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Review article

Obesity: An emerging driver of head and neck cancer

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ABSTRACT

Obesity has become pandemic and emerged as one of the most critical global health care problems worldwide since last century. Recent studies have demonstrated that there may be a causal link between obesity and higher risks and mortality of cancers, including prostate, breast, colon, and thyroid cancers, head and neck cancer (HNC). This review focuses on the relationship between obesity and HNC, and the molecular mechanism of abnormal lipid metabolism in HNC. Elucidating the mechanism may open up new possibilities for strategies to reduce risk and mortality of HNC in an increasingly obese population.

1. Introduction

Head and neck cancer (HNC), comprising cancers of oral cavity, pharynx, nasopharynx, larynx, paranasal sinuses and salivary glands, is considered to be the fifth most common cancer all over the world [1]. In the past few years, incidence trends of HNC have been significantly increasing from 13.77 to 20.39 per 100,000, which was mainly driven by the increase of oropharynx cancer and oral cancer [2–4]. Despite the treatment strategies for HNC have become more flexible and aggressive during the period, the 5-year overall survival rate still remains < 50% due to frequent development of locoregional recurrences, which affects around 30% of HNC patients. A precise treatment of patients with HNC is challenging, and the exploration of new molecular targets for HNC is urgently needed [5,6].

Traditionally HNC is concerned to be significantly related to tobacco use, alcohol consumption and virus infection [7]. Recent studies have demonstrated that there may be a causal link between obesity and higher risks and mortality of cancers, including prostate, breast, colon, and thyroid cancers [8–12]. Obesity, measured by a body mass index (BMI) greater than or equal to 30 kg/m^2 according to WHO, has been pandemic worldwide since last century. In 2015, it was estimated that the population of obese adults was > 700 million [13]. Being identified as a risk factor for a group of chronic diseases, such as cardiovascular disease, diabetes mellitus type 2, obesity has emerged as one of the most critical global health care problems, contributed to 4 million deaths and 120 million disability-adjusted life-years in 2015 [14–16]. While studies into causality are ongoing, treatment strategies to intervene effectively in patients with cancers and obesity have not yet entered routine clinical practice. Based on a literature search on the recent studies related, this review focuses on the relationship between obesity and HNC and the underlying mechanisms of abnormal lipid metabolism in HNC (Figs. 1, 2). Elucidating the key roles and specific mechanisms of obesity in HNC may provide new insights into the development of precision therapy for HNC and the exploration of new molecular targets.

Abbreviations: HNC, head and neck cancer; BMI, body mass index; WHR, waist-to-hip ratio; WC, waist circumference; OSCC, oral squamous cell carcinoma; PFS, progression-free survival; DSS, disease specific survival; TSCC, tongue squamous cell carcinoma; PUFAs, polyunsaturated fatty acids; EPA, eicosapentaenoic acid; DHA, docosahexaenoic acid; DAG oil, diacylglycerol oil; 4NQO, 4-nitroquinoline 1-oxide; PKC, protein kinase C; DAGL, diacylglycerol lipase; FAS, fatty acid synthase; FABPs, fatty acid-binding proteins; MMP, matrix metalloproteinase; MAPK, mitogen-activated protein kinase; HMG-CoA, 3-hydroxy-3-methylglutarylcoenzyme A; sPLA2, secretory phospholipase A2; CRP, C-reactive protein; LEPR, leptin receptor; WAT, white adipose tissue; CLS, crown-like structures; TAMs, tumor-associated macrophages; OS, overall survival; IR, insulin resistance

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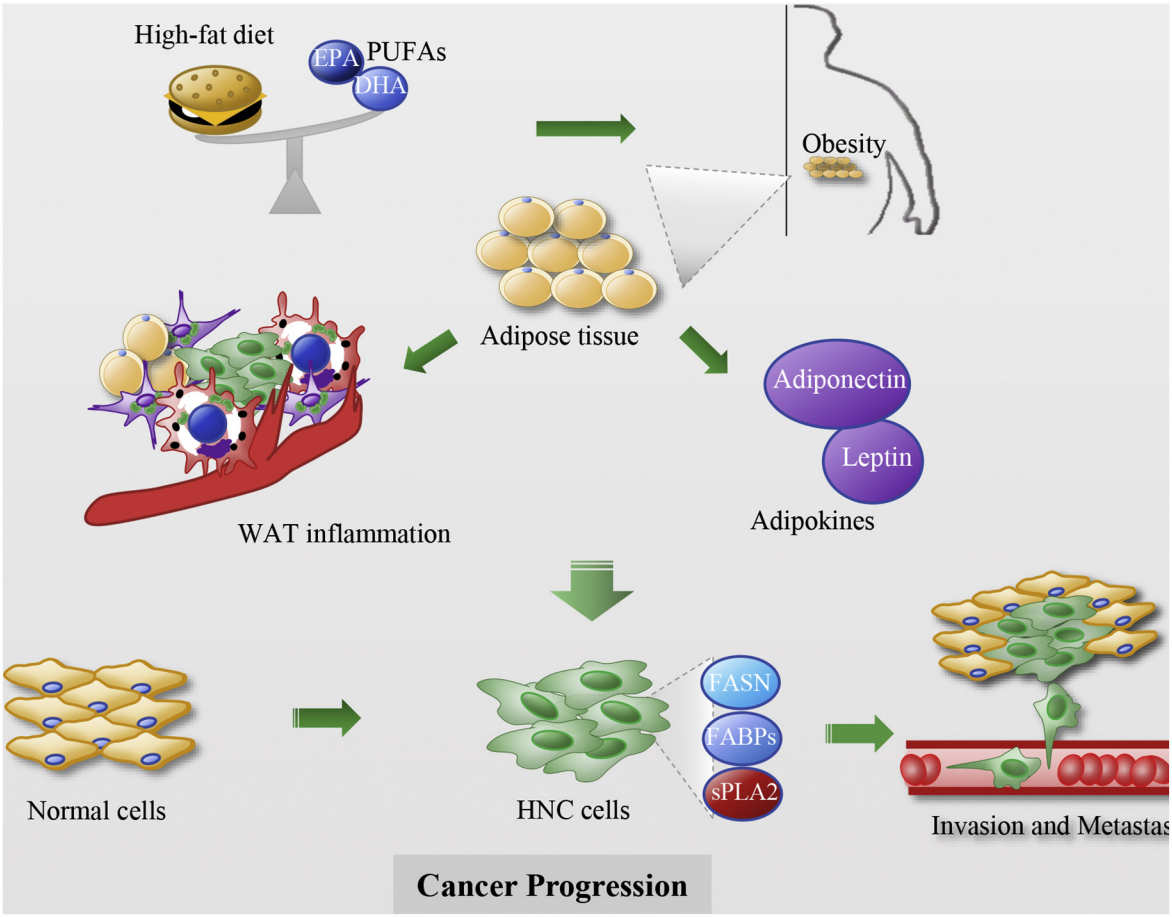

Fig. 1. The roles of obesity in the development of HNSCC. Obesity induced by the imbalance between a high-fat diet and PUFAs induces the development of HNSCC through white adipose tissue inflammation and adipokines.

1.1. Obesity and HNC

Currently the association between obesity and the risk of head and neck cancer is still controversial. Some cohort studies addressed that there was no etiologic relationship between BMI and HNC (with no statistically significance) [17,18]. But interestingly, some studies, including both cohort studies and case-control studies, reported that BMI was inversely associated with HNC and upper aerodigestive tract cancers [19–25]. A case-control study in East Asia including 921 cases and 806 controls suggested that being underweight, or leaness, (BMI < 18.5 kg/m^2) was associated with a higher HNC risk, while obesity was associated with a lower HNC risk [19]. A prospective NIH–AARP cohort study, containing 218,854 participants cancer free at baseline, showed an inverse association between HNC and BMI almost exclusively among current smokers [20]. However, in a pooled analysis of 20 available cohort studies, in which data from 1,941,300 participants had been involved, a positive association with BMI was found in never smokers, but not in former smokers or current smokers [26]. And BMI at age 20 appeared to be positive associated with HNC risk [21].

Despite the controversial relationship above, it seems acknowledged that waist-to-hip ratio (WHR) and waist circumference (WC), both measurement standards of central obesity (or abdominal obesity), were positively associated with HNC [20,26]. In another European prospective cohort study including 363,094 participants, WC and WHR were associated with greater risk of HNC among women, and the association for WHR was present only among smokers after stratification by smoking status [27].

Prediagnosis weight loss and low BMI (< 22.8 kg/m^2), usually accompanied by malnutrition, have been reported to be associated with poor prognosis in patients with oral cancers previously [28]. Besides, higher or increased BMI is related to a better outcome in HNC, including better survival, lower disease related mortality rates, less recurrence and distant metastasis rates [29–33]. But some studies addressed an opposite conclusion that obesity was positively associated with HNC outcome. A retrospective study including 576 oral squamous cell carcinoma (OSCC) patients without prediagnosis weight loss reported that obesity was an independent risk factor for the progression-free survival (PFS) and disease specific survival (DSS). Similarly, obesity was associated with a 5-fold increase in risk of death for patients with tongue squamous cell carcinoma (TSCC) compared to normal weight [34].

A finding called the “Obesity Paradox” is that obesity may contribute to longer life for population of specific diseases. The explanation is probably a consequence of selection bias. In view of weight loss and malnutrition, a few HNC patients also suffered from both disease and intensive therapy [30,32,35,36]. Thus, the independent effect of BMI on the risk and mortality of HNC is difficult to assess. Besides, alcoholic and smoking are also related to weight loss and central obesity, which could increase bias as well [29,37]. Therefore, we might need more studies in this field in the future to clarify the relationship between BMI and HNC, and the confounding must be eliminated as much as possible in order to get more accurate conclusions. Consequently, we might need more studies ensured that the start of exposure and the start of follow-up coincide in the future to clarify the relationship between BMI and HNC, and the confounding must be eliminated as much as possible in order to get more accurate conclusions.

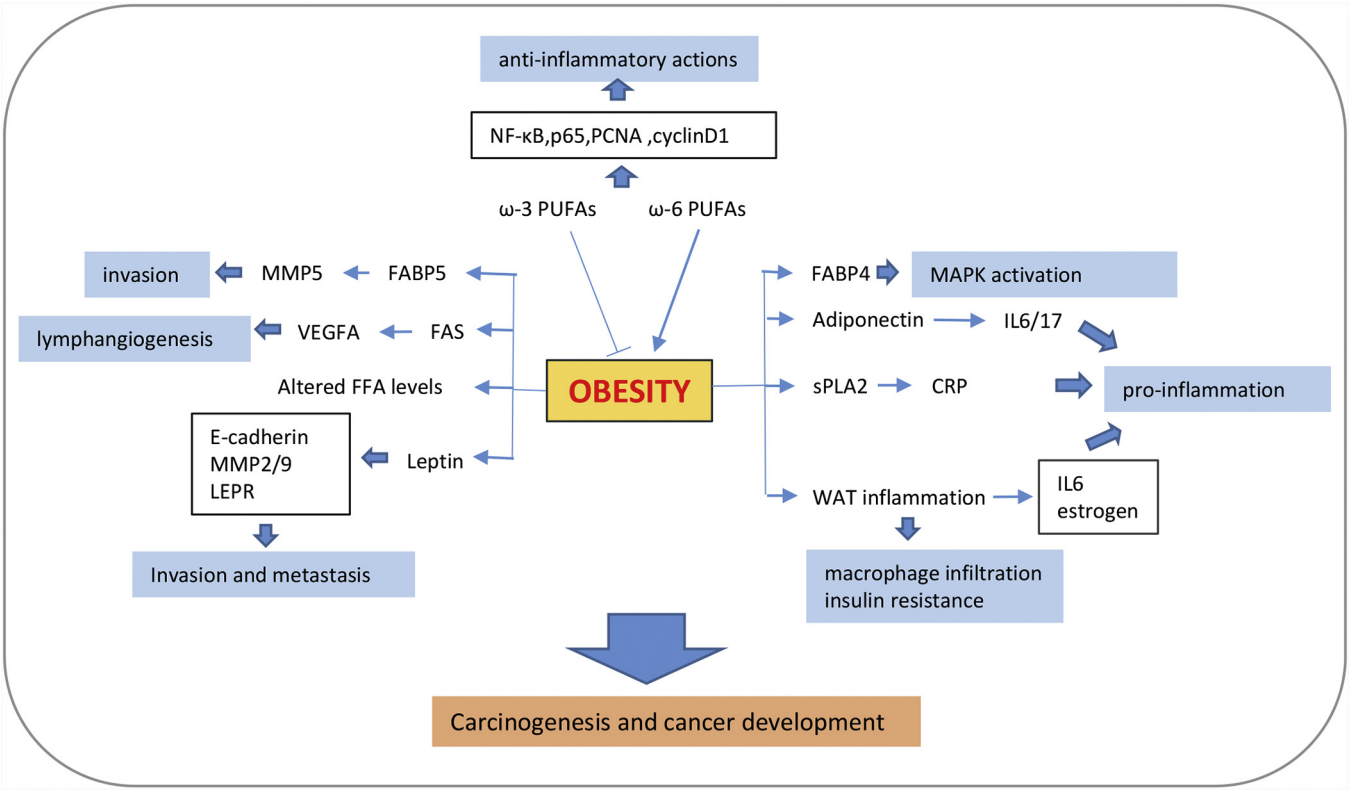

Fig. 2. The specific mechanisms by which obesity promotes cancer. Obesity facilitates tumor-associated inflammation, macrophage infiltration, angiogenesis, invasion and metastasis through a variety of pathways thereby promoting HNSCC progression.

1.2. High-fat diet and HNC

Nowadays the importance of dietary exposures in cancer has been gradually realized. Consumption of fruit and vegetables, especially those rich in vitamins and carotenoids, has been suggested to be inversely associated with HNC by some prospective studies [38–40]. It's in line with the healthy dietary patterns following public health recommendation [41]. On the contrary, the so-called “fried foods, high-fat and processed meats, and sweets” pattern has been observed to increase the risk of HNC, but this was limited to laryngeal cancer [42]. In addition, the “fats” diet pattern, including monounsaturated, polyunsaturated and saturated fatty acids and vitamin E, was also positively associated with laryngeal cancer, but inversely correlated with oral and pharyngeal cancer [43]. Compared to the direct relation between the “animal unsaturated fatty acids” pattern and laryngeal cancer risk, there was no significant association between the “vegetable unsaturated fatty acids” pattern and laryngeal cancer risk [44], yet the “unsaturated fats” pattern was inversely associated with oral cancer risk [45].

The long-chain omega-3 polyunsaturated fatty acids (PUFAs), including eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), have been proved to inhibit the occurrence of cancer *in vivo*, whereas omega-6 PUFAs have a proinflammatory effect and promote cancer [46]. In the tissue with perineural or lymphovascular invasion of OSCC, compared to the negative invasion tissue, the level of EPA and DHA was significantly reduced [47]. One study demonstrated that the low omega-6/omega-3 fatty acid diet (omega-6/omega-3 = 2) reduced oral aberrant cell proliferation and oral cancer incidence by effectively inhibiting expression of NF-κB, p65, PCNA and cyclinD1. And both the tumor volume and tumor burden were positively correlated with omega-6/omega-3 fatty acid ratio [48]. Omega-3 PUFAs seemed to also exert a protective effect to mice with salivary gland adenocarcinomas induced by 9,10-dimethyl-1,2-benzanthracene [49]. EPA had a potent inhibitory capacity for the growth of premalignant and malignant keratinocytes in oral cavity than that for the growth of normal keratinocytes *in vitro* by inducing over-stimulation of ERK1/2, whereas DHA was less selective [50]. EPA and DHA may also exert anti-inflammatory actions by suppressing the activation of the TLR4 signaling pathway which could be induced by lipopolysaccharides or saturated fatty acids [51]. It was showed that HNC patients with 2 g of EPA per day to maintain albumin and total protein concentrations, had an obvious improvement in the overall health status and tolerance to antineoplastic treatment with significantly decreased levels of IL-1β and TNF-α [52]. This indicated that PUFAs might play an important role in a chronic inflammatory status of HNC.

The administration of diacylglycerol oil (DAG oil), a mixture of 1,3-DAG and 1,2-DAG, was associated with significant increase in the incidence of 4-nitroquinoline 1-oxide (4NQO) induced TSCC in Tg male rats, but not female Tg and wide rats, possibly through a direct effect on the tongue epithelium by stimulating protein kinase C (PKC) [53]. While dietary 1,3-DAG had been found to reduce fat deposition in the viscera and body of rats, no anti-obesity or lipid-lowering effects of DAG oil were reported [54]. Diacylglycerol lipase (DAGL), catalyzing the hydrolysis of DAG to 2-arachidonoylglycerol and free fatty acid, was implicated in lipid homeostasis and adiposity. High DAGL-alpha (DAGLA) expression in OSCC was highly correlated with the tumor growth, indicating that DAGLA silencing had an anticancer effect [55].

2. Mechanisms of the link between obesity and HNC

2.1. FAS

Fatty acid synthase (FAS), responsible for the endogenous synthesis of saturated long-chain fatty acids, is over expressed in some human cancers such as prostate [56], breast [57], bladder [58], melanoma [59] and OSCC [60,61]. FAS is necessary for cell proliferation in OSCC, which could be suppressed by the FAS inhibitor cerulenin [62]. And the expression of FAS was significantly correlated with the presence of lymphatic permeation, perineural infiltration, and metastatic lymph

nodes in OSCC patients [63]. Orlistat, another inhibitor of FAS, reduces the growth, migration and metastasis of TSCC, particularly the number of metastatic cervical lymph nodes *in vivo* [64]. Orlistat and cerulenin could induce the apoptosis of cancer cells [65]. Furthermore, orlistat had antiangiogenic properties by strongly stimulating the secretion of VEGFA165b, an antiangiogenic VEGFA variant, while cerulenin might affect lymphangiogenesis by differentially regulating the production of VEGF-C and -D in cancer cells.

2.2. FABPs

Fatty-acid-binding proteins (FABPs), a family of proteins that are involved in fatty acid metabolism, are proved to be associated with several types of human cancer, for example, stomach [66], ovary [67] and prostate carcinomas [68]. FABP5 has been reported to be upregulated in oral carcinomas, yet the way it's involved in progression remains undecided [69,70]. Although FABP5 expression was detected in both primary tumors and metastatic lymph nodes, the former was up to 4-fold higher than the latter one, indicating that metastasis of TSCC was associated with down-regulation of FABP5 [71]. On the contrary, an adverse conclusion was that upregulated FABP5 expression in oral cancer cells increased cell proliferation, invasiveness, and metastasis by stimulating matrix metalloproteinase 9 (MMP9) expression, which could be significantly suppressed by silencing FABP5 In addition, the invasive ability of three oral cancer cell lines was proportional to their FABP5 expression [72]. The expression of FABP5 in the tongue carcinoma-adjacent epithelium was enhanced and also detected in all carcinoma tissues, while FABP4-positive cells were distributed randomly and frequently located at peripheries of tumor cell nests. Notwithstanding there is a correlation identified between oral carcinoma progression and FABP5 staining, not FABP4 staining [73], FABP4 was detected to be expressed in TSCC tissues, not in normal areas. FABP4-specific siRNA suppressed the growth of TSCC *in vitro* and down-regulated mitogen-activated protein kinase (MAPK) and phosphorylated MAPK [74].

2.3. HMG-CoA reductase

3-Hydroxy-3-methylglutarylcoenzyme A (HMG-CoA) reductase, which could convert HMG-CoA to mevalonate, a key precursor of cholesterol biosynthesis, is a rate-limiting enzyme of the mevalonate pathway. HMG-CoA reductase has been reported to be activated by increased Sp1 mediated SREBP-2 expression during high fat diet feeding [75]. Statins, known as HMG-CoA reductase inhibitors, could regulate hepatic cholesterol biosynthesis and reduce serum levels of low-density lipoprotein cholesterol by inhibiting mevalonate and isoprenoid biosynthesis [76]. Statins therapy is recommended for the treatment of hyperlipidemia and prevention of cardiovascular dis [77].

Recent studies have indicated that HMG-CoA reductase may be a potential anticancer therapeutic target and statins also possess some antitumor effects [78,79]. A case-control study, involving 11,030 total sampled patients, observed an inverse association between statin usage and HNC occurrence [80]. Statins could affect HNC cell proliferation, trigger cell apoptosis, suppress metastasis and increase the cytostatic efficacy of cisplatin and docetaxel by inhibiting RhoC activity, Ras/extracellular signal-regulated kinase, β1-integrin, phosphorylated FAK and phosphorylated ERK [81–86]. Some retrospective cohort studies showed that HNC patients with statin exposure were demonstrated to have improved outcomes, supporting the role of statins as a potential adjuvant anti-neoplastic agent in HNC [87,88]. More important, it was reported that statins could overcome radioresistance through the suppression of the mevalonate pathway thereby becoming a promising therapeutic strategy [89].

2.4. sPLA2

Secretory phospholipase A2 (sPLA2), belonging to the group of acute phase reactant family, is overexpressed or highly activated in several human diseases such as diabetes and cancer. The plasma level of sPLA2-IIA was not only shown to be increased in HNC, but also be positively correlated with the circulating levels of some proinflammatory factors such as C-reactive protein (CRP). HNC patients with lower sPLA2-IIA concentrations ($< 4\,\mu g/L$) were observed to have a relatively prolonged survival time [90]. Besides, the mean value of sPLA2 activity was higher in OSCC than adjacent normal tissues, which was significantly negatively correlated with that of linoleic acid (18:2n-6) [47].

2.5. Adiponectin

Adiponectin, an adipokine produced predominantly by adipocytes, is reported to be adversely associated with the risk of various cancers such as breast [91], pancreatic [92], and prostate cancer [93]. Decreased circulating adiponectin levels, which could be found in patients with obesity [94], were shown to be correlated with the risk of TSCC. And local adiponectin levels in tumor tissue were adversely associated with the stage of tumor-node-metastasis by inhibiting migration of cancer cells, but not proliferation, yet adiponectin receptor levels remained unchanged [95]. Besides, compared with patients with premalignant oral lesion, serum adiponectin levels were significantly increased in HNC patients, which could be declined by the treatment of 1,25(OH)2D3. And the levels of pro-inflammatory cytokines (IL-6, IL-17) and leptin were negatively correlated with the level of adiponectin [96].

2.6. Leptin

Leptin, a hormone mostly secreted by adipose tissue, is known to be an integral component of the homeostatic loop of body weight regulation. Basically, obese people have higher level of leptin [97]. Some studies suggest that leptin could directly contribute to progression of cancers, including breast, thyroid and oesophageal cancer [98–100]. However, the reduction of circulating leptin level could be detected in patients with cancers including OSCC, and the salivary level of leptin was also observed to be reduced [101,102]. Patients received resection operation for oral tumor with prolonged fasting significantly decreased leptin level and this alteration was reversed by nutrition support [103]. Given these patients also suffered with weight loss, the decrease of serum leptin may possibly be related to the decrease in body fat mass.

Leptin was reported to be widely expressed in oral melanomas in dogs, and the expression of leptin in salivary gland tumors was much higher compared to healthy parotid tissues [104,105]. Though it was demonstrated that there was no link between the expression of leptin in SCC and tumors arising in head and neck [106], the recurrence of malignancy in patients with SCC of laryngeal was significantly related to leptin expression [107]. It was reported that leptin-treated OSCC cells, compared to the control group, expressed increased mRNA levels of mir-210, E-cadherin, Col1A1, MMP2, and MMP9 while decreased level of caspase-3 was observed, resulting in the promotion of migration and proliferation and the inhibition of apoptosis, which indicated the obvious correlation between leptin and the development of oral cancer [108]. Moreover, topically administered leptin was found to accelerate epithelial cell migration of oral mucosa and enhancing angiogenesis as well [109].

The leptin receptor (LEPR), encoded by LEPR gene, is a single membrane-spanning receptor of leptin. The mutations in LEPR gene may increase the risk of HNC by influencing the expression and function of it. The presence of the Arg223 allele in the LEPR gene, which was also known as Gln223Arg polymorphism, dramatically increased risk of early disease relapse and disease-specific death in oral and

oropharyngeal cancer, while low LEPR expression showed a significant association with lymph node metastases [110]. Besides, LEPR (A668G) G allele was revealed to be prominently associated with the risk and development of OSCC [111–113].

2.7. White adipose tissue (WAT) inflammation

Previously, adipose tissue used to be considered merely a deposit of energy. Recent years, it has been recognized to be an endocrine gland associated with inflammation through secreting some molecules. Accumulating evidence shows that obesity is able to cause systemic inflammation, which could promote the development and progression of several malignancies [114]. Chronic adipose tissue inflammation, largely due to the proinflammatory actions of bone-marrow derived white adipose tissue (WAT) macrophages, is early implicated in the development of obesity complications [115]. Some studies have demonstrated that WAT inflammation is independently associated with shortened distant recurrence-free survival in patients with breast cancer [116]. Macrophage infiltration in WAT is positively correlated with BMI and could be detected histologically by the presence of crown-like structures (CLS), and it is also important to distinguish CLS macrophages from tumor-associated macrophages (TAMs) [117]. Tongue weight and percentage of tongue fat were found to increase with BMI and weight gain [118]. In one of Iyengar NM's studies, patients with TSCC, who had tongue WAT inflammation meantime measured by the existence of CLS, were observed to have increased tumor thickness, vascular invasion, worse DSS and overall survival (OS) [119].

WAT inflammation is demonstrated to be correlated with increased circulating levels of IL-6, insulin resistance(IR), altered levels of adipokines and increased levels of aromatase, the rate-limiting enzyme for estrogen biosynthesis [116,120]. Avilés-Jurado FX's study showed that HNC patients with high IR levels had lower disease-free survival rates than those with low IR levels [121]. The HNC tumor cells are dependent on glucose for energy production, thus, a higher supply of glucose and/or insulin might promote survival of tumor cells and be related to a poorer outcome [122]. Besides, WAT inflammation could regulate the activation of nuclear factor-κB, a transcription factor that activates the expression of proinflammatory mediators.

3. Conclusion and perspectives

The prevalence of obesity has been pandemic all over the world in recent decades, and several obesity-induced diseases such as cardiovascular disease and diabetes mellitus type 2 have also been a burden on society. At the same time, the incidence of malignancies including HNC has also been growing. Though it's reported that BMI was inversely associated with the risk of HNC and higher BMI could lead to a better outcome in HNC patients, the reverse conclusion that obesity increased the risk of death for TSCC patients has been drawn. Thus, it is suggested that the controversial association between obesity and HNC needs further studies to be clarified in the future.

High-fat diet could bring about obesity and high risks of HNC, and changing life-style appropriately may be able to benefit more than we thought. FAS was significantly correlated with metastatic lymph nodes in OSCC, which could be inhibited by the inhibitor of FAS, orlistat. The relationship of FABP5 and OSCC remained disputatious. Leptin and adiponectin, secreted by adipocytes, were related to HNC in contrast. Decreased circulating adiponectin levels were shown to be correlated with the risk of TSCC, while leptin could impact the recurrence of LSCC and the invasion and metastasis of oral cancer. In spite of no specific preventative or therapeutic approaches about anti-obesity has been used on HNC patients currently, targeting obesity seems to be a promising and novel treatment strategy in the future.

Declaration of Competing Interest

The authors declare no conflict of interest.

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