Available online at www.sciencedirect.com

SciVerse ScienceDirect

Current Opinion in Pharmacology

Cholesterol and breast cancer development

Christiane Danilo and Philippe G Frank

Breast cancer is the most commonly occurring type of cancer in the world. Among the environmental factors believed to be responsible for this phenomenon, cholesterol has recently received considerable attention. Epidemiologic studies have provided inconclusive results, indicating that there may be a relationship between abnormal plasma cholesterol levels and breast cancer risk. However, more compelling evidence has been obtained in laboratory studies, and they indicate that cholesterol is capable of regulating proliferation, migration, and signaling pathways in breast cancer. *In vivo* studies have also indicated that plasma cholesterol levels can regulate tumor growth in mouse models. The recognition of cholesterol as a factor contributing to breast cancer development identifies cholesterol and its metabolism as novel targets for cancer therapy.

Address
Department of Stem Cell Biology and Regenerative Medicine, Kimmel Cancer Center, Thomas Jefferson University, Philadelphia, PA 19107, USA

Corresponding author: Frank, Philippe G (philippe.frank@jefferson.edu)

Current Opinion in Pharmacology 2012, **12**:677–682

This review comes from a themed issue on **Endocrine and metabolic diseases**

Edited by **Sandrine Silvente-Poirot** and **Marc Poirot**

For a complete overview see the Issue and the Editorial

Available online 3rd August 2012

1471-4892/$ – see front matter,

http://dx.doi.org/10.1016/j.coph.2012.07.009

Introduction

Breast cancer is the most commonly diagnosed cancer among women and the second leading cause of cancer deaths among women in the United States. In 2012, an estimated 226,870 women will be diagnosed with breast cancer, and 39,510 will die from the disease [1]. Worldwide, breast cancer is the most frequently occurring cancer among women with over 1.3 million cases diagnosed yearly [2]. The greatest incidence of breast cancer is in the Western world. Several aspects associated with Western lifestyles are known risk factors for breast cancer. A diet high in saturated fats, early menarche, low parity, and advanced age at the first pregnancy are established risk factors of breast cancer [3]. All of these risks are more common in Western countries. Only 10% of breast cancer cases are estimated to have a genetic basis [3]. In the Western world, environmental factors appear to have a larger contribution to the incidence of breast cancer than genetic factors. Consequently, studies have shown that Americans of Japanese descent have an incidence of the disease similar to that of Americans of European descent [3].

Several epidemiological studies have shown a link between obesity, weight gain, a diet high in saturated fats and increased risk of cancer development [3–5]. Both obesity and diets high in saturated fats are associated with alterations in lipid profiles, specifically a decrease in high-density lipoprotein cholesterol (HDL-C) levels [6•]. Accordingly, alterations in lipoprotein profiles are often seen among breast cancer patients [7–9], and patients with advanced disease often show lower levels of total cholesterol, a phenomenon known as the preclinical effect of cancer [10]. However, the role of cholesterol in breast cancer is still unclear. Often, cancer patients display low serum cholesterol levels, and this is generally believed to be a consequence, not a cause, of the disease. Cancer cells are believed to have an increased requirement for cholesterol because it is essential for membrane synthesis in dividing cells, maintaining membrane rigidity, and formation of microdomains known as lipid rafts, which organize signaling molecules within cells. Cholesterol is also the precursor of vitamin D and estrogen, which plays a key role in the etiology of breast cancer.

This review examines recent epidemiologic and molecular evidence that suggests a role for cholesterol in breast cancer.

Cholesterol and breast cancer: epidemiologic evidence

In the early 90s, Boyd and McGuire hypothesized that factors influencing HDL-C levels often coincide with factors that influence breast cancer risk thus suggesting a relationship between high HDL-C levels and increased risk of breast cancer [11]. Subsequent studies have corroborated this hypothesis [12]. However, this observation is not necessarily causal since many case-control and prospective studies have yielded varying results. Cholesterol has a clearly established role in the etiology of cardiovascular disease (CVD). High circulating levels of low-density lipoprotein cholesterol (LDL-C) are directly related to increased risk of CVD whereas high levels of HDL-C are inversely associated with risk of CVD [13]. Accordingly, many investigators have examined the link between increased risk of breast cancer development and plasma LDL-C and HDL-C levels.

Collectively, older studies have been inconclusive and suggest that there may be no relationship [14–16], an

inverse relationship [7,17], or a positive relationship [9,12] between breast cancer risk and high cholesterol levels. Recent studies have failed to provide a clearer picture. In a recent prospective study from South Korea, where cholesterol levels and breast cancer rates are on the rise, post-menopausal women with high serum cholesterol were shown to have a 31% greater risk of breast cancer than women with low serum cholesterol levels [18•]. This effect became insignificant when body mass index (BMI) was controlled for, indicating that the effect may be due to obesity and not necessarily high serum cholesterol levels. A possible limitation of this study is that only total cholesterol levels, but not individual triglyceride, HDL-C or LDL-C levels, were examined. Three other studies [19•,20,21] examined the relationship between breast cancer risk and the metabolic syndrome, which is characterized partly by dyslipidemia and specifically low plasma HDL-C levels. Two of these reports [20,21] did not find any association between breast cancer risk and HDL-C levels. In both cases, researchers were unsuccessful at finding an association between HDL-C levels and breast cancer risk. The third study found that in both pre-menopausal and post-menopausal women, there was a decreased risk of breast cancer with increased total plasma cholesterol levels [19•].

In a separate Korean case-control study, Kim *et al.* only investigated the effect of HDL-C on breast cancer risk and found that high levels of HDL-C were associated with reduced breast cancer risk, but only in premenopausal women with a low BMI [6•]. The authors also attempted to link low HDL-C levels with the hormonal receptor status of tumors from patients, that is, whether the tumors were estrogen receptor (ER) positive (+) or negative (−). They reported that low levels of HDL-C and high levels of triglycerides were associated with an increased risk of developing ER- tumors [6•]. An earlier prospective study conducted in the USA has corroborated this report [22•]. Upon examination of patients in the Atherosclerosis Risk in Communities Study (ARIC), who developed breast cancer, only pre-menopausal women with decreased levels of HDL-C were shown to be at increased risk of developing breast cancer. Interestingly, this result was independent of BMI.

There is evidence suggesting a positive relationship between total plasma cholesterol levels and breast cancer risk. In a recent prospective study, researchers determined the relationship between total cholesterol and all cancers. Although they were not able to draw a general conclusion about the role of total cholesterol in all cancers, they were able to identify a positive relationship between total cholesterol and breast and prostate cancer risk [23••]. Women with total cholesterol levels over 240 mg/dL had a greater risk of developing breast cancer than women with cholesterol levels below 160 mg/dL [23••].

Recent studies have examined the relationship between plasma cholesterol levels and breast cancer risk. However, like older studies, new studies have provided inconclusive results and have obtained limited data demonstrating a relationship between breast cancer risk and plasma cholesterol levels.

Dietary cholesterol and breast cancer

The study of dietary cholesterol and its role in cancer dates back nearly half a century. Since then, large prospective studies have not found a clear relationship between dietary cholesterol and breast cancer development. However, Hu *et al.* [24••] have recently conducted a study that examined cholesterol intake and cancer risk. They showed that increased cholesterol consumption leads to increased postmenopausal but not premenopausal breast cancer risk [24••]. In agreement with these findings, a study conducted in Uruguay, where breast cancer rates are on the rise, has shown that women who consume large quantities of cholesterol are at increased risk of developing breast cancer [25]. Although the amount of data to support the role of dietary cholesterol in breast cancer is limited, it does indicate that increased dietary cholesterol intake results in increased breast cancer risk.

Cholesterol and breast cancer: insight from laboratory studies

It is difficult to draw conclusions from epidemiological studies owing to the intrinsic limitations associated with this type of study. For this reason, it has become imperative to take into account data from more controlled laboratory environments.

Many groups have been able to show that lipoproteins are capable of stimulating growth of breast cancer cells *in vitro* [26,27,28•,29•]. The pro-proliferative effect of LDL appears to be dependent on the status of the ER in breast cancer cell lines since only ER- breast cancer cells lines display increased proliferation in the presence of LDL [29•]. In the same study [29•], the authors found that ER- basal-like cells store more cholesteryl esters than ER+ cells. Under specific conditions, accumulation of free cholesterol in macrophages treated with acetylated LDL and an inhibitor of the enzyme acyl-CoA:cholesterol acyltransferase 1 (ACAT1) has been associated with a cytotoxic effect of excess free cholesterol [30]. Interestingly, proliferation of both ER+ and ER- cells was sensitive to ACAT inhibition. In addition to enhancing proliferation, the same group showed in a separate study that LDL can also increase migration of ER- breast cancer cells. This effect could also be reduced by the addition of a pharmacologic inhibitor of ACAT1 [31•]. Similarly, Paillasse *et al.* [32•] have found that ACAT inhibition decreases cellular proliferation and invasion in two tumor cell lines. Furthermore, the availability of cholesteryl esters increased proliferation and invasiveness of normal cells indicating that cholesteryl esters may contribute to a

tumor-promoting phenotype [32•]. Another study showed that breast cancer cell lines treated with auraptene, a naturally occurring ACAT inhibitor, also displayed decreased cellular proliferation, invasion, and colony formation [33•]. Taken together, these results indicate that cholesteryl esters synthesis and/or accumulation may play a role in the development and progression of breast cancer.

The use of pharmacological inhibitors of intracellular cholesterol transport (e.g. U18666A or progesterone) and/or biosynthesis may also lead to the accumulation of cholesterol metabolites that may affect tumor formation. Importantly, these inhibitors are not always very specific as in the case of progesterone, which regulates intracellular cholesterol movement but is also a known modulator of the progesterone receptor [34] and an inhibitor of DHCR24/seladin-1 [35]. U18666A is a widely used chemical utilized to block the intracellular trafficking of cholesterol. However, U18666A also inhibits squalene-hopen cyclase [36] DHCR24 [37], EBP/D8D7I [38], or cholesterol epoxide hydrolase [39••]. Interestingly, the use of these inhibitors can also affect cellular proliferation [37,39••]. These studies suggest that cholesterol metabolites may potentially contribute to the development of tumors.

Many studies have also examined the effect of HDL on breast cancer cells. Interestingly, HDL increases cellular proliferation of human breast cancer cell lines *in vitro* [28•,40,41•]. HDL obtained from normolipidemic patients does not have an effect on migration, invasion, or metastasis; however, oxidized HDL and HDL derived from diabetic patients have the ability to promote migration, invasion, and metastasis [40,41•,42•]. These studies indicate a role for diabetes, a component of the metabolic syndrome, in the development and progression of breast cancer.

Another older study has suggested that the pro-proliferative effect of HDL may be mediated by the scavenger receptor class B, type I (SR-BI, sometimes referred to as CLA-1) [28•]. SR-BI is an HDL receptor that mediates cellular cholesterol influx and efflux. Cao *et al.* [43••] have shown that human breast tumors display an upregulation of SR-BI mRNA and protein levels [43••]. They also showed that transfecting human breast cancer cells with a dominant-negative mutant of SR-BI inhibits cellular proliferation, indicating a possible role of SR-BI in breast cancer. More recently, work from our laboratory has shown that, when fed a high fat/high cholesterol diet, a breast cancer mouse model develop larger, more aggressive tumors faster and develop more pulmonary metastasis than mice fed a normal chow diet. Interestingly, the tumors excised from mice fed the high fat/high cholesterol diet showed increased expression of SR-BI [44••]. These findings indicate a potential role for SR-BI in the etiology of breast cancer and corroborates the results obtained by Cao *et al.* [43••]. Another study has investigated the effect of a high fat/high cholesterol diet on tumor growth [45••]. In this study, apolipoprotein E-deficient ($Apoe^{-/-}$) mice were used. These mice develop large atherosclerotic lesions when challenged with a high fat/high cholesterol diet since ApoE is a major ligand for the low density lipoprotein receptor (LDL-R). Upon injection of two mouse mammary cancer cell lines, Met-1 and Mvt-1, $Apoe^{-/-}$ mice developed larger tumors and more pulmonary metastasis than the wild-type mice. Furthermore, when treated with cholesterol *in vitro*, these cells showed activation of the PI3K/Akt pathway. Accordingly, when treated with an inhibitor of PI3K, the $Apoe^{-/-}$ mice developed smaller tumors than vehicle-treated mice [45••].

Laboratory studies regarding breast cancer and cholesterol have provided a clearer picture for a role of cholesterol in breast cancer development and progression than did epidemiologic studies. Cholesterol, and more specifically, lipoproteins appear to have a pro-proliferative effect on breast cancer cells and elevated plasma cholesterol levels in mouse models of breast cancer lead to larger, more aggressive tumors.

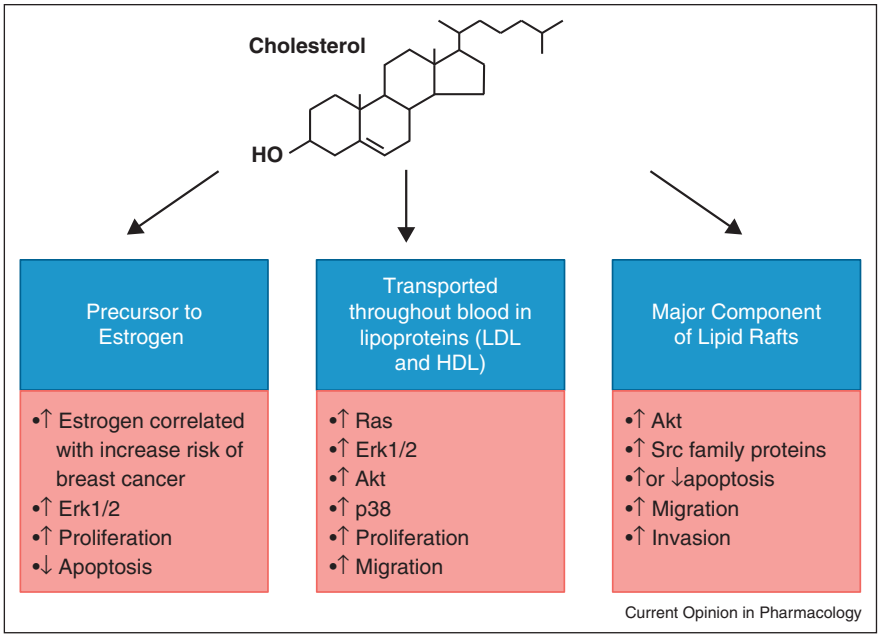
Cholesterol and prostate cancer

There is also recent evidence to support the hypothesis that cholesterol plays a role in another hormonally influenced cancer, prostate cancer. Accordingly, studies have shown that an increase in serum cholesterol levels owing to a high cholesterol diet causes an increase in prostate cancer cell xenograft tumors. These tumors display increased cholesterol content in plasma membrane lipid rafts and a significant increase in the activation of Akt, which is involved in many cellular pathways and frequently activated in a variety of cancers [46]. This group also showed that the growth of xenograft prostate tumors can be inhibited by ezetimibe, an inhibitor of intestinal cholesterol absorption [47•]. In agreement with these findings, we showed that in a mouse model of prostate cancer, the transgenic adenocarcinoma of the mouse prostate (TRAMP) model mice fed a high fat/high cholesterol diet develop larger tumors than TRAMP mice fed a chow diet [48•]. Subsequent studies have shown that HDL stimulates prostate cancer cell growth *in vitro* and can activate Erk1/2 and Akt signaling pathways [49•,50].

Conclusions

Breast cancer is a multifactorial disease, and epidemiological studies indicate that one contributing factor is the Western lifestyle, characterized partly by a diet rich in cholesterol. Increasing evidence demonstrates the role that cholesterol and its carriers, the lipoproteins, play in the development and progression of breast cancer. Laboratory studies indicate that cholesterol affects the growth and metastatic potential of breast cancer through

Figure 1



Potential mechanisms by which cholesterol plays a role in breast cancer. Cholesterol is a precursor to estrogen, which has a clearly established role in breast cancer [58]. Elevated estrogen levels are associated with increased breast cancer risk. Estrogen activates signaling pathways, which increases proliferation of a number of breast cancer cell lines and decreases apoptosis [58]. Lipoproteins such as HDL and LDL carry insoluble cholesterol throughout the circulatory system. HDL and LDL have been shown to activate cellular proliferation and migration [54] as well as signaling pathways including Ras, Erk1/2 [52,53], Akt [53], and p38 [51] associated with breast cancer development. Cholesterol is an integral part of lipid rafts, which act as a platform for signaling molecules such as Akt and Src family kinases [55,57]. Additionally, lipid rafts regulate apoptosis [55], migration and invasion [56].

several potential mechanisms that ultimately affect the proliferative and migratory potential of breast cancer cells (Figure 1). Many studies have elucidated the role played by both HDL and LDL lipoproteins in the regulation of intra-cellular signaling cascades in endothelial cells [51,52]. Interestingly, many of these pathways have been implicated in human cancer development. For example, studies in endothelial cells indicate that LDL can activate p38 mitogen activated protein kinase (MAPK) [51], while HDL has been shown to activate numerous signaling pathways including Ras [52], Erk1/2 [52], and Akt [53] and, as a consequence, promotes migration of endothelial cells [54]. Lipoproteins may similarly stimulate these signaling pathways in epithelial cells during breast cancer initiation and progression. Cholesterol is also required for the formation of lipid rafts (reviewed in [55–57]), which can serve in human cancer development as platforms for several signaling cascades, including Ras, Akt, and Src signaling [55], migration, and invasion [56]. Pharmacological disruption of lipid rafts has been shown to alter cellular growth and survival and is an emerging target in anti-cancer treatment [55]. Reducing plasma cholesterol levels may disrupt lipid raft formation and thereby inhibit cell signaling events involved in breast cancer development. Finally, cholesterol is a precursor of estrogen, and high levels of estrogen are associated with an increased risk of breast cancer (reviewed in reference [58]). Briefly, estrogen can stimulate several cellular signaling pathways by binding to the estrogen receptor and initiating pro-survival and pro-proliferative cellular signaling events. Although it is not known whether plasma cholesterol levels can affect estrogen levels directly, it is reasonable to hypothesize that plasma cholesterol levels may regulate estrogen levels.

The findings discussed herein suggest a role for cholesterol in breast cancer growth and development. Although the mechanisms responsible for this role have not yet been unequivocally established, it is clear that cholesterol itself and its carriers, the lipoproteins, are able to affect cellular proliferation, migration, and survival, key attributes of tumor biology. Given the abundance of cholesterol in the Western diet, the ability to effectively target this molecule or its metabolism and moderate its downstream effectors would be a tremendous advance in breast cancer prevention and treatment.

Acknowledgements

P.G. Frank was supported by a grant obtained from the Susan G. Komen Foundation.

References and recommended reading

Papers of particular interest, published within the period of review, have been highlighted as:

- • of special interest
- •• of outstanding interest

1. Siegel R, Naishadham D, Jemal A: **Cancer statistics, 2012**. *CA Cancer J Clin* 2012, **62**:10-29.

2. Jemal A, Bray F, Center MM, Ferlay J, Ward E, Forman D: **Global cancer statistics**. *CA Cancer J Clin* 2011, **61**:69-90.

3. McPherson K, Steel CM, Dixon JM: **ABC of breast diseases. Breast cancer-epidemiology, risk factors, and genetics**. *BMJ* 2000, **321**:624-628.

4. Lof M, Weiderpass E: **Impact of diet on breast cancer risk**. *Curr Opin Obstet Gynecol* 2009, **21**:80-85.

5. McMillan DC, Sattar N, McArdle CS: **ABC of obesity. Obesity and cancer**. *BMJ* 2006, **333**:1109-1111.

6. • Kim Y, Park SK, Han W, Kim DH, Hong YC, Ha EH, Ahn SH, Noh DY, Kang D, Yoo KY: **Serum high-density lipoprotein cholesterol and breast cancer risk by menopausal status, body mass index, and hormonal receptor in Korea**. *Cancer Epidemiol Biomarkers Prev* 2009, **18**:508-515.

This large prospective study is the first of its kind to examine the relationship between HDL-C levels, breast cancer, and hormonal receptor status of the tumor.

7. Furberg AS, Veierod MB, Wilsgaard T, Bernstein L, Thune I: **Serum high-density lipoprotein cholesterol, metabolic profile, and breast cancer risk**. *J Natl Cancer Inst* 2004, **96**:1152-1160.

8. Potischman N, McCulloch CE, Byers T, Houghton L, Nemoto T, Graham S, Campbell TC: **Associations between breast cancer, plasma triglycerides, and cholesterol**. *Nutr Cancer* 1991, **15**:205-215.

9. Ray G, Husain SA: **Role of lipids, lipoproteins and vitamins in women with breast cancer**. *Clin Biochem* 2001, **34**:71-76.

10. Kritchevsky SB, Kritchevsky D: **Serum cholesterol and cancer risk: an epidemiologic perspective**. *Annu Rev Nutr* 1992, **12**:391-416.

11. Boyd NF, McGuire V: **Evidence of association between plasma high-density lipoprotein cholesterol and risk factors for breast cancer**. *J Natl Cancer Inst* 1990, **82**:460-468.

12. Ferraroni M, Gerber M, Decarli A, Richardson S, Marubini E, Crastes de Paulet P, Crastes de Paulet A, Pujol H: **HDL-cholesterol and breast cancer: a joint study in northern Italy and southern France**. *Int J Epidemiol* 1993, **22**:772-780.

13. Martin SS, Blumenthal RS, Miller M: **LDL cholesterol: the lower the better**. *Med Clin North Am* 2012, **96**:13-26.

14. Gaard M, Tretli S, Urdal P: **Risk of breast cancer in relation to blood lipids: a prospective study of 31,209 Norwegian women**. *Cancer Causes Control* 1994, **5**:501-509.

15. Mady EA: **Association between estradiol, estrogen receptors, total lipids, triglycerides, and cholesterol in patients with benign and malignant breast tumors**. *J Steroid Biochem Mol Biol* 2000, **75**:323-328.

16. Moorman PG, Hulka BS, Hiatt RA, Krieger N, Newman B, Vogelman JH, Orentreich N: **Association between high-density lipoprotein cholesterol and breast cancer varies by menopausal status**. *Cancer Epidemiol Biomarkers Prev* 1998, **7**:483-488.

17. Vatten LJ, Foss OP: **Total serum cholesterol and triglycerides and risk of breast cancer: a prospective study of 24,329 Norwegian women**. *Cancer Res* 1990, **50**:2341-2346.

18. • Ha M, Sung J, Song YM: **Serum total cholesterol and the risk of breast cancer in postmenopausal Korean women**. *Cancer Causes Control* 2009, **20**:1055-1060.

This prospective study has examined the relationship between plasma cholesterol levels and breast cancer risk and found that women with increased plasma cholesterol levels have increased risk of developing breast cancer.

19. • Bjorge T, Lukanova A, Jonsson H, Tretli S, Ulmer H, Manjer J, Stocks T, Selmer R, Nagel G, Almquist M *et al.*: **Metabolic syndrome and breast cancer in the me-can (metabolic syndrome and cancer) project**. *Cancer Epidemiol Biomarkers Prev* 2010, **19**:1737-1745.

20. Kabat GC, Kim M, Chlebowski RT, Khandekar J, Ko MG, McTiernan A, Neuhouser ML, Parker DR, Shikany JM, Stefanick ML *et al.*: **A longitudinal study of the metabolic syndrome and risk of postmenopausal breast cancer**. *Cancer Epidemiol Biomarkers Prev* 2009, **18**:2046-2053.

21. Rosato V, Bosetti C, Talamini R, Levi F, Montella M, Giacosa A, Negri E, La Vecchia C: **Metabolic syndrome and the risk of breast cancer in postmenopausal women**. *Ann Oncol* 2011, **22**:2687-2692.

22. • Kucharska-Newton AM, Rosamond WD, Mink PJ, Alberg AJ, Shahar E, Folsom AR: **HDL-cholesterol and incidence of breast cancer in the ARIC cohort study**. *Ann Epidemiol* 2008, **18**:671-677.

23. •• Kitahara CM, Berrington de Gonzalez A, Freedman ND, Huxley R, Mok Y, Jee SH, Samet JM: **Total cholesterol and cancer risk in a large prospective study in Korea**. *J Clin Oncol* 2011, **29**:1592-1598.

In this study, researchers have examined the relationship between plasma cholesterol levels and all cancer types. They demonstrate a reduced breast cancer risk in women associated with low plasma cholesterol levels.

24. •• Hu J, La Vecchia C, de Groh M, Negri E, Morrison H, Mery L: **Dietary cholesterol intake and cancer**. *Ann Oncol* 2011, **23**:491-500.

This prospective study has examined the relationship between dietary cholesterol and all types of cancers and found an increase in breast cancer risk among women who consume elevated levels of dietary cholesterol.

25. Ronco AL, De Stefani E, Stoll M: **Hormonal and metabolic modulation through nutrition: towards a primary prevention of breast cancer**. *Breast* 2010, **19**:322-332.

26. Rotheneder M, Kostner GM: **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* 1989, **43**:875-879.

27. Gospodarowicz D, Lui GM, Gonzalez R: **High-density lipoproteins and the proliferation of human tumor cells maintained on extracellular matrix-coated dishes and exposed to defined medium**. *Cancer Res* 1982, **42**:3704-3713.

28. • Pussinen PJ, Karten B, Wintersperger A, Reicher H, McLean M, Malle E, Sattler W: **The human breast carcinoma cell line HBL-100 acquires exogenous cholesterol from high-density lipoprotein via CLA-1 (CD-36 and LIMPII analogous 1)-mediated selective cholesteryl ester uptake**. *Biochem J* 2000, **349**:559-566.

This is the first study to establish a role for the HDL-C receptor, SR-BI, in breast cancer. Researchers found that breast cancer cells proliferate more in the presence of HDL and that this is mediated by SR-BI.

29. • Antalis CJ, Arnold T, Rasool T, Lee B, Buhman KK, Siddiqui RA: **High ACAT1 expression in estrogen receptor negative basal-like breast cancer cells is associated with LDL-induced proliferation**. *Breast Cancer Res Treat* 2010, **122**:661-670.

This study shows that only ER- breast cancer cell lines respond to the pro-proliferative effects of LDL-C, and that this effect can be mitigated by inhibition of ACAT1.

30. Warner GJ, Stoudt G, Bamberger M, Johnson WJ, Rothblat GH: **Cell toxicity induced by inhibition of acyl coenzyme A:cholesterol acyltransferase and accumulation of unesterified cholesterol**. *J Biol Chem* 1995, **270**:5772-5778.

31. • Antalis CJ, Uchida A, Buhman KK, Siddiqui RA: **Migration of MDA-MB-231 breast cancer cells depends on the availability of exogenous lipids and cholesterol esterification**. *Clin Exp Metastasis* 2010, **28**:733-741.

32. • Paillasse MR, de Medina P, Amouroux G, Mhamdi L, Poirot M, Silvente-Poirot S: **Signaling through cholesterol esterification: a new pathway for the cholecystokinin 2 receptor involved in cell growth and invasion**. *J Lipid Res* 2009, **50**:2203-2211.

33. • de Medina P, Genovese S, Paillasse MR, Mazaheri M, Caze-Subra S, Bystricky K, Curini M, Silvente-Poirot S, Epifano F, Poirot M: **Auraptene is an inhibitor of cholesterol esterification and a modulator of estrogen receptors**. *Mol Pharmacol* 2010, **78**:827-836.

34. Edwards DP: **Regulation of signal transduction pathways by estrogen and progesterone**. *Annu Rev Physiol* 2005, **67**:335-376.

35. Lindenthal B, Holleran AL, Aldaghlas TA, Ruan B, Schroepfer GJ Jr, Wilson WK, Kelleher JK: **Progestins block cholesterol synthesis to produce meiosis-activating sterols**. *FASEB J* 2001, **15**:775-784.

36. Sexton RC, Panini SR, Azran F, Rudney H: **Effects of 3 beta-[2-(diethylamino)ethoxy]androst-5-en-17-one on the synthesis of cholesterol and ubiquinone in rat intestinal epithelial cell cultures**. *Biochemistry* 1983, **22**:5687-5692.

37. Battista MC, Guimond MO, Roberge C, Doueik AA, Fazli L, Gleave M, Sabbagh R, Gallo-Payet N: **Inhibition of DHCR24/seladin-1 impairs cellular homeostasis in prostate cancer**. *Prostate* 2010, **70**:921-933.

38. Moebius FF, Reiter RJ, Bermoser K, Glossmann H, Cho SY, Paik YK: **Pharmacological analysis of sterol delta8-delta7 isomerase proteins with [3H]ifenprodil**. *Mol Pharmacol* 1998, **54**:591-598.

39. •• de Medina P, Paillasse MR, Segala G, Poirot M, Silvente-Poirot S: **Identification and pharmacological characterization of cholesterol-5,6-epoxide hydrolase as a target for tamoxifen and AEBS ligands**. *Proc Natl Acad Sci USA* 2010, **107**:13520-13525.

In this paper, the authors link cholesterol metabolism with selective ER modulators activity.

40. Pan B, Ren H, Lv X, Zhao Y, Yu B, He Y, Ma Y, Niu C, Kong J, Yu F *et al.*: **Hypochlorite-induced oxidative stress elevates the capability of HDL in promoting breast cancer metastasis**. *J Transl Med* 2012, **10**:65.

41. • Pan B, Ren H, Ma Y, Liu D, Yu B, Ji L, Pan L, Li J, Yang L, Lv X *et al.*: **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* 2011, **131**:70-82.

42. • Pan B, Ren H, He Y, Lv X, Ma Y, Li J, Huang L, Yu B, Kong J, Niu C *et al.*: **HDL of patients with type 2 diabetes mellitus elevates the capability of promoting breast cancer metastasis**. *Clin Cancer Res* 2012, **18**:1246-1256.

43. •• Cao WM, Murao K, Imachi H, Yu X, Abe H, Yamauchi A, Niimi M, Miyauchi A, Wong NC, Ishida T: **A mutant high-density lipoprotein receptor inhibits proliferation of human breast cancer cells**. *Cancer Res* 2004, **64**:1515-1521.

This study shows that the HDL receptor, SR-BI, is expressed at increased levels in human breast cancer tissue compared to normal breast tissue, and that breast cancer cell proliferation is inhibited by the inhibition of SR-BI.

44. •• Llaverias G, Danilo C, Mercier I, Daumer K, Capozza F, Williams TM, Sotgia F, Lisanti MP, Frank PG: **Role of cholesterol in the development and progression of breast cancer**. *Am J Pathol* 2011, **178**:402-412.

The authors of this study show that a mouse model of breast cancer treated with a high fat-high cholesterol diet develop larger, more advanced tumors than control mice.

45. •• Alikhani N, Ferguson RD, Novosyadlyy R, Gallagher EJ, Scheinman EJ, Yakar S, Leroith D: **Mammary tumor growth and pulmonary metastasis are enhanced in a hyperlipidemic mouse model**. *Oncogene* 2012, in press, http://dx.doi.org/10.1038/onc.2012.113.

Using a genetically altered hyperlipidemic mouse model, the authors show that these mice develop larger tumors and have increased metastasis than normolipidemic mice.

46. Zhuang L, Kim J, Adam RM, Solomon KR, Freeman MR: **Cholesterol targeting alters lipid raft composition and cell survival in prostate cancer cells and xenografts**. *J Clin Invest* 2005, **115**:959-968.

47. • Solomon KR, Pelton K, Boucher K, Joo J, Tully C, Zurakowski D, Schaffner CP, Kim J, Freeman MR: **Ezetimibe is an inhibitor of tumor angiogenesis**. *Am J Pathol* 2009, **174**:1017-1026.

48. • Llaverias G, Danilo C, Wang Y, Witkiewicz AK, Daumer K, Lisanti MP, Frank PG: **A Western-type diet accelerates tumor progression in an autochthonous mouse model of prostate cancer**. *Am J Pathol* 2010, **177**:3180-3191.

49. • Sekine Y, Demosky SJ, Stonik JA, Furuya Y, Koike H, Suzuki K, Remaley AT: **High-density lipoprotein induces proliferation and migration of human prostate androgen-independent cancer cells by an ABCA1-dependent mechanism**. *Mol Cancer Res* 2010, **8**:1284-1294.

50. Sekine Y, Suzuki K, Remaley AT: **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* 2011, **71**:690-699.

51. Bulat N, Waeber G, Widmann C: **LDLs stimulate p38 MAPKs and wound healing through SR-BI independently of Ras and PI3 kinase**. *J Lipid Res* 2009, **50**:81-89.

52. Grewal T, de Diego I, Kirchhoff MF, Tebar F, Heeren J, Rinninger F, Enrich C: **High density lipoprotein-induced signaling of the MAPK pathway involves scavenger receptor type BI-mediated activation of Ras**. *J Biol Chem* 2003, **278**:16478-16481.

53. Mineo C, Yuhanna IS, Quon MJ, Shaul PW: **High density lipoprotein-induced endothelial nitric-oxide synthase activation is mediated by Akt and MAP kinases**. *J Biol Chem* 2003, **278**:9142-9149.

54. Seetharam D, Mineo C, Gormley AK, Gibson LL, Vongpatanasin W, Chambliss KL, Hahner LD, Cummings ML, Kitchens RL, Marcel YL *et al.*: **High-density lipoprotein promotes endothelial cell migration and reendothelialization via scavenger receptor-B type I**. *Circ Res* 2006, **98**:63-72.

55. George KS, Wu S: **Lipid raft: a floating island of death or survival**. *Toxicol Appl Pharmacol* 2012, **259**:311-319.

56. Murai T: **The role of lipid rafts in cancer cell adhesion and migration**. *Int J Cell Biol* 2011, **2012**:763283.

57. Simons K, Toomre D: **Lipid rafts and signal transduction**. *Nat Rev Mol Cell Biol* 2000, **1**:31-39.

58. Yager JD, Davidson NE: **Estrogen carcinogenesis in breast cancer**. *N Engl J Med* 2006, **354**:270-282.