Curr Obes Rep (2017) 6:195–203
DOI 10.1007/s13679-017-0263-x

OBESITY TREATMENT (CM APOVIAN, SECTION EDITOR)

Insights into the Link Between Obesity and Cancer

Sarah E. Ackerman[1] · **Olivia A. Blackburn**[1,2] · **François Marchildon**[1] · **Paul Cohen**[1,3]

Published online: 22 April 2017

Abstract
Purpose of Review Adipocytes have adapted to store energy in the form of lipid and also secrete circulating factors called adipokines that signal to other tissues to coordinate energy homeostasis. These functions are disrupted in the setting of obesity, promoting the development of diseases such as diabetes, cardiovascular disease, and cancer.
Recent Findings Obesity is linked to an increased risk of many types of cancer and increased cancer-related mortality. The basis for the striking association between obesity and cancer is not well understood.
Summary Here, we review the cellular and molecular pathways that appear to be involved in obesity-driven cancer. We also describe possible therapeutic considerations and highlight important unanswered questions in the field.

This article is part of the Topical Collection on *Obesity Treatment*

Sarah E. Ackerman, Olivia A. Blackburn, and François Marchildon contributed equally to this work.

✉ Paul Cohen
pcohen@rockefeller.edu

Sarah E. Ackerman
sackerman@rockefeller.edu

Olivia A. Blackburn
oblackburn@rockefeller.edu

François Marchildon
fmarchildo@rockefeller.edu

[1] Laboratory of Molecular Metabolism, The Rockefeller University, New York, NY, USA

[2] Weill Cornell/Rockefeller/Sloan Kettering Tri-Institutional MD-PhD Program, New York, NY, USA

[3] The Rockefeller University, 1230 York Avenue, Box 223, New York, NY 10065, USA

Keywords Obesity · Cancer · Adipocyte · Tumor microenvironment · Leptin · Adiponectin · Adipokine · Metastasis

Introduction

Obesity currently affects one third of adults in the USA [1]. Obesity develops when energy intake chronically exceeds energy expenditure and is defined by a body mass index (BMI) greater than or equal to 30. In the USA, hospitalization and health care costs attributable to obesity are estimated to be $147B/year [2]. Overweight and obese individuals are at increased risk of developing type 2 diabetes, hypertension, cardiovascular disease, and non-alcoholic fatty liver disease [3]. Prospective studies and meta-analyses have also clearly demonstrated that obesity is a risk factor for many types of cancers and is associated with worsened prognosis [4, 5]. This review briefly presents the epidemiological evidence linking obesity to cancer and then focuses on the established and proposed mechanisms underpinning the association between obesity and cancer (Fig. 1).

Epidemiological Evidence

The association between obesity and cancer risk and mortality was firmly established with a seminal study published in 2003 by Calle et al. [4]. This prospective study showed that cancer patients with a BMI above 40 had mortality rates that were 52% higher for men and 62% higher for women. Since then, many other epidemiological reports have shown a correlation between obesity and cancer [6, 7••]. The American Society of Clinical Oncology recently noted that obesity is overtaking tobacco use as the most significant preventable lifestyle risk

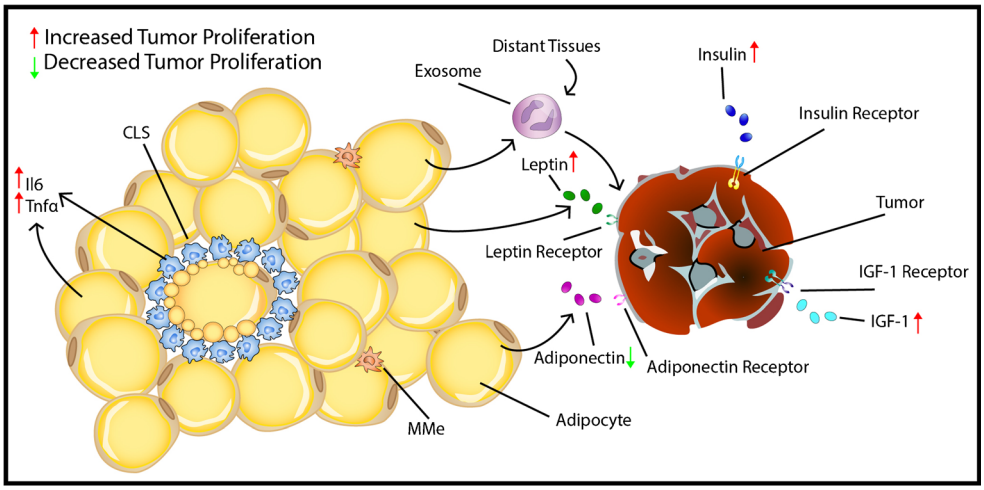

Fig. 1 Schematic of biological pathways involved in linking obesity and cancer

factor for cancer mortality [8]. The risk and mortality from cancers of the thyroid, esophagus, liver, gallbladder, colon, and kidney as well as non-Hodgkin's lymphoma and multiple myeloma are particularly associated with obesity in both sexes [4, 5]. This trend is also strong for endometrial and postmenopausal breast cancer in women and for prostate cancer in men. The mechanisms behind the connection between obesity and cancer have not yet been fully elucidated.

The Obesity Syndrome

Obesity is defined by an excess of adipose tissue, which consists of adipocytes or fat cells, as well as immune cells, stromal cells, blood vessels, and neurons. Three distinct types of adipocytes have been described in mammals: white, brown, and beige. White adipose tissue (WAT) functions mainly to store nutrients as lipid [9]. In contrast, brown adipose tissue (BAT) has high levels of uncoupling protein 1 (UCP1), which uncouples oxidative phosphorylation from ATP synthesis, thereby dissipating energy as heat [10]. Beige adipose comes from a distinct lineage to BAT, but can be activated to acquire a more brown-like phenotype [11].

In the setting of obesity, WAT undergoes hypertrophy and hyperplasia which results in physiologic changes. These include elevated levels of free fatty acids (FFA) and triglycerides, increased blood glucose, and insulin resistance which results in increased insulin production by the pancreas. Insulin resistance can also lead to glucose intolerance and hyperglycemia, providing an environment that can promote cancer cell proliferation [12].

All adipose depots are involved in energy metabolism and secrete factors called adipokines that can have whole body endocrine effects. In the setting of obesity, these endocrine functions become dysregulated. Leptin and adiponectin are among the best characterized adipokines. Leptin expression correlates positively with obesity, whereas adiponectin expression negatively correlates with adiposity. Obese WAT also produces inflammatory cytokines such as tumor necrosis factor alpha (TNFα), interleukin 6 (IL-6), interleukin 1 beta (IL-1β), and transforming growth factor beta (TGFβ) [13]. The release of these cytokines attracts and activates monocytes and macrophages which secrete inflammatory cytokines and contribute to the development of insulin resistance. Over time, the localized inflammation in the adipose tissue can have systemic effects. Although all adipose depots can secrete pro-inflammatory factors, obese visceral adipose is most strongly associated with metabolic dysfunction and poor cancer outcomes, suggesting distinct biological effects regulated by this fat depot. This review explores how local and systemic dysregulation of adipose tissue caused by obesity is linked to cancer.

Insulin and Insulin-Like Growth Factor Signaling

In the setting of obesity, systemic levels of insulin and insulin-like growth factor 1 (IGF-1) are increased. These hormones act both locally by stimulating receptors present on tumor cells and globally by altering overall metabolism. Hyperinsulinemia has been identified as an independent risk factor for breast cancer development, and insulin-sensitizing therapies can reduce metastatic burden in mice [14, 15]. Several cancer cell types express the insulin receptor, which activates the phosphatidylinositol-4,5-bisphosphate 3-kinase (PI3K) pathway, leading to proliferation and tumor progression [16]. In addition to promoting proliferation, hyperinsulinemia via signaling in hepatocytes leads to increased production of insulin-like growth factor 1 (IGF-1) and repressed secretion of IGF-1 binding proteins, leading to an increase in bioavailable IGF-1.

Stimulating the IGF-1 receptor on cancer cells activates the mitogen-activated protein kinase (MAPK) pathway, promoting many types of cancer, specifically skin and pancreatic

cancer initiation and progression in vitro [17, 18]. When mice susceptible to colorectal cancer are treated with an IGF-1 receptor inhibitor that disrupts downstream signaling, tumor burden is significantly reduced [19••]. Colorectal cancer growth is reduced upon orthotopic implantation into IGF-1 deficient mice [20]. This suggests an important role for insulin and IGF-1 in the progression of obesity-driven cancers.

Adipokines and Cytokines

Adipokines produced by adipose tissue and cytokines produced by immune cells control a wide range of processes including inflammation, feeding behavior, and cellular signaling. Dysregulation of these circulating factors in the setting of obesity can affect distant organs, like the liver and pancreas, as well as the local microenvironment [21•]. This section will discuss the roles of key adipokines and cytokines, which are altered in obesity and have been linked to cancer.

Leptin

Leptin is a hormone that coordinates energy homeostasis by signaling from adipose to the hypothalamus [22]. In the setting of obesity, serum leptin levels positively correlate with fat mass. Patients with breast cancer that overexpresses the leptin receptor have an unfavorable prognosis independent of other risk factors [23]. When peripheral leptin signaling is disrupted in a mouse model of spontaneous breast cancer, there is dramatically reduced tumor burden compared to mice with intact leptin signaling [24].

Mechanistically, leptin can signal directly to cancer cells through the OB-R leptin receptor and downstream activation of the PI3K and MAPK pathways. Additionally, leptin promotes angiogenesis through vascular endothelial growth factor (VEGF) signaling and hypoxia inducible factor 1 alpha (HIF-1α) stabilization [21•]. Furthermore, leptin overexpression promotes invasion of human pancreatic cancer cell lines in vitro through the production of matrix metalloproteinase 13 (MMP-13) [21•]. In vivo, pancreatic cancer cell lines that overexpress the leptin receptor have accelerated growth and metastasis. Furthermore, leptin receptor expression in tumors is significantly higher in patients with lymph node metastases and is positively correlated with MMP-13 expression [21•]. This suggests that in addition to systemic effects, leptin can signal directly to some tumors to promote growth.

Adiponectin

Adiponectin is secreted by adipocytes and can act on other tissues to increase insulin sensitivity [25]. It also has anti-inflammatory properties [26]. In contrast to leptin, adiponectin has been shown to attenuate tumor progression. Serum adiponectin levels are reduced in the obese state and are inversely correlated with the progression of several cancers, including breast cancer, pancreatic cancer, and colorectal cancer [27–29]. Furthermore, adiponectin directly signals to cancer cells which express the adiponectin receptor, reducing cellular proliferation and inducing apoptosis [30]. Adiponectin signals through several pathways, including the AMP-activated protein kinase (AMPK), mammalian target of rapamycin (mTOR), and nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) pathways [31, 32].

Other Candidate Adipokines

Nicotinamide phosphoribosyltransferase (NAMPT) is a ubiquitous enzyme that catalyzes the rate-limiting step in NAD synthesis. NAMPT can also be secreted and has been referred to in this context as visfatin. Serum visfatin levels are positively correlated with visceral adiposity [33]. Elevated circulating levels of visfatin have been implicated in the progression of gastric cancer, colorectal carcinoma, and several other cancer types [34–36]. Breast cancer patients with higher visfatin levels have poorer disease free and overall survival. In vitro, visfatin promotes breast cancer cell viability through the activation of abelson murine leukemia viral oncogene homolog 1 (C-ABL) and signal transducer and activator of transcription 3 (STAT3). High visfatin levels are associated with tumor stage and lymph node metastasis [37]. Furthermore, serum levels of visfatin are positively associated with inflammation, lymph node metastasis, and anemia in colorectal cancer patients [38]. It remains unclear whether visfatin has a role in cancer risk or a causal role in obesity-driven cancer progression. Moreover, the exact mechanism of action of visfatin in tumorigenesis is still vague [39].

Omentin-1 is an anti-inflammatory adipokine produced by visceral adipose [40, 41]. Omentin-1 enhances insulin stimulated glucose uptake in vitro, and serum levels of omentin-1 are reduced in patients with type 2 diabetes mellitus (T2DM) [40]. Furthermore, omentin-1 levels are lower in the setting of obesity and other insulin-resistant states [42]. Serum omentin-1 levels are dramatically reduced in patients with renal cell carcinoma [43]. The mechanism by which omentin-1 can affect cancer progression is not well established. However, treatment with omentin-1 can induce apoptosis of hepatocellular carcinoma (HCC) cells in vitro and enhance the stability of the tumor suppressor, p53 [44, 45].

Inflammatory Cytokines

TNFα and IL-6 are associated with insulin resistance as well as changes in the inflammatory tumor microenvironment [46]. While TNFα and IL-6 are expressed in adipose tissue, these

cytokines are mainly secreted from adipose resident immune cells [47]. TNFα activates NF-κb, which is important in the development of many cancers. Specifically, different subunits of NF-κb are necessary for the development of colitis and colonic epithelial cell turnover in colitis-associated carcinogenesis [48]. Recently, TNFα has been shown to activate inhibitor of nuclear factor kappa-B kinase subunit beta (IKK-B), which stabilizes X-box binding protein 1 (XBP1) to improve glucose homeostasis in lean mice. In obese mice, however, the normal activation of IKKB does not occur, disrupting downstream signaling, and leading to insulin resistance [49•].

IL-6 is a pro-inflammatory cytokine which activates STAT3, an oncogene involved in cancer progression [50]. STAT3 is activated by TNFα and IL-6 in HCC and colitis-associated cancer (CAC) [51, 52]. Interestingly, in the context of thyroid cancer, STAT3 is a negative regulator of tumor growth [53]. IL-6 also regulates the inflammatory tumor microenvironment in pancreatic cancer. IL-6 has been shown to have paracrine effects on early HCC and autocrine effects on the malignant progression of both HCC progenitor cells and breast cancer [54, 55]. Obesity is associated with the production of pro-inflammatory cytokines, but their specific role in obesity driven cancer progression has not been fully clarified.

Inflammation and Immune Cells

Inflammation and expansion of the adipose tissue in the setting of obesity mimics chronic tissue injury, with an influx of immune cells, such as macrophages, T cells, and NK cells [56–58], production of pro-inflammatory mediators, tissue remodeling, and angiogenesis [56]. Some tumors such as breast, prostate, and gynecologic cancers develop within adipose tissue. Thus, the microenvironment of these types of cancer contains immune cells and adipocytes. Obese mice also have increased fibrosis and inflammation of the mammary adipose, which promotes breast tumorigenesis [59].

As adipose tissue expands in obesity, it becomes hypoxic, leading to adipose cell death. These dying adipocytes are surrounded by rings of macrophages, which are known as crown-like structures (CLS). Elevated numbers of CLS in mammary adipose tissue are associated with a worse prognosis in patients with early breast cancer [60]. Interestingly, mice which were formerly obese (FOb) have fewer CLS than obese mice, though still more than lean controls [61•]. Despite this decrease in CLS, there was no decrease in mammary tumor burden between obese and FOb animals. Additionally, FOb mice had elevated levels of IL-6, TNFα, matrix metalloprotease 9 (MMP-9), and IL-1β, similar to obese mice and both significantly higher than lean mice. This suggests that CLS density is related to more rapid cancer progression, but may not be the only factor. In early stage squamous cell carcinoma of the tongue, a retrospective study indicates that increased CLS density in the local white adipose is associated with worse disease-specific survival and overall survival in patients [62]. CLS can be used as a prognostic factor, but the mechanism by which these macrophages may increase tumor initiation and progression remains unclear.

It had long been believed that obesity drives activation of adipose tissue macrophages (ATMs) [63]. ATMs activated by obesity secrete IL-1β, an inflammatory cytokine that has been shown to promote breast cancer progression [64••]. In this study, the authors hypothesize that the obese tumor microenvironment recruits macrophages which have an activated NLRC4 inflammasome. This leads to increased IL-1β, which drives breast cancer progression through vascular endothelial growth factor A (VEGFA) expression and angiogenesis. It has also been shown that a class IIa histone deacetylase (HDAC) inhibitor, TMP195, can stimulate macrophages to have an anti-tumor phenotype. This inhibitor reduces tumor burden and pulmonary metastases in a macrophage-dependent mouse model of breast cancer [65].

Recently, a subset of ATMs has been described that are phenotypically distinct from classically activated M1 or anti-inflammatory M2 macrophages. These macrophages are known as metabolically activated macrophages (MMe) and express specific markers such as Perilipin 2 (PLIN2) and ATP Binding Cassette Subfamily A Member 1 (ABCA1) [66]. Furthermore, ATMs respond to obesity by activating the lysosomal metabolism of lipids [67]. This does not occur with traditional M1 activation. The increased metabolism of lipids affects adipose tissue secretion of nonesterified fatty acids. From this data, it is clear that metabolic ATM activation is distinct from classical M1 activation. This new subset of macrophages has not yet been studied in the context of cancer, but may play a key role in the tumor microenvironment.

Exosomes

Most cell types secrete exosomes, which are nanovesicles that contain proteins and/or nucleic acids [68]. Adipose tissue secretes exosomes that can interact with cancer cells. Lazar et al. showed that adipose exosomes contain proteins related to fatty acid oxidation (FAO), which travel to nearby melanoma cells and reprogram FAO metabolism of the cancer cell [69•]. Furthermore, exosomes reprogramming FAO are increased in obesity and potentiate tumor cell migration. There is also evidence that microRNAs (miRNAs) are present in exosomes and can regulate gene expression in distant tissues [70••]. This suggests that exosomes from adipose tissue may be able to alter gene expression in distant tumor cells.

The Role of Obesity in Metastasis

Metastasis accounts for over 90% of cancer deaths [71]. Obese patients have an increased risk of metastasis as well as decreased disease-free and overall survival. Successful establishment of macroscopic metastases involves: invasion into surrounding tissues, intravasation into the circulatory system, extravasation into the metastatic site, and establishment and expansion of micrometastasic foci [72••]. Pre-clinical studies have clearly demonstrated that obesity enhances metastasis in models of melanoma and lung cancer, but the mechanism is unclear [73].

The earliest step in metastasis involves epithelial-to-mesenchymal transition (EMT). This process is characterized by increased migration and invasion, reduced apoptosis, and augmented expression of extracellular matrix proteins in tumor cells [74]. A prospective study of estrogen-receptor (ER)+ breast cancer patients showed that obesity promotes metastasis and an upregulation of EMT genes [75]. Moreover, co-culturing obese adipocyte stem cells with breast cancer cells increases expression of EMT genes in the cancer cells [76]. Heterotypic signals from the tumor microenvironment presumably stimulate the acquisition of EMT traits in cancer cells. For instance, the secretion of inflammatory cytokines IL-6 and TGFβ from both adipocytes and adipose stromal cells promotes EMT of breast cancer cells [77, 78]. Additionally, leptin has been shown to induce the expression of EMT-related genes in breast cancer models [79]. The findings outlined above clearly illustrate that obesity can promote EMT traits, although the pathways underpinning this effect are unclear.

Intravasation of cancer cells into the circulatory system and establishment of microscopic foci in distant tissues are other essential steps in metastasis which may be affected by obesity. In ovarian cancer as well as a number of other abdominal and pelvic malignancies, the omental visceral fat depot is a favored site of metastatic dissemination [80•]. Interestingly, ovarian cancer cells generally seed the omental adipose tissue but only marginally disseminate into other adipose depots. This suggests that metastasis of cancer cells to adipose tissue may depend on the nature of the fat depot. Fat droplets from the omental adipose provide metabolic energy to ovarian cancer cells, driving tumor growth and invasion to the omental depot. The acquisition of these traits is lost upon deletion of fatty acid binding protein 4 (Fabp4), suggesting that Fabp4 is required for invasion [80•]. In vitro breast, gastric, and colon cancer cells show invasion toward primary omental adipocytes compared to serum-free control media, suggesting a similar mechanism among different cancer types. Another pathway linking obesity and metastasis is hyperinsulinemia. In a mouse model of breast cancer, the number of lung metastases was increased in the setting of hyperinsulinemia, which is dependent on vimentin expression [81••]. The pro-inflammatory environment in obesity may also potentiate extravasation and dissemination of breast cancer cells into metastatic niches. In pulmonary metastasis, inflammatory monocytes are recruited and activated by the chemokine (C-C motif) ligand 2 (CCL2) pathway [82]. Blocking this pathway abrogates extravasation and dissemination of breast cancer cells in the lungs. These studies were performed in lean mice, but given that recruitment of monocytes by CCL2 and metastatic dissemination are both promoted in obesity, it is conceivable that this pathway might be relevant in the setting of obesity. Together, few studies have investigated the mechanism of cancer cell intravasation, extravasation, and seeding of distant tissues in the setting of obesity and it remains unclear which pathways are key in metastasis in obesity.

Repurposing Diabetes and Cholesterol-Lowering Drugs for Cancer Treatment in Obesity

As the correlation between obesity and increased cancer mortality has become clear, there is an increased interest in repurposing diabetes and cholesterol lowering drugs, commonly used by patients with obesity and metabolic syndrome, for cancer therapy.

Metformin

Type 2 diabetes mellitus (T2DM) is a common co-morbidity associated with obesity and is an independent predictor of risk, relapse, and mortality for many types of cancers [83]. Metformin improves glycemic control and insulin resistance and is a safe and effective drug for the management of T2DM [84]. Its mechanism of action involves a decrease in hepatic gluconeogenesis involving the AMPK, PI3K/Akt, and mTOR pathways [85]. In vitro evidence suggests that metformin directly inhibits cancer cell growth and induces apoptosis [86]. Furthermore, metformin decreases cancer recurrence by directly inducing cancer stem cell death [87]. Meta-analyses indicate that metformin is associated with decreased cancer risk and mortality [88, 89]. Thus, metformin may decrease cancer progression indirectly through improvement of insulin sensitivity in the host as well as by directly acting on cancer cells.

Thiazolidinediones

Thiazolidinediones (TZDs) are a family of pharmacological agents functioning as peroxisome proliferator-activated receptor gamma (PPARγ) agonists and have been prescribed to treat T2DM in the past. Retrospective investigations suggest that TZD treatment is associated with a meaningful decrease in lung cancer risk among patients diagnosed with diabetes [90]. In addition, meta-analyses indicate that TZD use is

associated with increased survival in diabetic women with breast cancer [91]. TZDs can improve dyslipidemia and hyperglycemia by enhancing insulin sensitivity through activation of PPARγ target genes. TZDs can induce cancer cell cycle arrest by stimulating the induction of phosphatase and tensin homolog (PTEN), and TZDs can sensitize cancer cells to TNF-related apoptosis-inducing ligand (TRAIL)-induced death by repressing cyclin D3 expression in a PPARγ-independent manner [92, 93]. TZD treatment causes cell growth arrest and apoptosis of non-small cell lung carcinoma cells by a mechanism involving growth arrest and DNA-damage inducible protein (GADD153) [94].

Statins

Statins are the most widely prescribed class of medication for hypercholesterolemia. There is evidence suggesting that cancer patients taking statins have improved survival. Meta-analyses have suggested that statin use is associated with a decreased risk of hepatocellular and colorectal carcinoma, as well as decreased cancer-specific mortality, independent of cancer type [95]. In breast cancer, retrospective reports suggest that statin use decreases the risk of recurrence [96]. Statins inhibit the rate-limiting enzyme of the cholesterol biosynthesis pathway, which in turn reduces blood cholesterol. Cholesterol can be found in the circulation as low density lipoprotein (LDL) and this biochemical species can be taken up in cells by the low-density lipoprotein receptor (LDLR). Increased LDL levels can promote mitosis of breast and prostate cancer cells. Moreover, high LDLR expression in breast cancer patients has been positively associated with relapse and poor outcomes [97]. Upon cellular uptake of LDL, a negative feedback pathway involving sterol regulatory element-binding protein-2 (SREBP-2) represses LDLR expression [98]. For unclear reasons, this feedback mechanism is broken in some cancer cells and thus cellular uptake of cholesterol never halts. In addition, LDL can potentiate PI3K/Akt signaling in breast cancer cells resulting in enhanced cell proliferation [99]. Interestingly, breast cancer growth and metastasis are potentiated by the actions of cytochrome P450 oxidase CYP27A1 which oxidizes cholesterol into 27-hydroxycholesterol [100].

Conclusion

The alarming association between obesity and cancer poses a significant public health risk. A growing body of basic, translational, and clinical investigators has been exploring the underlying basis for this connection. Several important questions remain unanswered. First, while obesity per se appears to increase cancer risk and progression, it is not yet clear whether specific phenotypes of adipose tissue play a role. For example, subcutaneous and visceral adiposity almost certainly confer different levels of risk, and this may differ across cancer types and individuals. Second, the full spectrum of local and systemic signals by which obesity promotes oncogenesis remains to be defined. As additional factors are identified, dissecting their biological functions will provide new insights into the basic biology linking obesity to cancer. Finally, ongoing and future studies will be important in clarifying the effect of interventions such as weight loss and exercise. Understanding the impact and mechanism of action of these and other treatment interventions will be required if we are to disrupt the deleterious association between obesity and cancer.

Acknowledgements We thank David Ackerman for the assistance in preparing the figure.

Compliance with Ethical Standards

Conflict of Interest Sarah E. Ackerman, Olivia A. Blackburn, François Marchildon, and Paul Cohen declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

References

Papers of particular interest, published recently, have been highlighted as:
- • Of importance
- •• Of outstanding importance

1. Flegal KM, Carroll MD, Kit BK, Ogden CL. Prevalence of obesity and trends in the distribution of body mass index among US adults, 1999–2010. JAMA. 2012;307:491–7.
2. Finkelstein EA, Trogdon JG, Cohen JW, Dietz W. Annual medical spending attributable to obesity: payer-and service-specific estimates. Health Aff. 2009;28:w822–31.
3. Global BMI Mortality Collaboration, Di Angelantonio E, ShN B, Wormser D, Gao P, Kaptoge S, et al. Body-mass index and all-cause mortality: individual-participant-data meta-analysis of 239 prospective studies in four continents. Lancet. 2016;388:776–86.
4. Calle EE, Rodriguez C, Walker-Thurmond K, Thun MJ. Overweight, obesity, and mortality from cancer in a prospectively studied cohort of U.S. adults. N Engl J Med. 2003;348:1625–38.
5. Renehan AG, Tyson M, Egger M, Heller RF, Zwahlen M. Body-mass index and incidence of cancer: a systematic review and meta-analysis of prospective observational studies. Lancet. 2008;371:569–78.
6. Bhaskaran K, Douglas I, Forbes H, dos-Santos-Silva I, Leon DA, Smeeth L. Body-mass index and risk of 22 specific cancers: a population-based cohort study of 5·24 million UK adults. Lancet. 2014;384:755–65.
7.•• Arnold M, Pandeya N, Byrnes G, Renehan AG, Stevens GA, Ezzati M, et al. Global burden of cancer attributable to high body-mass index in 2012: a population-based study. Lancet Oncol. 2015;16:36–46. **Population-based study that suggests that 3.6% of all new cancers in adults are attributable to increased BMI.**

8. Ligibel JA, Alfano CM, Courneya KS, Demark-Wahnefried W, Burger RA, et al. American Society of Clinical Oncology position statement on obesity and cancer. J Clin Oncol. 2014;32:3568–74.
9. Rosen ED, Spiegelman BM. What we talk about when we talk about fat. Cell. 2014;156:20–44.
10. Cohen P, Spiegelman BM. Brown and beige fat: molecular parts of a thermogenic machine. Diabetes. 2015;64:2346–51.
11. Harms M, Seale P. Brown and beige fat: development, function and therapeutic potential. Nat Med. 2013;19:1252–63.
12. Goodwin PJ, Stambolic V. Impact of the obesity epidemic on cancer. Annu Rev Med. 2015;66:281–96.
13. Osborn O, Olefsky JM. The cellular and signaling networks linking the immune system and metabolism in disease. Nat Med. 2012;18:363–74.
14. Ferguson RD, Novosyadlyy R, Fierz Y, Alikhani N, Sun H, Yakar S, et al. Hyperinsulinemia enhances c-Myc-mediated mammary tumor development and advances metastatic progression to the lung in a mouse model of type 2 diabetes. Breast Cancer Res. 2012;14:R8.
15. Gunter MJ, Hoover DR, Yu H, Wassertheil-Smoller S, Rohan TE, Manson JE, et al. Insulin, insulin-like growth factor-I, and risk of breast cancer in postmenopausal women. J Natl Can Inst. 2009;101:48–60.
16. Ulanet DB, Ludwig DL, Kahn RC, Hanahan D. Insulin receptor functionally enhances multistage tumor progression and conveys intrinsic resistance to IGF-1R targeted therapy. Proc Natl Acad Sci U S A. 2010;107:10791–8.
17. Bol DK, Kiguchi K, Gimenez-Conti I, Rupp T, DiGiovanni J. Overexpression of insulin-like growth factor-1 induces hyperplasia, dermal abnormalities, and spontaneous tumor formation in transgenic mice. Oncogene. 1997;14:1725–34.
18. Lopez T, Hanahan D. Elevated levels of IGF-1 receptor convey invasive and metastatic capability in a mouse model of pancreatic islet tumorigenesis. Cancer Cell. 2002;1:339–53.
19.•• Sanchez-Lopez E, Flashner-Abramson E, Shalapour S, Zhong Z, Taniguchi K, Levitzki A, et al. Targeting colorectal cancer via its microenvironment by inhibiting IGF-1 receptor-insulin receptor substrate and STAT3 signaling. Oncogene. 2015;35:1–11. **This paper describes a cell-autonomous mechanism through which IGF-1 and STAT3 stimulate tumorigenesis in the CPC-APC mouse model. This can be attenuated with the use of a small-molecule that inhibits both the IGF-1 receptor and STAT3.**
20. Wu Y, Yakar S, Zhao L, Hennighausen L, LeRoith D. Circulating insulin-like growth factor-I levels regulate colon cancer growth and metastasis. Cancer Res. 2002;62:1030–5.
21.• Fan Y, Gan Y, Shen Y, Cai X, Song Y, Zhao F, et al. Leptin signaling enhances cell invasion and promotes the metastasis of human pancreatic cancer via increasing MMP-13 production. Oncotarget. 2015;6:16120–34. **This study investigates the role of the leptin receptor expressed on human pancreatic cancer cells. Treatment with leptin promotes invasion and upregulates MMP-13 expression, but not cell proliferation.**
22. Vaisse C, Halaas JL, Horvath CM, Darnell JE, Stoffel M, Friedman JM. Leptin activation of Stat3 in the hypothalamus of wild-type and ob/ob mice but not db/db mice. Nat Genet. 1996;14:95–7.
23. Miyoshi Y, Funahashi T, Tanaka S, Taguchi T, Tamaki Y, Shimomura I, et al. High expression of leptin receptor mRNA in breast cancer tissue predicts poor prognosis for patients with high, but not low, serum leptin levels. Int J Cancer. 2006;118:1414–9.
24. Park J, Kusminski CM, Chua SC, Scherer PE. Leptin receptor signaling supports cancer cell metabolism through suppression of mitochondrial respiration in vivo. Am J Path. 2010;177:3133–44.
25. Berg A, Combs TP, Du X, Brownlee M, Scherer PE. The adipocyte-secreted protein Acrp30 enhances hepatic insulin action. Nat Med. 2001;7:947–53.
26. Kadowaki T, Yamauchi T, Kubota N, Hara K, Ueki K, Tobe K. Adiponectin and adiponectin receptors in insulin resistance, diabetes, and the metabolic syndrome. J Clin Invest. 2006;116:1784–92.
27. Grote VA, Kaaks R, Nieters A, Tjonneland A, Halkjaer J, Overvad K, et al. Inflammation marker and risk of pancreatic cancer: a nested case-control study within the EPIC cohort. Br J Cancer. 2012;106:1866–74.
28. Shahar S, Salleh R, Ghazali A, Koon P, Mohamud W. Roles of adiposity, lifetime physical activity and serum adiponectin in occurrence of breast cancer among Malaysian women in Klang Valley. Asian Pac J Cancer Prev. 2010;11:61–6.
29. An W, Bai Y, Deng SX, Gao J, Ben QW, Cai QC, et al. Adiponectin levels in patients with colorectal cancer and adenoma: a meta-analysis. Eur J Cancer Prev. 2012;21:126–33.
30. Brakenhielm E, Veitonmäki N, Cao R, Kihara S, Matsuzawa Y, Zhivotovsky B, et al. Adiponectin-induced antiangiogenesis and antitumor activity involve caspase-mediated endothelial cell apoptosis. Proc Natl Acad Sci U S A. 2004;101:2476–81.
31. Dalamaga M, Diakopoulos KN, Mantzoros CS. The role of adiponectin in cancer: a review of current evidence. Endocr Rev. 2012;33:547–94.
32. Kim AY, Lee YS, Kim KH, Lee JH, Lee HK, Jang S-H, et al. Adiponectin represses colon cancer cell proliferation via AdipoR1- and -R2-mediated AMPK activation. Mol Endocrinol. 2010;24:1441–52.
33. Berndt J, Klöting N, Kralisch S, Kovacs P, Fasshauer M, Schön MR, et al. Plasma visfatin concentrations and fat depot-specific mRNA expression in humans. Diabetes. 2005;54:2911–6.
34. Nakajima TE, Yamada Y, Hamano T, Furuta K, Matsuda T, Fujita S, et al. Adipocytokines as new promising markers of colorectal tumors: adiponectin for colorectal adenoma, and resistin and visfatin for colorectal cancer. Cancer Sci. 2010;101:1286–91.
35. Grolla AA, Travelli C, Genazzani AA, Sethi JK. Extracellular nicotinamide phosphoribosyltransferase, a new cancer metabokine. Br J Pharmacology. 2016;173:2182–94.
36. Chen W, Dong G, He S, Xu T, Wang X, Liu N, et al. Identification of benzothiophene amides as potent inhibitors of human nicotinamide phosphoribosyltransferase. Bioorg Med Chem Lett. 2016;26:765–8.
37. Hung AC, Lo S, Hou M, Lee YC, Tsai CH, Chen YY, et al. Extracellular visfatin-promoted malignant behavior in breast cancer is mediated through c-Abl and STAT3 activation. Clin Cancer Res. 2016;22:4478–90.
38. Neubauer K, Misa I, Diakowska D, Kapturkiewicz B, Gamian A, Krzystek-Korpacka M. Nampt/PBEF/visfatin upregulation in colorectal tumors, mirrored in normal tissue and whole blood of colorectal cancer patients, is associated with metastasis, hypoxia, IL1β, and anemia. Biomed Res Int. 2015;2015:523930.
39. Fukuhara A, Matsuda M, Nishizawa M, Segawa K, Tanaka M, Kishimoto K, et al. Visfatin: a protein secreted by visceral fat that mimics the effects of insulin. Science. 2005;307:426–30.
40. Yang RZ, Lee MJ, Hu H, Pray J, Wu HB, Hansen BC, et al. Identification of omentin as a novel depot-specific adipokine in human adipose tissue: possible role in modulating insulin action. Am J Physiol Endocrinol Metab. 2006;290:E1253–61.
41. Tan BK, Adya R, Farhatullah S, Chen J, Lehnert H, Randeva HS. Metformin treatment may increase omentin-1 levels in women with polycystic ovary syndrome. Diabetes. 2010;59:3023–31.
42. Yan P, Liu D, Long M, Ren Y, Pang J, Li R. Changes of serum omentin levels and relationship between omentin and adiponectin concentrations in type 2 diabetes mellitus. Exp Clin Endocrinol Diabetes. 2011;119:257–63.
43. Shen XD, Zhang L, Che H, Zhang YY, Yang C, Zhou J, et al. Circulating levels of adipocytokine omentin-1 in patients with renal cell cancer. Cytokine. 2016;77:50–5.

44. Cabia B, Andrade S, Carreira MC, Casanueva FF, Crujeiras AB. A role for novel adipose tissue-secreted factors in obesity-related carcinogenesis. Obes Rev. 2016;17:361–76.
45. Zhang Y, Zhou L. Omentin-1, a new adipokine, promotes apoptosis through regulating Sirt1-dependent p53 deacetylation in hepatocellular carcinoma cells. Eur J Pharmacol. 2013;698:137–44.
46. Hotamisligil GS, Shargill NS, Spiegelman BM. Adipose expression of tumor necrosis factor-alpha: direct role in obesity-linked insulin resistance. Science. 1993;259:87–91.
47. Khandekar MJ, Cohen P, Spiegelman BM. Molecular mechanisms of cancer development in obesity. Nat Rev Cancer. 2011;11:886–95.
48. Burkitt MD, Hanedi AF, Duckworth CA, Williams JM, Tang JM, O'Reilly LA, et al. NF-κB1, NF-κB2 and c-Rel differentially regulate susceptibility to colitis-associated adenoma development in C57BL/6 mice. J Pathol. 2005;236:326–36.
49.• Liu J, Ibi D, Taniguchi K, Lee J, Herrema H, Akosman B, et al. Inflammation improves glucose homeostasis through IKKβ-XBP1s interaction. Cell. 2016;167:1052–66. **IKKB-mediated inflammation is a positive regulator of glucose homeostasis. Overexpression of IKKB in the livers of obese mice results in increased X-box binding protein 1 activity, reduced ER stress, and improved insulin sensitivity and glucose homeostasis.**
50. Chang Q, Daly L, Bromberg J. The IL-6 feed-forward loop: a driver of tumorigenesis. Semin Immunol. 2014;26:48–53.
51. Grivennikov S, Karin E, Terzic J, Mucida D, Yu GY, Vallabhapurapu S, et al. IL-6 and Stat3 are required for survival of intestinal epithelial cells and development of colitis-associated cancer. Cancer Cell. 2009;15:103–13.
52. Park EJ, Lee JH, Yu GY, He G, Ali SR, Holzer RG, et al. Dietary and genetic obesity promote liver inflammation and tumorigenesis by enhancing IL-6 and TNF expression. Cell. 2010;140:197–208.
53. Couto JP, Daly L, Almeida A, Knauf JA, Fagin JA, Sobrinho-Simoes M, et al. STAT3 negatively regulates thyroid tumorigenesis. Proc Natl Acad Sci U S A. 2012;109:E2361–70.
54. He G, Dhar D, Nakagawa H, Font-Burgada J, Ogata H, Jiang Y, et al. Identification of liver cancer progenitors whose malignant progression depends on autocrine IL-6 signaling. Cell. 2013;155:384–96.
55. Lin C, Liao W, Jian Y, Peng Y, Zhang X, Ye L, et al. CGI-99 promotes breast cancer metastasis via autocrine interleukin-6 signaling. Oncogene. 2017; doi:10.1038/onc.2016.525.
56. Iyengar NM, Gucalp A, Dannenberg AJ, Hudis CA. Obesity and cancer mechanisms: tumor microenvironment and inflammation. J Clin Oncol. 2016;34:4270–6.
57. Braune J, Weyer U, Hobusch C, Mauer J, Brüning JC, Bechmann I, et al. IL-6 regulates M2 polarization and local proliferation of adipose tissue macrophages in obesity. J Immunol. 2017;198:2927–34.
58. Mauro C, Smith J, Cucchi D, Coe D, Fu H, Bonacina F, et al. Obesity-induced metabolic stress leads to biased effector memory CD4(+) T cell differentiation via PI3K p110δ-Akt-mediated signals. Cell Metab. 2017;25:593–609.
59. Seo HS, Jo JK, Ku JM, Choi HS, Choi YK, Woo JK, et al. Induction of caspase-dependent extrinsic apoptosis by apigenin through inhibition of signal transducer and activator of transcription 3 (STAT3) signalling in HER2-overexpressing BT-474 breast cancer cells. Biosci Rep. 2015;35:e00276.
60. Morris PG, Hudis CA, Giri D, Morrow M, Falcone DJ, Xhou XK, et al. Inflammation and increased aromatase expression occur in the breast tissue of obese women with breast cancer. Cancer Prev Res. 2011;4:1021–9.
61.• Rossi EL, de Angel RE, Bowers LW, Khatib SA, Smith LA, Van Buren E, et al. Obesity-associated alterations in inflammation, epigenetics, and mammary tumor growth persist in formerly obese mice. Cancer Prev Res. 2016;9:339–48. **This study investigates breast cancer risk of mice which are formerly obese (FOb). Interestingly, they find that FOb show the same increased tumor growth trend as obese mice, when compared to lean mice.**
62. Iyengar NM, Ghossein RA, Morris LG, Zhou XK, Kochar A, Morris PG, et al. White adipose tissue inflammation and cancer-specific survival in patients with squamous cell carcinoma of the oral tongue. Cancer. 2016;122:3794–802.
63. Patsouris D, Li PP, Thapar D, Chapman J, Olefsky JM, Neels JG. Ablation of CD11c-positive cells normalizes insulin sensitivity in obese insulin resistant animals. Cell Metab. 2008;8:301–9.
64.•• Kolb R, Phan L, Borcherding N, Liu Y, Janowski AM, Xie Q, et al. Obesity-associated NLRC4 inflammasome activation drives breast cancer progression. Nat Commun. 2016;7:13007. **This study describes a novel pathway connecting obesity and breast cancer. The authors demonstrate show a mechanistic link between adipose tissue, macrophages, and tumor proliferation.**
65. Guerriero JL, Sotayo A, Ponichtera HE, Castrillon JA, Pourzia AL, Schad S, et al. Class IIa HDAC inhibition reduces breast tumours and metastases through anti-tumour macrophages. Nature. 2017;543:428–32.
66. Kratz M, Coats BR, Hisert KB, Hagman D, Mutskov V, Peris E, et al. Metabolic dysfunction drives a mechanistically distinct proinflammatory phenotype in adipose tissue macrophages. Cell Metab. 2014;20:614–25.
67. Xu X, Grijalva A, Skowronski A, van Eijk M, Serlie MJ, Ferrante AW. Obesity activates a program of lysosomal-dependent lipid metabolism in adipose tissue macrophages independently of classic activation. Cell Metab. 2009;18:816–30.
68. Tickner JA, Urquhart AJ, Stephenson SA, Richard DJ, O'Byrne KJ. Functions and therapeutic roles of exosomes in cancer. Front Oncol. 2014;4:127.
69.• Lazar I, Clement E, Dauvillier S, Milhas D, Ducoux-Petit M, LeGonidec S, et al. Adipocyte exosomes promote melanoma aggressiveness through fatty acid oxidation: a novel mechanism linking obesity and cancer. Cancer Res. 2016;76:4051–7. **Adipocytes can secrete exosomes which can reprogram fatty acid oxidation in melanoma cells and increase tumor aggressiveness.**
70.•• Thomou T, Mori MA, Dreyfuss JM, Konishi M, Sakaguchi M, Wolfrum C, et al. Adipose-derived circulating miRNAs regulate gene expression in other tissues. Nature. 2017;542:450–5. **Exosomes from adipose can contain miRNAs which can regulate gene expression in distant tissues.**
71. Weigelt B, Peterse JL, van't Veer LJ. Breast cancer metastasis: markers and models. Nat Rev Cancer. 2005;5:591–602.
72.•• Lambert AW, Pattabiraman DR, Weinberg RA. Emerging biological principles of metastasis. Cell. 2017;168:670–91. **This extensive review covers the cellular and molecular mechanisms underpinning the process of metastasis.**
73. Mori A, Sakurai H, Choo MK, Obi R, Koizumi K, Yoshida C, et al. Severe pulmonary metastasis in obese and diabetic mice. Int J Cancer. 2006;119:2760–7.
74. Kalluri R, Weinberg RA. The basics of epithelial-mesenchymal transition. J Clin Invest. 2009;119:1420–8.
75. Fuentes-Mattei E, Velazquez-Torres G, Phan L, Zhang F, Chou PC, Shin JH, et al. Effects of obesity on transcriptomic changes and cancer hallmarks in estrogen receptor-positive breast cancer. J Natl Cancer Inst. 2014;106:piidju158.
76. Strong AL, Ohlstein JF, Biagas BA, Rhodes LV, Pei DT, Tucker HA, et al. Leptin produced by obese adipose stromal/stem cells enhances proliferation and metastasis of estrogen receptor positive breast cancers. Breast Cancer Res. 2015;17:112.
77. Walter M, Liang S, Ghosh S, Hornsby PJ, Li R. Interleukin 6 secreted from adipose stromal cells promotes migration and invasion of breast cancer cells. Oncogene. 2009;28:2745–55.s.

78. Liang Q, Li L, Zhang J, Lei Y, Wang L, Liu DX, et al. CDK5 is essential for TGF-β1-induced epithelial-mesenchymal transition and breast cancer progression. Sci Rep. 2013;3:2932.
79. Yan D, Avtanski D, Saxena NK, Sharma D. Leptin-induced epithelial-mesenchymal transition in breast cancer cells requires β-catenin activation via Akt/GSK3- and MTA1/Wnt1 protein-dependent pathways. J Biol Chem. 2012;287:8598–612.
80.• Nieman KM, Kenny HA, Penicka CV, Ladanyi A, Buell-Gutbrod R, Zillhardt MR, et al. Adipocytes promote ovarian cancer metastasis and provide energy for rapid tumor growth. Nat Med. 2011;17:1498–503. **Description of a molecular mechanisms for ovarian cancer cell dissemination in the omental fat depot.**
81.•• Zelenko Z, Gallagher EJ, Tobin-Hess A, Belardi V, Rostoker R, Blank J, et al. Silencing vimentin expression decreases pulmonary metastases in a pre-diabetic mouse model of mammary tumor progression. Oncogene. 2017;36:1394–403. **This paper investigates the role of insulin resistance in lung metastasis of mammary tumors.**
82. Qian BZ, Li J, Zhang H, Kitamura T, Zhang J, Campion LR, et al. CCL2 recruits inflammatory monocytes to facilitate breast-tumour metastasis. Nature. 2011;475:222–5.
83. Coughlin SS, Calle EE, Teras LR, Petrelli J, Thun MJ. Diabetes mellitus as a predictor of cancer mortality in a large cohort of US adults. Am J Epidemiol. 2004;159:1160–7.
84. Knowler WC, Barrett-Connor E, Fowler SE, Hamman RF, Lachin JM, Walker EA, et al. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. N Engl J Med. 2002;346:393–403.
85. Birsoy K, Possemato R, Lorbeer FK, Bayraktar EC, Thiru P, Yucel B, et al. Metabolic determinants of cancer cell sensitivity to glucose limitation and biguanides. Nature. 2014;508:108–12.
86. Zakikhani M, Dowling R, Fantus IG, Sonenberg N, Pollak M. Metformin is an AMP kinase-dependent growth inhibitor for breast cancer cells. Cancer Res. 2006;66:10269–73.
87. Hirsch HA, Iliopoulos D, Tsichlis PN, Struhl K. Metformin selectively targets cancer stem cells, and acts together with chemotherapy to block tumor growth and prolong remission. Cancer Res. 2009;69:7507–11.
88. Wu L, Zhu J, Prokop LJ, Murad MH. Pharmacologic therapy of diabetes and overall cancer risk and mortality: a meta-analysis of 265 studies. Sci Rep. 2015;5:10147.
89. Gandini S, Puntoni M, Heckman-Stoddard BM, Dunn BK, Ford L, et al. Metformin and cancer risk and mortality: a systematic review and meta-analysis taking into account biases and confounders. Cancer Prev Res. 2014;7:867–85.
90. Govindarajan R, Ratnasinghe L, Simmons DL, Siegel ER, Midathada MV, Kim L, et al. Thiazolidinediones and the risk of lung, prostate, and colon cancer in patients with diabetes. J Clin Oncol. 2007;25:1476–81.
91. He X, Esteva FJ, Ensor J, Hortobagyi GN, Lee MH, Yeung SC. Metformin and thiazolidinediones are associated with improved breast cancer-specific survival of diabetic women with HER2+ breast cancer. Ann Oncol. 2012;23:1771–80.
92. Teresi RE, Shaiu CW, Chen CS, Chatterjee VK, Waite KA, Eng C. Increased PTEN expression due to transcriptional activation of PPARgamma by Lovastatin and Rosiglitazone. Int J Cancer. 2006;118:2390–8.
93. Lu M, Kwan T, Yu C, Chen F, Freedman B, Schafer JM, et al. Peroxisome proliferator-activated receptor gamma agonists promote TRAIL-induced apoptosis by reducing survivin levels via cyclin D3 repression and cell cycle arrest. J Biol Chem. 2005;280:6742–51.
94. Satoh T, Toyoda M, Hoshino H, Monden T, Yamada M, Shimizu H, et al. Activation of peroxisome proliferator-activated receptor-gamma stimulates the growth arrest and DNA-damage inducible 153 gene in non-small cell lung carcinoma cells. Oncogene. 2002;21:2171–80.
95. Kopel E, Maor E, Goldenberg I. Statin use and reduced cancer-related mortality. N Engl J Med. 2013;368:575–6.
96. Nielsen SF, Nordestgaard BGG, Bojesen SE. Statin use and reduced cancer-related mortality. N Engl J Med. 2012;367:1792–802.
97. Rudling MJ, Ståhle L, Peterson CO, Skoog L. Content of low density lipoprotein receptors in breast cancer tissue related to survival of patients. Br Med J. 1986;292:580–2.
98. Zelcer N, Hong C, Boyadjian R, Tontonoz P. LXR regulates cholesterol uptake through idol-dependent ubiquitination of the LDL receptor. Science. 2009;325:100–4.
99. Alikhani N, Ferguson RD, Novosyadlyy R, Gallagher EJ, Scheinman EJ, et al. Mammary tumor growth and pulmonary metastasis are enhanced in a hyperlipidemic mouse model. Oncogene. 2013;32:961–7.
100. Nelson ER, Wardell SE, Jasper JS, Park S, Suchindran S, et al. 27-hydroxycholesterol links hypercholesterolemia and breast cancer pathophysiology. Science. 2013;342:1094–8.