, D. Kandath, S. Kouz, N. Tahirkheli, D. Mason, S.E. Nissen, ACCELERATE Investigators, Evacetrapib and Cardiovascular Outcomes in High-Risk Vascular Disease, N. Engl. J. Med. 376 (2017) 1933–1942. https://doi.org/10.1056/NEJMoa1609581.
[324] G.G. Schwartz, A.G. Olsson, M. Abt, C.M. Ballantyne, P.J. Barter, J. Brumm, B.R. Chaitman, I.M. Holme, D. Kallend, L.A. Leiter, E. Leitersdorf, J.J.V. McMurray, H. Mundl, S.J. Nicholls, P.K. Shah, J.-C. Tardif, R.S. Wright, dal-OUTCOMES Investigators, Effects of dalcetrapib in patients with a recent acute coronary syndrome, N. Engl. J. Med. 367 (2012) 2089–2099. https://doi.org/10.1056/NEJMoa1206797.
[325] P.J. Barter, M. Caulfield, M. Eriksson, S.M. Grundy, J.J.P. Kastelein, M. Komajda, J. Lopez-Sendon, L. Mosca, J.-C. Tardif, D.D. Waters, C.L. Shear, J.H. Revkin, K.A. Buhr, M.R. Fisher, A.R. Tall, B. Brewer, ILLUMINATE Investigators, Effects of torcetrapib in patients at high risk for coronary events, N. Engl. J. Med. 357 (2007) 2109–2122. https://doi.org/10.1056/NEJMoa0706628.
[326] HPS3/TIMI55–REVEAL Collaborative Group, L. Bowman, J.C. Hopewell, F. Chen, K. Wallendszus, W. Stevens, R. Collins, S.D. Wiviott, C.P. Cannon, E. Braunwald, E. Sammons, M.J. Landray, Effects of Anacetrapib in Patients with Atherosclerotic Vascular Disease, N. Engl. J. Med. 377 (2017) 1217–1227. https://doi.org/10.1056/NEJMoa1706444.

[327] A co-operative trial in the primary prevention of ischaemic heart disease using clofibrate. Report from the Committee of Principal Investigators, Br Heart J. 40 (1978) 1069–1118. https://doi.org/10.1136/hrt.40.10.1069.
[328] T.B. Newman, S.B. Hulley, Carcinogenicity of lipid-lowering drugs, JAMA. 275 (1996) 55–60.
[329] X. Lian, G. Wang, H. Zhou, Z. Zheng, Y. Fu, L. Cai, Anticancer Properties of Fenofibrate: A Repurposing Use, J Cancer. 9 (2018) 1527–1537. https://doi.org/10.7150/jca.24488.
[330] S. Bonovas, G.K. Nikolopoulos, P.G. Bagos, Use of fibrates and cancer risk: a systematic review and meta-analysis of 17 long-term randomized placebo-controlled trials, PLoS ONE. 7 (2012) e45259. https://doi.org/10.1371/journal.pone.0045259.
[331] J.H. Olsen, C. Johansen, H.T. Sørensen, J.K. McLaughlin, L. Mellemkjaer, F.H. Steffensen, J.F. Fraumeni, Lipid-lowering medication and risk of cancer, J Clin Epidemiol. 52 (1999) 167–169. https://doi.org/10.1016/s0895-4356(98)00147-4.
[332] A. Keech, R.J. Simes, P. Barter, J. Best, R. Scott, M.R. Taskinen, P. Forder, A. Pillai, T. Davis, P. Glasziou, P. Drury, Y.A. Kesäniemi, D. Sullivan, D. Hunt, P. Colman, M. d'Emden, M. Whiting, C. Ehnholm, M. Laakso, FIELD study investigators, Effects of long-term fenofibrate therapy on cardiovascular events in 9795 people with type 2 diabetes mellitus (the FIELD study): randomised controlled trial, Lancet. 366 (2005) 1849–1861. https://doi.org/10.1016/S0140-6736(05)67667-2.
[333] V. Gardette, V. Bongard, J. Dallongeville, D. Arveiler, A. Bingham, J.-B. Ruidavets, P. Amouyel, B. Haas, P. Ducimetière, J. Ferrières, Ten-year all-cause mortality in presumably healthy subjects on lipid-lowering drugs (from the Prospective Epidemiological Study of Myocardial Infarction [PRIME] prospective cohort), Am. J. Cardiol. 103 (2009) 381–386. https://doi.org/10.1016/j.amjcard.2008.09.092.
[334] L. Tenkanen, M. Mänttäri, P.T. Kovanen, H. Virkkunen, V. Manninen, Gemfibrozil in the treatment of dyslipidemia: an 18-year mortality follow-up of the Helsinki Heart Study, Arch. Intern. Med. 166 (2006) 743–748. https://doi.org/10.1001/archinte.166.7.743.
[335] H.B. Rubins, S.J. Robins, D. Collins, C.L. Fye, J.W. Anderson, M.B. Elam, F.H. Faas, E. Linares, E.J. Schaefer, G. Schectman, T.J. Wilt, J. Wittes, Gemfibrozil for the secondary prevention of coronary heart disease in men with low levels of high-density lipoprotein cholesterol. Veterans Affairs High-Density Lipoprotein Cholesterol Intervention Trial Study Group, N. Engl. J. Med. 341 (1999) 410–418. https://doi.org/10.1056/NEJM199908053410604.
[336] J.K. Huttunen, O.P. Heinonen, V. Manninen, P. Koskinen, T. Hakulinen, L. Teppo, M. Mänttäri, M.H. Frick, The Helsinki Heart Study: an 8.5-year safety and mortality follow-up, J. Intern. Med. 235 (1994) 31–39. https://doi.org/10.1111/j.1365-2796.1994.tb01029.x.
[337] Z. Iakobishvili, T. Hasin, R. Klempfner, N. Shlomo, I. Goldenberg, R. Brenner, R. Kornowski, Y. Gerber, Association of Bezafibrate Treatment With Reduced Risk of Cancer in Patients With Coronary Artery Disease, Mayo Clin. Proc. 94 (2019) 1171–1179. https://doi.org/10.1016/j.mayocp.2018.10.026.
[338] V.S. Kamanna, M.L. Kashyap, Mechanism of action of niacin, Am. J. Cardiol. 101 (2008) 20B-26B. https://doi.org/10.1016/j.amjcard.2008.02.029.
[339] P.L. Canner, K.G. Berge, N.K. Wenger, J. Stamler, L. Friedman, R.J. Prineas, W. Friedewald, Fifteen year mortality in Coronary Drug Project patients: long-term

benefit with niacin, J. Am. Coll. Cardiol. 8 (1986) 1245–1255. https://doi.org/10.1016/s0735-1097(86)80293-5.
[340] HPS2-THRIVE Collaborative Group, M.J. Landray, R. Haynes, J.C. Hopewell, S. Parish, T. Aung, J. Tomson, K. Wallendszus, M. Craig, L. Jiang, R. Collins, J. Armitage, Effects of extended-release niacin with laropiprant in high-risk patients, N. Engl. J. Med. 371 (2014) 203–212. https://doi.org/10.1056/NEJMoa1300955.
[341] X. Ma, Q. Song, X. Gao, Reconstituted high-density lipoproteins: novel biomimetic nanocarriers for drug delivery, Acta Pharm Sin B. 8 (2018) 51–63. https://doi.org/10.1016/j.apsb.2017.11.006.

Figure legends, tables, figures, schemes

Figure 1. Molecular pathways involved in accumulation of unesterified cholesterol (UC) and its effects on downstream oncogenic signaling pathways. (A) Both LDLR and SR-BI are upregulated in breast cancer cells, thereby increasing lipoprotein cholesterol uptake. The UC accumulation activates PI3K/Akt/ERK1/2 signaling together with its conversion to 27-HC, promoting proliferation and metastasis through the activation of c-Myc and EMT genes. OLR1 expression is also upregulated in breast cancer cells and induces tumor growth and migration via NF-kB activation. (B) LDLR is a main driver of UC accumulation in prostate cancer cells and its conversion into esterified cholesterol (EC) by ACAT1, thereby promoting cancer progression. The loss of PTEN activates PI3K/Akt/mTOR signaling, which in turn upregulates SREBP2 and LDLR. Lethal prostate tumors also present higher levels of SQLE. The AR potentiates UC accumulation by upregulating DHCR24 and SREBP2 and inhibiting ABCA1 expression. OLR1 expression also induces proliferation and metastasis. (C) LDLR is upregulated in epithelial thyroid cancer cells promoting an accumulation of UC and its conversion into 27HC, thereby promoting proliferation and metastasis. (D) Both LDLR and OLR1 are upregulated in pancreatic cancer cells along an increased expression of DHCR24, HMGCR and ACAT1, inducing proliferation and metastasis. Caveolin-1 also promotes tumor growth and metastasis via NF-kβ. (E) Both LDLR and ACAT1 are upregulated in ovarian cancer cells concomitant with an increase of UC and EC accumulation. CYP27A1 is highly expressed in ovarian cancer cells, inducing 27-HC accumulation and promoting proliferation and invasion. IL-4 signalling is increased in tumor associated macrophages, which in turn promotes PI3K activity and mTOR-mediated Akt phosphorylation and stimulates ABCA1-mediated cholesterol efflux,

transferring cholesterol to ovarian cancer cells through SR-BI. Common pathways are indicated with the same color in each cancer cell type.

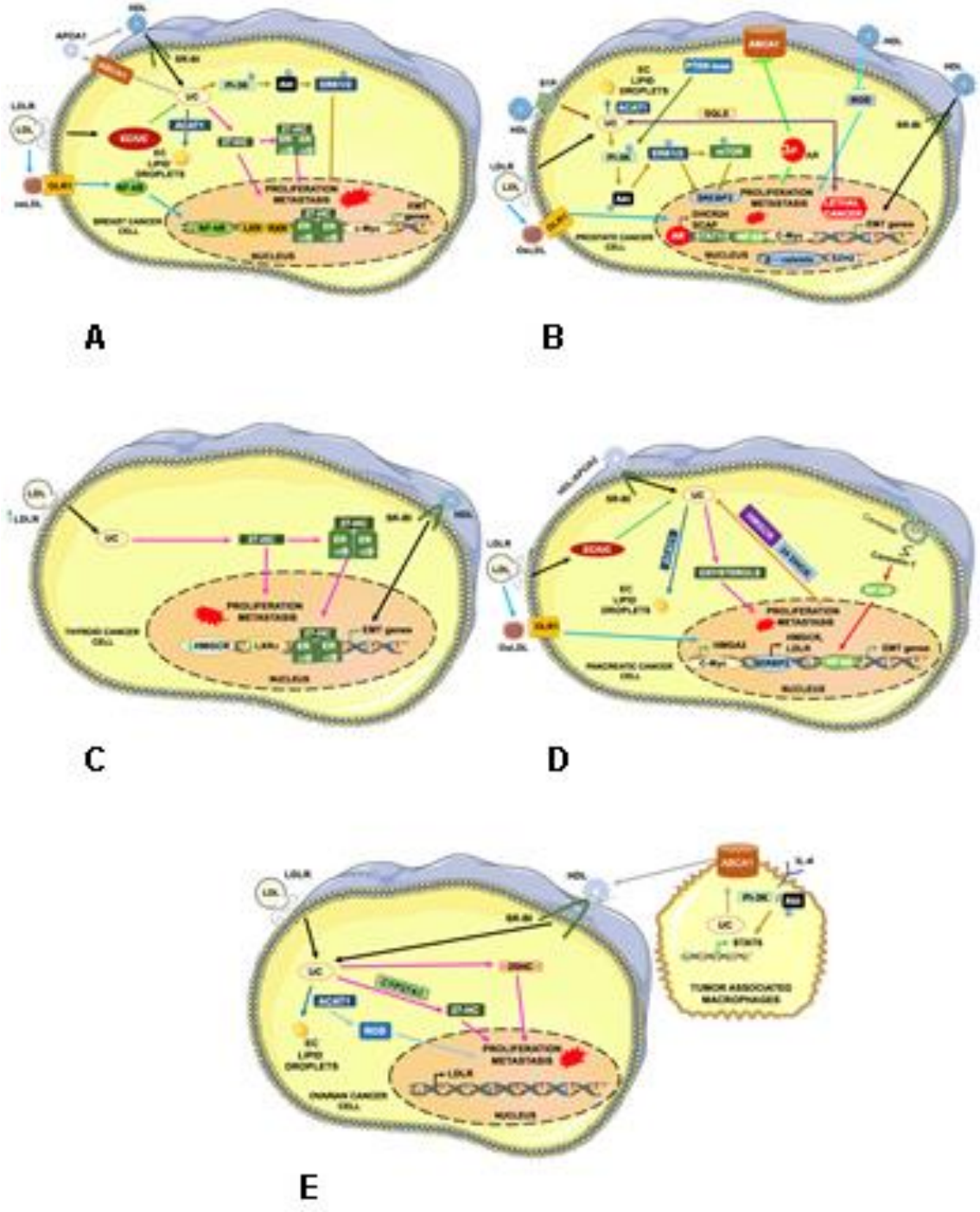
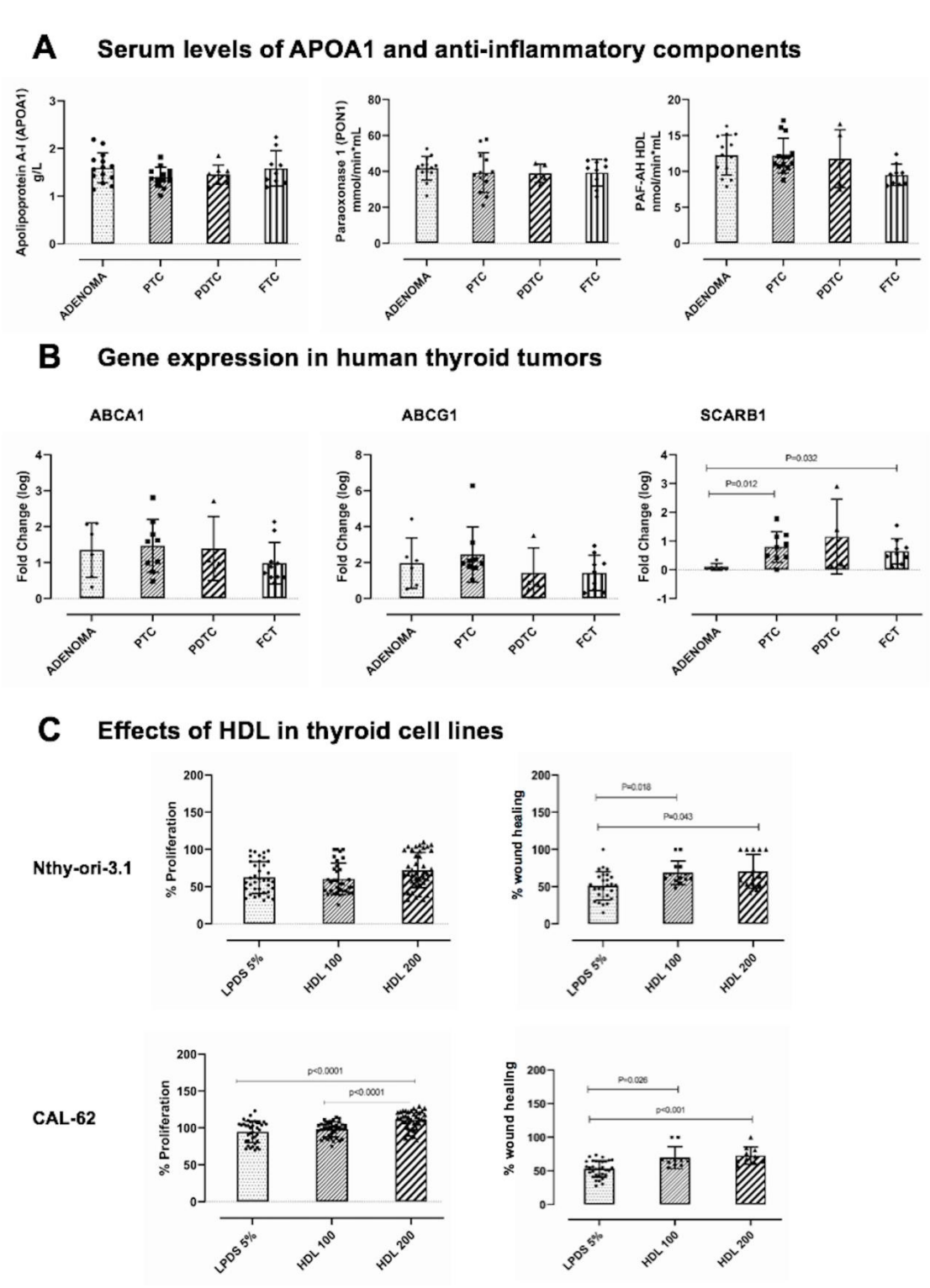


Figure 2. HDL antioxidant and anti-inflammatory components are not altered in patients with thyroid cancer, but HDL promotes proliferation and migration in anaplastic thyroid cell lines. (A) APOA1 levels and HDL antioxidant and anti-inflammatory activities in patients' serum. Values are means ± SEM of 13 PTC, 5 PDTC, 9 FTC, and 13 adenoma samples. (B) Real-time PCR quantification of relative mRNA expression of ABCA1, ABCG1, and SCARB1 in human thyroid tumors. Values are means ± SEM of 9 PTC, 4 PDTC, 10 FTC, and 6 adenoma tissues. (A and B) ANOVA plus Tukey's post-test was used to compare the groups. (C) Effects of HDL on proliferation and migration of thyroid follicular epithelial cells (Nthy-ori-3.1) and anaplastic thyroid cells (CAL-62). Both were treated 24 h with HDL (at 100 and 200 μg/mL of APOA1) compared with cells maintained in basal conditions (5% of lipoprotein-depleted serum, LPDS). Values are means ±SEM. Proliferation assay: the number of replicates in Nthy-ori-3.1 experiment was 38, 35 and 40 for LPDS, 100 μg/mL and 200 μg/mL of HDL, respectively; 37, 38 and 40 for LPDS, 100 μg/mL and 200 μg/mL of HDL, respectively, in CAL62 cells. Migration assay: the number of replicates in Nthy-ori-3.1 experiment was 26, 13 and 15 for LPDS, 100 μg/mL and 200 μg/mL of HDL, respectively; 32, 10 and 10 for LPDS, 100 μg/mL and 200 μg/mL of HDL, respectively, in CAL62 cells. The exogenous administration of HDL upregulated 1.5 and 2.3 fold SCARB1 in Nthy-ori-3.1 and CAL62 cells, respectively ($p=0.0009$ and 0.014, respectively, vs LPDS 5%). Kruskal-Wallis test was used to compare the groups.

Figure 2


A
Serum levels of APOA1 and anti-inflammatory components
Apolipoprotein A-I (APOA1) g/L
Paraoxonase 1 (PON1) mmol/min*mL
PAF-AH HDL nmol/min*mL
ADENOMA
PTC
PDTC
FTC
B
Gene expression in human thyroid tumors
ABCA1
ABCG1
SCARB1
Fold Change (log)
P=0.032
P=0.012
FCT
C
Effects of HDL in thyroid cell lines
Nthy-ori-3.1
CAL-62
% Proliferation
% wound healing
P=0.018
P=0.043
p<0.0001
p<0.0001
P=0.026
p<0.001
LPDS 5%
HDL 100
HDL 200