ABSTRACT
Cancer is a disease of the most dangerous diseases of our time. The great majority of cancers, some 90–95% of cases, are due to environmental factors and 25% of cancer cases worldwide are caused by overweight or obesity, and a sedentary lifestyle. These lifestyle patterns may increase cancer risk by several mechanisms including increased estrogens and testosterone, hyperlipidemia, hyperinsulinemia, and insulin resistance, increased inflammation, and depressed immune function. Cancer is caused by impaired energy metabolism due to impaired mitochondrial function, which is linked with abnormal lipid metabolism. Increased dietary fat or cholesterol has been reported to be a risk factor for the development of certain cancers. Also, lipids play an important role in the transmission of signals and energy saving, as well as providing the building blocks necessary for cell growth, in addition, protects them from inappropriate conditions and gives it resistance against therapies used. Cancer cells often have characteristic changes in metabolism, so it was necessary to understand the mechanism of lipid metabolism to be able to develop new treatments targeting lipid metabolism pathway to eliminate cancer cells. Therefore, the present study providing a view of cancer cell metabolism and the role of different lipid species in growth, proliferation, signaling and other functions that maintain cancer cells, as well as the prevention and treatments that based on lipid metabolism pathway.

KEYWORD: Cancer, lipid metabolism in cancer cells, obesity, cancer treatment, prevention.

INTRODUCTION
Cancer is the name given to a collection of related diseases. In all types of cancer, some of the body’s cells begin to divide without stopping and spread into surrounding tissues, which is made up of trillions of cells. Some of the earliest evidence of cancer is found among fossilized bone tumors, human mummies in ancient Egypt, and ancient manuscripts. As of today more than 100 carcinogens (chemical, physical and biological) were identified. From many of these carcinogens associations recognized long before, scientists understood the mechanism by which the cancer was produced. The continuing research is discovering new carcinogens, explaining how they cause cancer and providing insight into ways to prevent it.

Lipids are hydrophobic or amphipathic (hydrophilic and lipophilic) small molecules, which are large macromolecular polymers formed by the chemical linking of several small constituent molecules. The majority of adult mammalian tissues satisfy their lipid requirements through the uptake of free fatty acids (FFAs) and lipoproteins, such as low-density lipoprotein (LDL), from the bloodstream. Fatty acid (FA) and cholesterol biosynthesis are restricted to a subset of tissues, including liver, adipose and lactating breast tissues. Increased lipogenesis is a well-known hallmark of cancer as lipids, such as fatty acids and cholesterol, can be readily metabolized to provide energy and building materials for the rapidly dividing cells. Cancer cells are said to be capable of producing nearly 95% of their saturated and mono-unsaturated fatty acids de novo, even in the presence of adequate dietary supplies. The elevated rates of lipid synthesis occur through over expressed of various lipogenic enzymes. So, inhibited activity of lipogenic enzymes is reflected by decreased tumor growth and may lead to apoptosis of some cancer cells.

This study aims to highlight the lipid metabolism in cancer cells and the role of different lipid species in...
growth, proliferation, signaling and other functions that maintain cancer cells, as well as the treatments that based on lipid metabolism pathway.

**Lipid metabolism in cancer cell**
Lipid metabolism in cancer cells is regulated by the common oncogenic signaling pathways, and is believed to be important for the initiation and progression of tumors.[8]

**a-Fatty Acids (FA) metabolism**
Cancer cells seem to be highly dependent on de novo lipogenesis for their proliferation and survival. As it frequently exhibit alterations in fatty acid metabolism to sustain growth and proliferation, fulfill energy requirements and provide metabolites for anabolic processes.[11] The FA building blocks come from either exogenous sources or from de novo FA synthesis. While most normal human cells prefer exogenous sources, tumors synthesize FA de novo[12] and often exhibit a shift toward FA synthesis.[13] To enter the bioactive pool, FAs require “activation” by covalent modification by CoA via fatty acyl-CoA synthetases. Once in the active pool, FAs can be esterified with glycerol or sterol backbones, generating triacylglycerols (TGs) or sterol esters (SEs), respectively, and then stored in lipid droplets (LDs) (Figure 1).[14]

The expression and activity of many enzymes involved in fatty acid synthesis, i.e., ATP citrate lyase (ACL), acetyl-CoA carboxylase (ACC) and fatty acid synthase (FASN), are up regulated in many types of cancers.[13] In addition to the intracellular signaling pathways, FASN expression is also affected by extracellular micro environmental stresses, such as hypoxia, low pH and nutrient starvation could activate several intracellular signaling pathways to promote FASN expression.[16]

**b-Synthesis of cholesterol**
Another important biosynthetic process within lipid metabolism is the mevalonate pathway, which facilitates the synthesis of cholesterol, increased dietary fat or cholesterol has been reported to be correlated with increased risk of the occurrence of certain cancers, such as breast[17], prostate[18] and colon cancers[19]. The first steps of cholesterol biosynthesis involve the condensation of acetyl-CoA with acetoacetyl CoA to form 3-hydroxy-3-methylglutaryl (HMG)-CoA. The reduction of HMG-CoA to mevalonate by HMG-CoA reductase (HMGCR) represents the rate-limiting reaction of the cholesterol synthesis pathway and is highly regulated.[20] It has been recently postulated that choleseryl ester accumulation in lipid droplets within prostate cancer cells is a causative factor underlying prostate cancer aggressiveness.[21]

**c-Phospholipid metabolism in cancer**
An aberrant choline phospholipid (PC) metabolism is another major hallmark of cancer cells. In deed alterations of choline phospholipid metabolism have been reported in ovarian cancer and also in breast cancer.[22] Altered choline phospholipid metabolism in ovarian cancer has been found to be linked with the regulation of FAS.[22] Moreover, the authors founded that phospholipids and their metabolism have been involved in ovarian cancer in several forms, including LPA, phospholipase A2 (PLA2), phospholipase D (PLD) and autotoxin (ATX).
Regulation factors of lipid bio-synthesis
Most adult mammalian cells acquire lipids from the bloodstream either as free fatty acids or complexed to proteins such as low-density lipoproteins. These lipids are obtained from dietary sources or are carbohydrate-derived fatty acids synthesized in the liver or in adipocytes, where they can also be stored in intracellular structures called lipid droplets. De novo fatty-acid biosynthesis in the adult organism occurs mainly in the liver, adipose tissue and the lactating breast. The acetyl groups for fatty-acid biosynthesis are provided mainly by citrate, which is produced by the tricarboxylic acid (TCA) cycle.8

1- Activation of oncogenic pathways stimulates lipid synthesis
i- The SREBP family
Master regulators of lipid biogenesis, many genes coding for enzymes involved in FA and cholesterol biogenesis are targets of the sterol regulatory element-binding proteins (SREBPs), a family of transcription factors that are crucial for maintaining cellular lipid homeostasis.24 SREBP-1 has two isoforms: SREBP-1a is the predominant isoform in most cultured cell lines, SREBP-1, the master regulator of lipogenic gene expression, are found to be overexpressed in a number of cancer or cancer cells, such as prostate cancer,25 ovarian cancer,26 breast cancer,27 lung cancer28 and colon cancer.29 At normal levels, SREBP-1c activates the FA biosynthetic pathway with responsive genes including ACLY, ACC, FAS, SCD-1, and GPAT. Therefore, inhibiting SREBP-1 in cancer cells could decrease FA synthesis gene expression and possibly prevent cancer cell proliferation.30

ii- The Phosphoinositide 3-kinase/Akt/ PKB (protein kinase B)
The phosphoinositide 3-kinase/Akt/PKB (protein kinase B) signaling pathway is frequently activated in human cancer.31 Insulin stimulates lipid synthesis and ACC activity in liver and adipose tissue32 and Akt can phosphorylate ATP-citrate lyase33 and activate the expression of several genes involved in cholesterol and fatty-acid biosynthesis.34

2- ATP-citrate lyase (ACLY)
ACLY bridges glucose metabolism and FA metabolism by converting six-carbon citrate to oxaloacetate and two-carbon acetyl-CoA, the precursor for FA synthesis. Knockdown of ACLY reduces the ability of cells to metabolize glucose to lipid, as shown murine lymphoid cells35 and in human adenocarcinoma cells.56 ACL produce the substrate acetyl-CoA from glycolytic product citrate.37 Its expression has been reported to be induced by androgen treatment (figure 2).

3- Acetyl-CoA-carboxylase (ACC-ase)
ACC-ase is generally considered to catalyze the first reaction of the fatty acid biosynthetic pathway, the formation of malonyl-CoA from acetyl-CoA and C02. This reaction actually takes place in two steps, which are catalyzed by a single enzyme complex. In the first reaction, which is ATP dependent, C02 (from HCO3-) is transferred by the biotin carboxylase portion of ACCase to a nitrogen of a biotin prosthetic group attached to the e-amino group of a lysine residue. In the second reaction, catalyzed by the carboxyltransferase, the activated C02 is transferred from biotin to acetyl-CoA to form malonyl-CoA89 (figure 2). The rate limiting step in the synthesis of fatty acids is the ATP-dependent conversion of acetyl CoA to malonyl CoA by the enzyme, ACAC. Two isoforms have been identified, ACAC1 (also called ACACA) and ACAC2 (also called ACACB). Physiological control of ACAC activity is mediated by hormones and nutritional status, with SREBP-1c playing a major role in regulating ACACA expression.40

4- Malonyl-CoA decarboxylase (MCD)
An important modulator of fatty acid oxidation, decarboxylates malonyl-CoA to acetyl-CoA, essentially reversing the reaction catalyzed by ACC. It was hypothesized that increased fatty acid availability would increase the expression and activity of heart and skeletal muscle MCD.56

5- Fatty acid synthase (FASN)
The most extensively studied of the lipogenic enzymes in the context of carcinogenesis is FASN8 FASN catalyze successive condensation reactions to form a fatty acid from malonyl-CoA and acetyl-CoA substrates, producing mainly 16-carbon palmitate. Concerning lipogenesis, most studies have concentrated on increased expression and activity of the de novo fatty acid synthesis enzyme, fatty acid synthase (FASN), with suggestions that FASN might function as an oncogene.43 Moreover, increased fatty acid synthesis due to increased levels of FASN has been observed in a multitude of cancers and is strongly correlated with a poor prognosis in many instances.8 Therefore, FASN over-expression may play a role in carcinogenesis. Additionally, FASN over expression is found to be associated with the advanced stage of colorectal cancer and liver metastasis, thus it may also play a role in the progression of cancer.44 Abundant evidences have shown that FASN contributes to both tumorigenesis and metastasis, and it becomes an ideal target for cancer therapy. Meanwhile, inhibition of FASN activity by FASN specific inhibitors or siRNA can significantly inhibit cancer or cancer cell growth, induce cancer cell apoptosis, and reduce the metastasis of several cancers45 (figure 2).

6- Acyl-CoA synthetase (ACS)
Utilization of fatty acids for either synthesis of neutral and phospholipids or as substrates for β-oxidation requires an activation step catalyzed by fatty acyl-CoA synthetase (ACS) isoenzyme that converts a free fatty acid to its respective CoA ester. The isoforms are characterized according to the chain length of their preferred substrate. The subset of isoenzymes that act on fatty acids with chain lengths between 16 and 22 carbons
are referred to as long chain fatty acyl CoA synthetases (ACSLs)[46](figure 2).

7-Stearoyl-CoA desaturase (SCD)
SCD catalyzes the introduction of double bonds into short-chain FAs in the C 9 position (mainly converting stearoyl-CoA to oleoyl-CoA).[47] It was reported that SCD mRNA levels were down regulated in prostate cancer relative to normal prostate epithelium. The median SCD expression levels were 150, 45 and 10 for normal[48], however, it was reported that an increase in both SCD1 mRNA and protein expression in prostate cancer relative to normal prostate, and demonstrated that inhibition of SCD1 activity induces growth arrest of prostate cancer cells in vitro as well as in vivo.[49]

Figure 2: Regulation of lipid metabolism by oncogenic signaling pathways. Many enzymes within the fatty-acid and cholesterol-biosynthesis pathways are regulated by SREBPs (highlighted by yellow boxes). Oncogenic activation of the PI3K ⁄ Akt pathway promotes glucose uptake and its use in lipid synthesis through activation of SREBP. AMPK is activated in response to low cellular energy levels and prevents lipid synthesis and stimulates b-oxidation through inhibition of ACC.

(ACAT, acetyl-CoA acetyltransferase; ACLY, ATP citrate lyase; ACSL, acyl-CoA synthetase long-chain; CPT1, carnitine palmitoyltransferase; ETC, electron transport chain; HMGCS, HMG coenzyme A synthase; IDH, isocitrate dehydrogenase; MCT, monocarboxylate transporter; pRB, retinoblastoma 1.[50]

Relationship between cancer and obesity
Obesity is caused by high-fat diets, sedentary living, genetic factors, and disorders of the endocrine system.[51] It can be measured as body weight, body weight relative to height or may be assessed by the distribution of fat in the body. Peripheral distribution of fat is two most widely used and clinically relevant classifications to assess the degree of obesity.[52] The World Health Organization (WHO) estimates that there were more than 1.4 billion overweight adults and at least 500 million obese adults worldwide in 2008.[53] In response to endocrine and metabolic signals from other organs, adipose tissue responds by either increasing or decreasing the release of free fatty acids an energy- providing fuel for skeletal muscle and other tissues. Adipose tissue is also important in the regulation of energy balance and lipid metabolism through the release of peptide hormones such as leptin, adiponectin, resistin, and tumor necrosis factor-α (TNFα).[54] Adipose tissue within the tumor microenvironment actively contributes to tumor growth and metastasis by functioning as an endocrine organ, through secretion of signaling molecules (such as adipokines, pro-inflammatory cytokines, proangiogenic factors and extracellular matrix constituents) and acting as an energy reservoir for embedded cancer cells.[55]

Mechanisms relating adiposity to cancer risk
Three main factors are considered to connect obesity and cancer: the insulin–IGF1 axis, sex hormones and poly-peptide hormones. Each of these three factors is intimately linked to endocrine and paracrine dysregulation of adipose tissue in obesity.[56] Increased insulin secretion and increased activity of insulin like growth factor 1 (IGF-1) that stimulates cell proliferation
and migration, inhibits apoptosis and enhances angiogenesis.[57] Obesity can contribute to carcinogenesis by activating the IGF1–insulin pathway, which traditionally stimulates intracellular signaling through mitogen activated protein kinases (MAPKs) or the PI3K AXIS cascade.[58]

Obese patients also have elevated levels of bioactive sex steroids due to higher production of estrogen by excess adipose tissue, and reduced levels of sex hormone binding globulin caused by hyperinsulinemia.[59] Sex steroids regulate cellular differentiation, proliferation and apoptosis and might act as tumor promoters (figure 3).[60] Cytochrome P450 aromatase, which is encoded by the CYP19 gene, converts androgens to estrogens.[61] The rate of conversion of androgens to estrogens is elevated in post-menopausal women with obesity[62] and an increased level of estrogens in these women is associated with an increased risk of breast cancer.[63]

Adipose tissue synthesizes polypeptide hormones such as adipokines, which includes leptin and adiponectin. Leptin stimulates cell proliferation and inhibits apoptosis and has been associated with cancer of the prostate, colorectum and breast.[64] Adiponectin has the opposite effect to leptin on cell growth, resulting in an inverse association with several cancers, but the secretion of adiponectin is suppressed by insulin and estrogen.[65]

Leptin is a 16 kD hormone produced by adipocytes, and is known primarily for its role in the mammalian central nervous system, where it regulates food intake. Leptin receptors are expressed in almost every tissue and have a dynamic role in many organ systems, including the regulation of cancer growth. Leptin levels rise dramatically during states of obesity, and as a result, this adipokine is thought to have a pivotal role at the interface of obesity and cancer development.[66] Leptin plasma levels and adipose tissue mRNA expression were measured in cancer patients. Breast cancer patients, but not colorectal cancer patients, had plasma levels and adipose tissue expression of leptin significantly higher than controls associated with elevated values of estrogen and progesterone receptors. These data suggest the possible use of leptin as a clinical marker.[67] Adiponectin is primarily known for its role in insulin sensitization of tissues such as muscle and liver. Long thought to act through an AMP kinase dependent signalling pathway, emerging evidence now suggests that adiponectin modulates the activity of a ceramidase, which leads to decreased intracellular levels of ceramides, improved insulin sensitivity and inhibition of apoptosis.[68] (figure 3).

Figure 3: Possible mechanisms linking obesity to cancer, including the influence of sex hormones, inflammation, cytokines, acute-phase reactants and stress.

(Abbreviations: NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis; SHBG, sex-hormone binding globulin.[69]

Cancers related to obesity
Excess body mass (obesity and overweight) is a risk factor for diseases including type 2 diabetes, cardiovascular disease, hypertension and several cancers; colorectum, pancreas, gallbladder, oesophagus, endometrium and breast cancer.[70] Tumors, such as breast, prostate, ovarian, gastric, renal and colon cancers, growth and/or metastasis predominantly occur as a result of the adipocyte rich microenvironments in which these tumors are found and reflect a role for adipocytes in tumor maintenance and progression.[71] Furthermore,
individuals with obesity are at an increased risk of developing colon cancer. Both Basal metabolic index (BMI) and weight gain are more strongly related to risk of breast cancer among postmenopausal. Otherwise, cancer of the uterine lining was the first cancer to be recognized as being related to obesity. There is convincing and consistent evidence from both case–control and cohort studies that overweight and obesity are associated strongly with endometrial cancer.

Studies of populations worldwide have revealed that the risk of kidney cancer is 1.5–3 times higher in overweight and obese individuals than in men and women of normal weight. Importantly, the obesity-associated risk of renal-cell cancer seems to be independent of blood pressure, indicating that hypertension and obesity might influence renal-cell cancer through different mechanisms. Moreover, obesity increases risk for adenocarcinoma of the esophagus by 2–3-fold, but is not associated with an increased risk of squamous-cell carcinoma of the esophagus. Also, results from many recent studies indicate that obesity is associated with an almost two fold increased risk for pancreatic cancer in men and women. Elevated free fatty acid uptake and hepatocellular carcinoma evidence from epidemiological studies suggested a link between obesity, manifested in the form of elevated fatty acids, and HCC tumor genesis and increased mortality.

**Link between lipid, carbohydrates and protein cancer metabolism**

The link between the glycolytic pathway and fatty-acid synthesis through the pentose phosphate pathway (hexose mono- phosphate shunt), (Figure 4) little attention was paid to endogenous fatty-acid synthesis and human cancer. In the 1950s, some studies showed elevated levels of fatty-acid synthesis in tumor tissues, although the potential significance of the observations was not appreciated. The link between de novo synthesis of FAs to the well-known tumor-associated increase in glycolysis, (The high levels of glycolysis provide both energy and precursors for FA synthesis) was reflected by a coordinated rise in lipogenic and glycolytic enzyme activities.

![Figure 4: Outline of fatty-acid synthesis from glucose to palmitate. Glucose is converted to acetyl-CoA by glycolysis and on to citrate in the mitochondria. The citrate is transported to the cytoplasm and is converted back to acetyl-CoA by citrate lyase. A portion of the acetyl-CoA is carboxylated to malonyl-CoA by acetyl-CoA carboxylase, the pace-setting enzyme of fatty-acid synthesis. Fatty-acid synthase performs the condensation of acetyl-CoA and malonyl-CoA to produce palmitate, a 16-carbon saturated fatty acid, which is dependent on nicotinamide adenine dinucleotide phosphate. Lipid synthesis requires the cooperation of glycolysis, the Krebs cycle, and the pentose phosphate shunt. As pyruvate must enter the mitochondria in this case, it avoids conversion to lactate and therefore cannot contribute to glycolysis-derived ATP. Meanwhile, it has been demonstrated that glutamine may be metabolized by the citric acid cycle in cancer cells and converted into lactate, producing NADPH for lipid biosynthesis and oxaloacetate for replenishment of Krebs cycle intermediates. A number of lipogenic enzymes utilize reduced nicotinamide adenine dinucleotide phosphate](image-url)
(NADPH) and acetyl-CoA generated from glucose and glutamine metabolism, to synthesize fatty acids and their derivatives. Therefore, the exacerbated lipogenesis in cancer cells is not only caused by the up regulation of lipid metabolizing enzymes, but is also directly coupled to other common metabolic pathways and their associated cell signaling pathways.\(^{[84]}\)

**Lipid and cancer progression**

**1-lipid metabolism as inducers to cancer cell**

The metabolism of cancer cells is reprogrammed in order to support their rapid proliferation. Elevated fatty acid synthesis is one of the most important aberrations of cancer cell metabolism. An enhancement of fatty acids synthesis is required both for carcinogenesis and cancer cell survival, as inhibition of key lipogenic enzymes slows down the growth of tumor cells and impairs their survival.\(^{[85]}\) Cancer cells exhibit increased demand for fatty acids, which are derived endogenously from citrate or taken up from exogenous sources. The elevated rates of lipid synthesis occur through increased expression of various lipogenic enzymes. Increasing lipid production is critical for cancer cell survival and expression of a central lipogenic enzyme, fatty acid synthase (FASN), is strongly correlated with cancer progression.\(^{[91]}\)

There is ample evidence supporting a causative role of lipid peroxidation in selected human cancers, including kidney, liver and skin and in degenerative diseases. 4-hydroxynonenal (4-HNE), the product of lipid peroxidation, represents one of the most bioactive and well-studied lipid alkenals and is biomarker for oxidative stress and important players for mediating a number of signaling pathways. The biological effects of 4-HNE are primarily due to covalent modification of important biomolecules including proteins, DNA and phospholipids containing amino group.\(^{[86]}\) 4-HNE-dG represents the best biomarker of the genotoxic effects of 4-HNE and were preferentially formed at the third base of codon 249 in the p53 gene, causing gene mutation and affecting diverse biological processes including cell cycle arrest, apoptosis, DNA repair and differentiation.\(^{[87]}\)

**2-Growth and proliferation**

The high proliferation of cancer cells requires large amounts of lipids as building blocks for biological membranes. The importance of membrane synthesis in cancer cells has been highlighted by the observation that the expression and activity of cholinekinase, an enzyme required for the synthesis of phosphatidylcholine and phosphatidyl ethanol amine (the major phospholipids found in cellular membranes) is increased in tumors from several tissues and correlates with poor prognosis.\(^{[88]}\)

**3-Energy homeostasis**

Cancer cells use large amounts of glucose for energetic and biosynthetic purposes\(^{[89]}\), resulting in a high rate of lactate production and secretion. This requires the activation of mechanisms that equilibrate the intracellular pH and can lead to the acidification of the tumor microenvironment.\(^{[90]}\) It is possible that one of the roles played by lipid synthesis in some cancer cells and conditions, is as a carbon sink to sequester excess pyruvate and avoid lactate production while still maintaining a high glycolytic rate. Furthermore, it may also contribute to redox balance. Hypoxia-tolerant organisms use NADP+, produced during lipid synthesis, as an electron acceptor when oxygen is not available.\(^{[91]}\) Additionally, it has been proposed that hypoxic cancer cells may follow a similar strategy.\(^{[92]}\)

Some tumor types exhibit increased dependence on lipid oxidation as their main energy source. One such example is prostate tumors, which generally display a low rate of glucose utilization\(^{[93]}\) show increased uptake of fatty acids like palmitate\(^{[94]}\) and over expression of some B-oxidation enzymes.\(^{[95]}\) FASN plays a role in regulation of energy homeostasis by enhancing cellular respiration in cancer cell. We demonstrate that endogenously synthesized lipids fuel fatty acid oxidation, particularly during metabolic stress and maintain energy homeostasis.\(^{[96]}\) Moreover, B-oxidation has also been shown to contribute to ATP production and to resistance to oxidative stress in glioblastoma cells, by providing substrates for NADPH and glutathione production, allowing cells to remove reactive oxygen species.\(^{[97]}\)

**4-Signaling functions of lipids**

Lipid signaling is a vital part of cell signaling and may occur via activation of G protein-coupled receptors (GPCRs) and members of lipid categories as signaling molecules and cellular messengers. These include sphingosine-1-phosphate, diacylglycerol (DAG), phosphatidylinositol phosphates (PIPs), phosphatidylserine, prostaglandins, steroid hormones such as estrogen, testosterone, cortisol and oxysterols such as 25-hydroxycholesterol.\(^{[98]}\) Other lipid second messengers include lysophosphatidic acid (LPA), phosphatidic acid (PA) and diacylglycerol (DAG), which are produced by the action of different phospholipases. LPA, which can also be produced by the extracellular lysophospholipase autotaxin (Tokumura et al., 2002), activates cell proliferation, migration and survival through binding to G-protein-coupled receptors.\(^{[99]}\)

Phosphoinositides are important second messengers that relay signals from activated growth factor receptors to the cellular machinery. One of the most prominent lipids of this class is phosphatidylinositol (3,4,5)-trisphosphate. This molecule is produced by PI3K in response to growth factor signaling and mediates the recruitment and activation of the serine/threonine kinase Akt. PI3P is also the substrate for phosphatase and tensin homologue (PTEN) and PTEN is one of the genes that is most frequently mutated or deleted in cancer.\(^{[100]}\) Furthermore, phospholipase D (PLD), is found in diverse organisms from bacteria to humans and functions in multiple cellular pathways. It has been increasingly recognized as
a critical regulator of cell proliferation and tumorigenesis and the expression and activity of PLD are elevated in many different types of human cancers.\[100\]

5- The structural roles of lipids
Lipids have important structural functions that are crucial for different aspects of the transformed phenotype. For example, cholesterol and other membrane lipids are required to form lipids have important structural functions. Phospholipids are commonly associated with cancer and have been identified in almost every type of malignancy.\[102\] Phospholipids are a major component of all cell membranes, spontaneously forming lipid bilayers.\[103\] Cholesterol is an important component of biological membranes as it modulates the fluidity of the lipid bilayer and also forms detergent-resistant microdomains called lipid rafts that coordinate the activation of some signal-transduction pathways\[104\] (figure 5).

![Figure 5: The functions of lipids in cancer cells. Lipids provide cancer cells with membrane building blocks, signaling molecules, posttranslational modifications of proteins and energy supply to support rapid cell proliferation. (GPCRs: G protein-coupled receptors; uPAR: Urokinase-type plasminogen activator receptor)]. [105]

6- lipid metabolism enzymes and stress factors
In response to glucose limitation, fatty acid can also be consumed through β-oxidation to provide key substitute energy for cancer cell survival. It is reported that stimulation of fatty acid oxidation is sufficient to maintain cell survival and protect cells from glucose withdrawal-induced death in Akt-over expressing glioblastoma.\[106\] In some types of cancers, such as prostate cancer, fatty acid oxidation is proposed to be a dominant bioenergetic pathway.\[107\]

Fatty acid synthase (FASN)
The FASN complex facilitates lipogenesis by synthesizing palmitate from its base components. FASN expression in normal adult tissues is generally very low or undetectable and it is significantly up regulated and correlates with poor prognosis in many types of cancer. The metabolic products of the FASN complex are rapidly consumed by actively dividing cells and recent data demonstrates that FASN expression is important for tumor growth and survival, suggesting that FASN is a metabolic oncogene.\[108\]

Up-regulation of fatty acid synthase gene expression and fatty acid synthase biosynthetic activity are molecular events accompanying the pathogenesis and natural history of cancer disease. First, the increased fatty acid synthase gene expression in precursor, preinvasive and invasive cancer lesions appears to represent an indirect, early epiphenomenon, occurring in response to a microenvironment containing regions of poor oxygenation and high acidity due to lack of an adequate angiogenesis and/or nutritional supply. Second, aberrant transduction cascades driven by cancer-associated oncogenic changes subvert the down regulatory effects of circulating fatty acids. Third, fatty acid synthase-
dependent endogenous fatty acid metabolism actively contributes to cancer evolution by specifically regulating the expression, activity and/or cellular localization of proteins closely related to malignant transformation and/or progression. The increased expression of fatty acid synthase (FASN) is associated with a poor prognosis in a variety of human malignancies, including ovarian cancer. The correlation between elevated FASN and enhanced tumour growth is attributed to the role of FASN activity in phospholipid synthesis. FAS activity is shown to drive phospholipid synthesis in the endoplasmic reticulum (ER), promoting ER homeostasis and, consequently, cell survival. Finally, some cancers, including breast and prostate, show increased expression of FASN, which suggests that fatty-acid synthesis plays an important role in cancer pathogenesis.

**Lipid and cancer complications**

1. **Metastasis**
   Directed cell migration requires the coordinated activation of several processes: cell polarization and elongation, formation of cell protrusions and attachment to components of the extracellular matrix and contraction of the cell body to generate a force for the movement of the cell body in the direction of the leading edge. Cell migration is induced in response to pro-migratory factors, including growth factors and chemokines but also by signaling lipids, such as prostaglandins (Figure 6).

![Figure 6: The roles of lipids in the tumor microenvironment](image)

Hyperlipidemia is a risk factor of lymphatic metastasis of early cancer in upper gastrointestinal tract. In blood or intestinal fluid, most cholesterol and triglyceride exist in a lipoprotein complex with apoproteins, and the major function of serum cholesterol is attributed to low-density lipoprotein (LDL), that can have various effects on tumor biology. The proliferation of some tumor cells is partially dependent on exogenous LDL-cholesterol possibly through LDL receptors. A pharmacological inhibition of hydroxy-3-methyl glutaryl coenzyme A reductase (HMG CoA reductase) has been shown to inhibit the growth of some cancer cells both in vitro and in vivo. HMG CoA-reductase inhibitors have also been reported to selectively inhibit the invasion step of human pancreatic cancer cells. Therefore, these findings suggest that increased LDL-cholesterol might be important for proliferation and invasion step of carcinoma cells.

2. **Adipose tissue as inducer to hypoxia**
   Tumor hypoxia is a hallmark of cancer that is associated with poor patient outcomes and resistance to chemotherapy. The rapid cellular proliferation and expansion of adipose tissue also induces hypoxia, which triggers compensatory angiogenesis, so that limitations in

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
nutrient and oxygen supply can be overcome.\textsuperscript{[120]} Similar to that seen in tumor growth, the hypoxia in adipose tissue that occurs in the context of obesity induces expression of the transcription factor HIF1\alpha, which up regulates a profibrotic pathway involving extracellular matrix proteins and pro-inflammatory cytokines (such as IL6, tumour necrosis factor [TNF] and CC motif chemokine 2).\textsuperscript{[121]} Hypoxia inducible genes involved in highly diverse processes in lipid biology. Examples include molecules with functions in lipid droplet formation, prostaglandin biosynthesis, lipid signaling systems and synthetic processes.\textsuperscript{[122]}

\section{Changes in Adipose Tissue in Cachexia}

Cachexia is commonly the cause of death in cases of advanced malignancy a multifaceted syndrome describing the loss of body mass as a result of both accelerated catabolism of fat and skeletal muscle and anorexia. It does not simply refer to a loss of body weight\textsuperscript{[123]} and can be differentiated from sarcopenia (age-induced loss of skeletal muscle) and starvation (body mass loss by nutrient deficiency and preferential loss of adipose tissue occurs).\textsuperscript{[124]}

Loss of adipose tissue in cachexia is primarily due to an increased lipolysis, since there is an increased turnover of both glycerol and free fatty acids (FFA) compared with normal subjects (figure 9)\textsuperscript{[128]} Adipocytes from cachectic subjects also show a two- to threefold increase in response to natriuretic peptide, which is attenuated by inhibition of hormone-sensitive lipase (HSL), but there is no increase in the basal lipolytic rate\textsuperscript{[126]} In many cases of cancer cachexia the greater proportion of weight loss is caused by depletion of body fat.\textsuperscript{[127]}

About half of all cancer patients show a syndrome of cachexia, characterized by loss of adipose tissue and skeletal muscle mass. Such patients have a decreased survival time, compared with the survival time among patients without weight loss.\textsuperscript{[128]} Triglyceride in adipocytes, which represents the major storage of fat, is mobilized by hydrolysis to glycerol and free fatty acids which are released into the plasma (figure 9). There were no significant differences in whole body glycerol and fatty acid kinetics between the weight-stable patients and the normal volunteers, but those with weight loss had significantly elevated rates of release into the plasma of both glycerol and free fatty acids.\textsuperscript{[129]}

\section{Tumor and host factors influencing adipose mass in cachexia}

Lipid mobilizing factor (LMF), secreted by cachexogenic tumors, Which acts to directly stimulate lipolysis through a cyclic AMP-mediated process.\textsuperscript{[130]} Cancer patients with weight loss have been shown to have an elevated level of a LMF, which appears to parallel the weight loss. This material acts directly on adipose tissue in a manner similar to the lipolytic hormones.\textsuperscript{[131]} In addition, production appeared to be related to the tumor mass because serum LMF levels were found to be reduced in cancer patients responding to chemotherapy.\textsuperscript{[132]}

Tumor Necrosis Factor-\alpha (TNF) is a cytokine initially described as an endotoxin-induced factor causing necrosis of tumors and subsequently shown to be identical to cachexin.\textsuperscript{[133]} The ability of TNF to induce cachexia in vivo naturally led to an extensive evaluation of its role in energy homeostasis. Adipose tissue expression of TNF is increased in obese rodents and humans and is positively correlated with adiposity and insulin resistance plasma TNF levels have been positively correlated with obesity and insulin resistance in some studies but not others.\textsuperscript{[134]}

TNF-\alpha induces Interleukins-6 (IL-6) secretion and synergizes with it in many of its actions, e.g., both stimulate other cytokines in a cascade, which has both pro inflammatory and anti-inflammatory components. Evidence for a role of IL-6 in the development of cancer cachexia has come mainly from studies using the murine colon-26 adenocarcinoma, where increasing levels of IL-6 correlated with the development of cachexia and treatment with a neutralizing antibody to IL-6, but not TNF- or interferon (IFN), attenuated the development of weight loss and other key parameters of cachexia.\textsuperscript{[135]}

\section{Prevention of cancer}

\subsection{Lipid diet}

Among dietary factors that have been suggested as risk factors for cancer, perhaps none has attracted as much attention as dietary fat intake. Some of the earliest reports that diet may modulate the risk of cancer were from rodent studies indicating that altering the fat composition of the diet may modify the rate and number of various tumors that may develop.\textsuperscript{[136]} Studies have found positive associations between several cancers such as prostate cancer\textsuperscript{[137]}, ovarian cancer\textsuperscript{[138]}, breast cancer\textsuperscript{[139]}, colon cancer\textsuperscript{[140]} etc and an intake of foods with high levels of saturated fats, such as red meat, eggs and dairy products. However, controversial results have also been reported about the role of high fat diet in carcinogenicity.\textsuperscript{[141]} Up to now, it is generally accepted that cis-mono unsaturated fatty acids MUFA and omega-3poly unsaturated fatty acids PUFAs are inversely associated with the increased risk of cancer, while saturated fatty acids SFA and omega-6 PUFAs are associated with the development of cancer.\textsuperscript{[142]}

The following are examples of diets (that should be eaten or not).

\subsection{Monounsaturated fatty acids}

It has been found that cancer incidence in the Mediterranean countries, where the main source of fat is olive oil, is lower than in other areas of the world. Such effects may be due the main MUFA in olive oil, oleic acid and to certain minor compounds such as squalene and phenolic compounds.\textsuperscript{[143]} Recent studies have also shown that canola oil, with high MUFA, oleic acid, can
decrease colon and breast cancer incidence significantly.\textsuperscript{144} It has demonstrated that the consumption of omega-3 fatty acids can slow the growth of cancer xenografts, increase the efficacy of chemotherapy and reduce the side effects of the chemotherapy or of the cancer.\textsuperscript{145} A similar contrast has been shown in the rat mammary cancer model, where diets containing a high proportion of n-6 fatty acid (n-6 FA) stimulate the growth of carcinogen-induced tumors, whilst the dietary addition of fish oils rich in long-chain n-3 FA causes an opposite effect.\textsuperscript{146}

**Polyunsaturated fatty acids**

Increasing evidences from animal and in vitro studies indicate that populations who ingest high amounts of omega-3 fatty acids in their diets have lower incidences of breast, colon and perhaps, prostate cancers.\textsuperscript{147} While dietary n-3 fatty acids (rich in ALA and EPA) may exert an anticarcinogenic action by altering the composition of cell membrane phospholipids, inhibiting amino acids (AA) metabolism and decreasing AA derived eicosanoids, as well as modulating the expression and function of numerous receptors, transcription factors and lipid derived signaling molecules.\textsuperscript{148} Diets containing n-6 fatty acids have been shown to induce breast cancer in experimental studies.\textsuperscript{149} N-6 Fatty acid N-6 fatty acids act as competitive inhibitors of n-6 fatty acid n-3 fatty acids in fat metabolism and it has been shown that the stimulatory or inhibitory effect of n-6 or n-3 fatty acids in experimental mammary carcinogenesis is abrogated by the addition of the other type of fatty acid.\textsuperscript{150}

Experimental studies show that the addition of n-6 FA stimulates the growth of human breast cancer (BC) cells in culture, and that dietary supplements of corn oil (rich in n-6 FA) stimulate growth and metastasis in human mammary cancer explants in immune suppressed mice.\textsuperscript{151} A higher omega-6/omega-3 PUFA ratio contributes to many diseases including cancer, cardiovascular and inflammation. Reducing the omega-6/omega-3 PUFA ratio can help lower the risk of initiation and development of cancer established a prostate-specific phosphatase and tension homolog (PTEN) knockout mouse model, and the result demonstrated that a dietary ratio of omega-6/omega-3 PUFA lower than 5 was effective in suppressing tumor growth and extending animal life span.\textsuperscript{152} The recent research suggested that a balanced ratio of omega-6/omega-3 PUFA (1:1) exerts a beneficial effects on cell function and physiology.\textsuperscript{153}

**Treatments that target lipid metabolism pathway in cancer**

Treatment of a variety of cell lines with fatty acid synthesis; FAS inhibitors induces endoplasmic reticulum ER stress in tumor cells, inducing cell death\textsuperscript{154} and inhibiting fatty acid synthesis.\textsuperscript{155} Treatment human ovarian cancer cells with a synthetic FAS inhibitor (C93) led to the activation of AMP activated protein kinase (AMPK) and cell death. Additionally, treatment of xenograft bearing mice with C93 also had a significant anti-tumor effect, causing a reduction in both tumor growth and volume.\textsuperscript{156} Metabolic oncogene is an important of tumor growth and survival, making it an attractive target for cancer therapy. Early small-molecule FASN inhibitors such as cerulenin, C75 and orlistat have been shown to induce apoptosis in several cancer cell lines and to induce tumor growth delay in several cancer xenograft models but their mechanism is still not well understood.\textsuperscript{157} The FAS inhibitor C75 has recently been shown to significantly reduce cell proliferation and induce apoptosis in ovarian clear cell carcinoma cell lines and was attributed to the down regulation of the oncogenic phosphoinositide-3-kinase (PI3K) signaling pathway.\textsuperscript{158}

A number of anti-cancer drugs are lipid-based or effective in terms of their ability to regulate lipid metabolism. Many anticancer drugs, such as cytarabine, daunorubicin, doxorubicin, etoposide, fludarabine, irinotecan, paclitaxel tamoxifen, taxol, vinblastine and vincristine, can impact ceramide accumulation by inducing ceramides synthase to catalyze de novo ceramide synthesis or by activating sphingomyelinase to catalyze sphingomyelinidegradation. Based on the structure of ceramide, ceramide analogs such as ceramidoids, 4,6-diene-ceramide, and C16-serinol are also used as anticancer drugs.\textsuperscript{160} A recent study demonstrated that ketogenic diet (high in linoleic acid; LAs and low in carbohydrates and protein) enhanced radiochemotherapy responses in lung cancer xenografts by a mechanism that may involve increased oxidative stress.\textsuperscript{161} Moreover, LA-containing CL is an abundant source of 4-HNE under oxidative stress condition and predisposes cancer cells to undergo apoptosis. Therefore, these results suggest that ketogenic diet (high in PUFAs, i.e., Docosahexaenoic acid; DHA, LA, and arachidonic acid), could serve as an effective adjuvant for improving responses to radio-chemo-therapies in the treatment of cancers by a mechanism linking mitochondrial 4-HNE formation, oxidative stress and lipid peroxidation.\textsuperscript{162} In recent treatments the scientist have used certain chemical substances that inhibit cancer growth throw inhibition of lipid metabolism enzymes (table 1) such as Acetyl-CoA inhibitor\textsuperscript{162}, A key enzyme linking glucose metabolism to lipid synthesis is ATP citrate lyase (ACL), which catalyzes the conversion of citrate to cytosolic acetyl-CoA. ACL inhibition by RNAi or the chemical inhibitor SB-204990 limits in vitro proliferation. The same treatments also reduce in vivo tumor growth and induce differentiation\textsuperscript{159},\textsuperscript{30} Mono acylglycerols (MAGL) inhibitor JZL184 and short hairpin RNAs that target (MAGL) due to its importance in hydrolyzes mono acylglycerols (MAGs) to release glycerol and a free fatty acid.\textsuperscript{155}

Recent work suggests that a mechanism for SREBP-1 repression preventing cancer cell proliferation is through loss of FA desaturation that is by causing lipotoxicity due to abnormally high levels of saturated FAs.
Inhibition of SREBP by 25-HC, fatostatin, and FGH10019 all cause a decrease in expression of SREBP-1 and SREBP-2 target genes and significantly reduce cellular growth in a variety of cancer cell lines.[163] Hydroxy-3-methylglutarylcoenzyme A reductase (HMGR) is the target for a class of cholesterol-lowering drugs known as statins. Statins show anti-proliferative activity in several cancer-cell lines, with the described effects ranging from cell cycle arrest (e.g. in breast cancer cells)[166] to apoptosis.[165] Statins may reduce the risk of esophageal cancer, colorectal cancer, gastric cancer, hepato-cellular carcinoma and possibly prostate cancer. Number of statins which are on the market: atorvastatin, fluvastatin, lovastatin, pitavastatin, pravastatin, rosuvastatin and simvastatin.

Table 1: Examples of chemical inhibitors of lipid enzymes that could reduce fatty acid availability.

<table>
<thead>
<tr>
<th>r</th>
<th>Drug (inhibitor)</th>
<th>Lipid enzymes</th>
<th>Comments</th>
<th>References</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>LY2940</td>
<td>ACLY</td>
<td>PI3K inhibitor</td>
<td>[159]</td>
</tr>
<tr>
<td>2</td>
<td>Metform AICA</td>
<td>ACC</td>
<td>Indirect, activates AMPK, FDA approved</td>
<td>[167]</td>
</tr>
<tr>
<td>3</td>
<td>Thiazolidinediones (TZDs)</td>
<td>ACS</td>
<td>SL4 specific, also activates PPARg, FDA approved</td>
<td>[168]</td>
</tr>
<tr>
<td>4</td>
<td>Orlistat Flavonoids Epigallocatechin-3-gallate (EGC)</td>
<td>FASN</td>
<td>-FDA approved - Naturally occurring - found in green tea</td>
<td>[169]</td>
</tr>
<tr>
<td>5</td>
<td>Fatostatin FGH10019</td>
<td>SREBP</td>
<td>Inhibits processing of SREBP-1 and SREBP-2</td>
<td>[163]</td>
</tr>
</tbody>
</table>

Conclusion and future prospective
Cancer is a disease in which cells divide in an irregular manner and in order to be able to grow and proliferation with large number in short time are gaining qualities different from normal cells. The changes of expression and activity of lipid metabolizing enzymes are directly regulated by the activity of oncogenic signals. The dependence of tumor cells on the dysregulated lipid metabolism suggests that proteins involved in this process are excellent chemotherapeutic targets for cancer treatment. Obesity is considered as the seriousness role in the incidence of cancer, which act as an inducer to specific types of cancer such as colon, breast, endometrial ect. Lipid metabolism is complex, most of the lipid metabolic enzymes have multiple isoforms, and these may be coupled to different lipid metabolic processes and can have different cellular localization or tissue distribution. The effect of blocking individual components of the pathways involved in the biosynthesis, uptake or remodeling of lipids needs to be evaluated not only in the context of cancer cell proliferation and survival but also within the more complex setting of cancer cell migration, invasion, tumour angiogenesis and metastasis formation. Therefore, successful therapies may be dependent upon understanding the specific metabolic abnormalities and lipid role for the particular types of cancer.

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bfarese@gladstone.ucsf.edu

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