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# Chemopreventive Effects of Alpha Lipoic Acid on Obesity-Related Cancers

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**Key Words**
Alpha lipoic acid · Anti-cancer property · Metabolism · Obesity · Obesity-related cancers

**Abstract**
***Background:*** It has been generally accepted that being overweight or obese is a risk factor for several types of cancers, including breast, thyroid, colon, pancreatic and liver. In fact, people who are obese have more fat tissues that can produce hormones, such as insulin or estrogen, which may cause cancer cells to grow. Alpha lipoic acid (ALA) is anorganosulfur compound derived from octanoic acid, which is produced in animals normally, and is essential for aerobic metabolism. ***Summary:*** Studies in both in vitro cells and in vivo animal models have shown that ALA inhibits the initiation and promotion stages of carcinogenesis, suggesting that ALA has considerable attention as a chemopreventive agent. This brief review collects the scattered data available in the literature concerning ALA and highlights its anti-cancer properties, intermediary metabolism and exploratory implications. ***Key Messages:*** Based on scientific evidences so far, ALA might be useful agents in the management or chemoprevention of obesity-related cancers.



## Introduction

*Obesity and Cancer*

Obesity is a condition in which a person has an abnormally high and unhealthy proportion of body fat [1]. To measure obesity, researchers commonly use a scale known as the body mass index (BMI) [1]. BMI is calculated by dividing a person's weight (in kilograms) by their height (in meters) squared [1, 2]. BMI provides a more accurate measure of obesity or indication of being overweight than just pointing to weight alone [2]. According to the most recent 2014 Cancer Progress Report from the American Association for Cancer Research, overweight/obesity is responsible for nearly 25% of the relative contribution to cancer incidence, which ranks second only to tobacco use [3]. Quite alarmingly, when obesity is combined with other related behaviors, including lack of physical activity and poor diet, the relative contribution rises to 33% of newly diagnosed cancer cases in the United States [4, 5]. Obesity is strongly tied to many of the most common types of cancers, including breast cancer, thyroid cancer, colorectal cancer, pancreatic cancer and liver cancer [6–10]. Obesity is also linked to poorer cancer outcomes, including increased risk of recurrence and of both cancer-specific and overall mortality [11, 12]. Hence, oncologists

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play a critical role in patient education, as well as in education of caregivers and families, regarding the importance of weight management [13]. Oncologists are also often the main source of referrals to appropriate sources where patients and their families can receive sound guidance [13, 14]. Key among the signaling pathways linking obesity and cancer is the PI3K/Akt/mammalian target of rapamycin (mTOR) cascade, which is a target of many of the obesity-associated factors and regulates cell proliferation and survival [15, 16]. Understanding the molecular and cellular mechanisms of the obesity-cancer connection is important in developing potential therapeutics [16]. The link between obesity and cancer underscores the recommendation to maintain a healthy body weight throughout life as one of the most important ways to protect against cancer [17].

*Alpha Lipoic Acid*

Alpha lipoic acid (ALA) is an organosulfur compound derived from octanoic acid [18]. ALA contains 2 sulfur atoms (at C6 and C8) connected by a disulfide bond and is thus considered to be oxidized although either sulfur atom can exist in higher oxidation states [18, 19]. The carbon atom at C6 is chiral and the molecule exists as 2 enantiomers (R)-(+)-lipoic acid and (S)-(–)-lipoic acid and as a racemic mixture (R/S)-lipoic acid (R/S-LA) [19]. ALA appears physically as a yellow solid and structurally contains a terminal carboxylic acid and a terminal dithiolane ring [19]. For use in dietary supplement materials and compounding pharmacies, the USP has established an official monograph for R/S-LA [20]. Basically, ALA is an anti-oxidant made by the body. It is found in every cell, where it helps turn glucose into energy [21]. Anti-oxidants attack 'free radical' waste products created when the body turns food into energy [22, 23]. Free radicals cause harmful chemical reactions that can damage cells, making it harder for the body to fight off infections [23]. Other antioxidants work only in water (such as vitamin C) or fatty tissues (such as vitamin E) [23]. However, ALA is both fat and water soluble, meaning that it can work throughout the body [23]. Antioxidants in the body are used up as they attack free radicals [22, 23]. But evidence suggests ALA may help regenerate these other antioxidants and make them active again [24]. In the cells of the body, ALA is changed into dihydlpoic acid and ALA is not the same as alpha linolenic acid, which is an omega-3 fatty acid that may help to keep the heart healthy [25]. Recently, it has been suggested that ALA is an essential mitochondrial co-factor, showing that ALA and its reduced counterpart dihydro lipoic acid form a potent redox couple with antioxidative functions, for which it is used as dietary supplement and for therapeutic purposes [26]. Further studies provided evidence that ALA is able to generate reactive oxygen species (ROS), which contribute to ALA-dependent cell death in lung cancer [27], breast cancer [28] and colon cancer [29], suggesting that ALA triggers the mitochondrial pathway of apoptosis in cancer cells. Importantly, considerable evidence suggests that ALA plays an important role in obesity-related cancers, that is, breast, thyroid, colon, pancreatic and liver [30–34]. Hence, this review focuses on the biological activities and multiple mechanisms of ALA in obesity-related cancers. Although scientific studies mainly investigated the effects of ALA on cancer prevention in vitro, this review summarizes the effects of ALA on the development and progression of cancer in animals.

## ALA and Breast Cancer

Breast cancer is the malignancy most frequently diagnosed and is the second most common cause of cancer deaths among women worldwide [35]. Also, in the United States, approximately 230,000 women were diagnosed with invasive breast cancer in 2012 and 39,500 deaths were expected, suggesting a need for new therapeutic approaches [35]. It has been shown that ALA reduces the matrix metalloproteinase activity in MDA-MB-231 human breast cancer cells [36]. This report also evaluated the effect of ALA on metastasis, showing that, after ALA treatment, cell motility, cell invasion and cell migration were significantly decreased [36]. In addition, it has been demonstrated that ALA induces p27 (kip1)-dependent cell cycle arrest and apoptosis in MCF-7 human breast cancer cells [37]. Specifically, this report suggested that ALA is able to scavenge ROS in MCF-7 human breast cancer cells and that the reduction of ROS is followed by cell growth arrest in the G1 phase of the cell cycle, via the specific inhibition of Akt pathway and the upregulation of the cyclin-dependent kinase inhibitor p27 (kip1), and by apoptosis, via changes of the ratio of the apoptotic-related protein Bax/Bcl-2 [37]. Recently, Feuerecker et al. [38] investigated the effects of ALA as a possible activator of pyruvate dehydrogenase on suppression of aerobic glycolysis and induction of SkBr3 breast cancer cell death. This report demonstrated that ALA reduces cell viability/proliferation, (18F)-FDG uptake and lactate production, and induces apoptosis, suggesting that the impaired uptake might be in part due to decreased cell proliferation and/or cell death caused by ALA [38]. However, it is also

possible that a shift to oxidative turnover caused cells to reduce uptake, since less glucose is needed to meet the demands for energy by switching over to oxidative respiration [39, 40]. In order to directly quantify the impact of ALA on the amount of pyruvate that is metabolized via pyruvate dehydrogenase, a novel technique, using pyruvate as a tracer for hyperpolarized carbon-13 magnetic resonance imaging, could open up new insights [41]. Using this technique could sustain the findings from the ELISA-based PDH assay that ALA increases the PDH activity after ALA treatment in cancer cells [38]. By contrast, the question whether the effects of ALA is caused by an increase of pyruvate dehydrogenase activity or by other mechanisms associated with the redox-properties of this compound could also be clarified in future experiments. ALA efficiently chemoprevented tumor appearance in APCmin mice, suggesting that even in experimental groups, where ALA overall reduced tumor risk (80 μg/day), ALA consistently stimulated the growth rate of established breast tumors [42]. Hence, the stimulation of breast cancer growth and inhibition of intestinal tumors by ALA indicate that diverse growth control mechanisms are modulated by ALA [42]. Furthermore, ALA exhibited a striking reduction of malathion-induced mammary tumor incidence and reversed intra-tumor histopathological alterations, showing that ALA suppresses proliferating cell nuclear antigen and p53 expression, induces apoptosis, and upregulates pro-apoptotic protein Bax [42]. These results provide the evidence that ALA exerts a chemopreventive effect in the breast hyperplastic and malignant changes by suppressing abnormal cell proliferation and inducing apoptosis with an oncostatic effects during an early-stage breast cancer [42].

### ALA and Thyroid Cancer

Thyroid cancer is a cancer originating from follicular or parafollicular thyroid cells [35]. These cells give rise to both well-differentiated cancers (i.e. papillary and follicular) and analastic thyroid cancer [43]. The second cell type, the C or parafollicular cell, produces the hormone calcitonin and is the cell of origin for medullary thyroid carcinoma [43, 44]. The most effective management of aggressive thyroid cancers is surgical removal of thyroid gland (thyroidectomy) followed by radioactive iodine ablation and TSH-suppression therapy [43]. Chemotherapy or radiotherapy may also be used in cases of distant metastases or advanced cancer stage, but 5-year survival rate is 97.8% in the United States [44]. It has been shown that ALA inhibits proliferation and epithelial mesenchymal transition of thyroid cancer cells [45]. This report has demonstrated that ALA suppresses thyroid cancer cell proliferation through the activation of AMPK and subsequent downregulation of mTOR-S6 signaling pathway [45]. This report further showed that ALA suppresses TGF-β production and inhibits the induction of p-Smad2 and twist by TGFβ1 or TGFβ2 [45]. Also, it has been reported that treatment with ALA increases sodium iodide symporter mRNA expression up to tenfold of control dose-dependently after 24 h of exposure [27]. This report also demonstrated that ALA increases phosphorylation of CREB and nuclear translocation of pCREB, and cotreatment of ALA and trichostatin A increase iodide uptake by threefold in TPC-1 thyroid cancer cells [27]. These results suggested that ALA could be a potential therapeutic agent for treatment of advanced thyroid cancer, possibly as an adjuvant therapy with other systemic therapeutic agents [27].

### ALA and Colon Cancer

Colorectal cancer (also known as colon cancer) is a cancer from uncontrolled cell growth in the colon or rectum [46]. Symptoms of colorectal cancer typically include rectal bleeding and anemia, which are associated with weight loss and changes in bowel habits, and most colorectal cancer occurs due to lifestyle and increasing age with only a minority of cases associated with underlying genetic disorders [46, 47]. Colorectal cancer is the third most commonly diagnosed cancer in the world, but it is more common in developed countries [47]. Around 60% of cases were diagnosed in the developed world [47]. It is estimated that worldwide, in 2008, 1.23 million new cases of colorectal cancer were clinically diagnosed, and that it killed 608,000 people [47]. It has been shown that exposure of HT29 human colon cancer cells to ALA or its reduced form dihydrolipoic acid (DHLA) for 24 h dose dependently increased caspase-3-like activity and was associated with DNA-fragmentation, suggesting that DHLA but not ALA was able to scavenge cytosolic $O_2^{-}$* in HT-29 human colon cancer cells, whereas both compounds increased $O_2^{-}$*-generation inside mitochondria [32]. This report concluded that ALA can effectively induce apoptosis in human colon cancer cells by a pro-oxidant mechanism that is initiated by an increased uptake of oxidizable substrates into mitochondria [32]. In fact, the underlying mechanism seems to be an enhancement of the uptake of monocarboxylates (pyruvate/lactate) from gly-

colysis into mitochondria followed by their oxidation in the citric acid cycle with increased delivery of reduction equivalents to the respiratory chain, which in turn drastically increases mitochondrial $O_2^-$ production [48, 49]. Hence, this high $O_2^-$-burden appears to overcome the intrinsically high antioxidative capacity of anti-apoptotic proteins and allows apoptosis in tumor cells to be executed [49]. Recently, I have demonstrated for the first time that AMPK/p53 Axis is essential for ALA-regulated metastasis such as adhesion, invasion, and colony formation in human and mouse colon cancer cells [50]. Also, it has been shown that ALA treatment led to a marked reduction in the RPS6KA4 mRNA level in multiple colorectal cancer cells and restoration of RPS6KA4 expression markedly attenuated α-LA induction of apoptosis in a p53-dependent manner [51]. In addition, this report showed that RPS6KA4 expression is activated by TNFα, whereas both basal and TNFα induction of RPS6KA4 are inhibited by the nuclear factor-κB (NF-κB) inhibitor BAY11-7082 or transfection of a dominant-negative mutant of NF-κB, indicating that NF-κB plays a crucial role in RPS6KA4 gene expression [51]. Impressively, DHL-TauZnNa, a newly synthesized ALA derivative, increased the proportion of cells in S phase and decreased that of cells in the G0/G1 phase in the cell cycle analysis of HT-29 human colon cancer cells, suggesting that DHL-TauZnNa may be expected to become a novel cancer therapeutic strategy through its induction of autophagy [52]. Interestingly, Rossi et al. [42] has shown that even in experimental groups, where ALA overall reduces tumor risk in colon cancer, ALA consistently stimulates the growth rate of established breast tumors. Hence, stimulation of breast cancer growth and inhibition of intestinal tumors by ALA indicate that diverse growth control mechanisms are modulated by ALA in different organs [42].

### ALA and Pancreatic Cancer

Pancreatic cancer is when cancer cells form within the pancreas, a glandular organ located behind the stomach [53]. Pancreatic cancer arises when cells in the pancreas, a glandular organ behind the stomach, begin to multiply out of control and form a mass [53]. These cancer cells have the ability to invade other parts of the body [53, 54]. There are many types of pancreatic cancer [54]. The most common, pancreatic adenocarcinoma, accounts for about 85% of cases, and the term 'pancreatic cancer' is sometimes used to refer only to that type [54, 55]. These adenocarcinomas start within the part of the pancreas, which makes digestive enzymes [55]. Several other types of cancer, which collectively represent the majority of the non-adenocarcinomas, can also arise from these cells [55]. One to 2 in every hundred cases of pancreatic cancer are found to be with neuroendocrine tumors, which arise from the hormone-producing cells of the pancreas [56]. Also, ductal pancreatic adenocarcinoma, the most common primary pancreatic malignancy, represents the fifth leading cause of cancer death in Western industrialized nations [57]. It has been shown that pre-treatment with ALA reduces oxidant formation, increases MMP, regulates UCP-2 mRNA and protein expression, increases glucose-induced ATP production, and restores glucose-stimulated insulin secretion in isolated rat islet cells [58]. Impressively, it has been shown that adding a combination of hydroxycitrate and ALA to chemotherapy improves effectiveness against pancreatic tumor development [59]. Of particular note are the results obtained in the treatment of an 80 year-old female who presented with ductal adenocarcinoma of the pancreas accompanied by liver metastases, suggesting that a treatment course using gemcitabine plus ALA and hydroxycitrate gave highly promising results [59]. Hence, this in vivo data suggest a possible advantage in using a treatment targeted at cancer metabolism in association with classical chemotherapy [59]. Also, Berkson et al. [60] depicted that an ALA/low dose naltrexone protocol in people with metastatic and nonmetastatic pancreatic cancer resulted in (18F)-FDG PET scans without evidence of disease approximately 4 months after treatment, suggesting that ALA holds the promise of having anti-proliferative properties when applied continuously.

### ALA and Liver Cancer

Liver cancer or hepatic cancer is a cancer that originates in the liver [61]. Primary liver cancer is globally the sixth most frequent cancer, and the second leading cause of cancer death [61]. Liver cancers are discovered through the use of medical imaging equipment (often by accident) or present themselves symptomatically as an abdominal mass, abdominal pain, yellow skin, nausea or liver dysfunction [62, 63]. The leading cause of liver cancer is cirrhosis that occurs due to infection caused by hepatitis B or hepatitis C, or due to excess consumption of alcohol [64]. In fact, in 2013, 300,000 deaths from liver cancer were due to hepatitis B, 343,000 due to hepatitis C and 92,000 due to heavy alcohol intake [64, 65]. Also, liver is

one of the most common sites for metastatic disease, and optimal management of hepatic metastases often requires a multidisciplinary approach [66]. It has been shown that ALA induces apoptosis in hepatoma cells via the PTEN/Akt pathway [67]. In addition, Fujii et al. [68] examined the modifying effect of co-administered ALA on the liver tissue environment surrounding pre-neoplastic hepatocellular lesions, with particular focus on hepatic macrophages and the mechanism behind the decrease in apoptosis of cells surrounding pre-neoplastic hepatocellular lesions during the early stages of hepatocellular tumor promotion. He showed that thioacetamide (TAA) increases the number and area of glutathione S-transferase placental form (GST-P)(+) liver cell foci and the numbers of proliferating and apoptotic cells in the liver but observed that co-administration with ALA suppresses these effects [68]. Also, he demonstrated that TAA increases the numbers of ED2(+), cyclooxygenase-2(+), and heme oxygenase-1(+) hepatic macrophages as well as the number of CD3(+) lymphocytes, but these effects are also suppressed by ALA [68]. Importantly, he suggested that ALA may also suppress the tumor-promoting activity by suppressing the DR5-mediated extrinsic pathway of apoptosis and the subsequent regeneration of liver cells outside GST-P(+) foci [68]. Moreover, it has been demonstrated that ALA induces apoptosis in 2 different hepatoma cell lines, FaO and HepG2, showing that ALA inhibits the growth of both cell lines as indicated by the reduction in cell number, the reduced expression of cyclin A and the increased levels of the cyclin/CDKs inhibitors, p27(Kip1) and p21(Cip1) [69]. This report further demonstrated that ALA-induced apoptosis was preceded by increased generation of ROS, and associated with p53 activation, increased expression of Bax, release of cytochrome c from mitochondria, caspases activation, decreased levels of survivin, induction of pro-apoptotic signaling (i.e. JNK) and inhibition of anti-apoptotic signaling (i.e. PKB/Akt) pathways [69]. Recently, Sudheesh et al. [70] has shown that the activities of mitochondrial enzymes and mitochondrial membrane potential ($\Delta\psi mt$) were significantly decreased and the level of ROS and MDA were significantly increased in Acetaminophen (APAP)-challenged rats. However, this report demonstrated that pretreatment with ALA could significantly prevent the APAP-induced mitochondrial damage such as an elevated level of ROS and lipid peroxidation, declined activities of respiratory chain complexes, Krebs' cycle dehydrogenases, and antioxidant status [70]. These results suggested that mitochondria and the kreb's cycle could be the main targets for liver cancer [70]. Furthermore, it has been demonstrated that ALA regulates liver enzymes, that is, alkaline phosphatase, aspartate aminotransferase, alanine aminotransferase, and gamma-glutamyl transferase [4]. The data also indicated the efficiency of ALA as a cancer inhibitor and a therapeutic influence [4]. These data suggested ALA as a potential therapeutic complement in the treatment or prevention of different pathologies that may be related to an imbalance of the cellular oxido-reductive status associated with malignancy [4]. By contrast, the administration of ALA in conditions associated with hepatic damage aggravates liver injury and stimulates the development of pre-neoplastic lesions, suggesting the need for caution when it is used in the presence of chronic liver injury [71].

## Conclusions

Obesity is a frequently overlooked factor that can contribute to an increased cancer risk, yet less than 10% of Americans are aware of this link [72]. According to the National Cancer Institute, an estimated 84,000 annual cancer cases are linked to obesity [73]. With rising obesity rates among young children in particular, it is becoming really important to understand this link [73]. Research has confirmed this perceptual shift, concluding that overweight/obese children are now nearly 25% less likely to be perceived as overweight compared to the previous decade [73]. Several studies have explored why being overweight or obese may increase cancer risk, and many studies have conducted investigations to determine anti-cancer agents [74, 75]. Among them, ALA has been shown to have anti-carcinogenic effects; these effects have been demonstrated at different sites in several experimental in vitro cell culture and in vivo animal models. However, studies did not look at ALA's all possible anticancer signaling pathways and a limited number of studies do not allow us to establish whether ALA may provide any protection in humans against cancer of any site. ALA is currently in clinical use for the treatment of diabetic neuropathy, while small clinical trials using combinations of ALA with known bioactive agents have been undertaken [76]. However, the use of the ALA is hampered by its instability and its rapid metabolism, suggesting that formulations containing ALA, in a form ensuring its stability and improving its bioavailability, can have important applications as medicines, nutritional supplements or cosmeceuticals [76]. Also, ALA as a mitochondrial cofactor termed 'mitochondrial nutrient' has been tested in a number of clinical trials such as alcohol-related liver

disease [77], diabetes-associated neuropathy [78], heart disease [79], HIV-1-related lipoatrophy [80] and mitochondrial diseases disease [81]. Also, there are only two clinical trial papers. Mantovani et al. [82] showed that several anti-oxidants including ALA are effective in reducing ROS levels and have the additional effect of increasing glutathione peroxidase activity in 28 advanced stage cancer patients with tumors at different sites. This result suggested that patients in both Performance Status (ECOG PS) 0–1 and ECOG PS 2–3 responded to antioxidant treatment [82]. In addition, it has been demonstrated in an open, non-randomized phase II study that oral administration of ALA (300 mg/day) increases the absolute lymphocyte count and serum levels of IL-2 and significantly decreases TNF alpha levels [83]. Also, this report demonstrated that a combination of IL-2 with oral antioxidant agent, ALA, in an intermittent schedule, repeated for a long-term period, is feasible, has a very low toxicity and results in the improvement of biological markers, which are predictive of patient outcome [83]. By contrast, direct evidence that ALA contributes to the development of obesity-related cancers has not been elucidated in clinical trials. Hence, further investigations are needed to demonstrate both the short- and long-term effects of ALA in clinical trials and investigate its safety for applications to cancer patients. Despite these limitations, based on scientific evidences so far, ALA might be useful agents in the management or chemoprevention of obesity-related cancers.


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