Lung cancer and obesity: A contentious relationship (Review)

VASILIKI EPAMEINONDAS GEORGAKOPOULOU[1], IOANNIS G. LEMPESIS[2], NIKOLAOS TRAKAS[3], PAGONA SKLAPANI[3], YUTONG HE[4] and DEMETRIOS A. SPANDIDOS[5]

[1]Department of Pathophysiology, Laiko General Hospital, National and Kapodistrian University of Athens, Athens 11527, Greece; [2]Medical Chronobiology Program, Division of Sleep Medicine and Circadian Disorders, Department of Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, MA 02115, USA; [3]Department of Biochemistry, Sismanogleio Hospital, Athens 15126, Greece; [4]Cancer Institute, The Fourth Hospital of Hebei Medical University, Shijiazhuang, Hebei 050010, P.R. China; [5]Laboratory of Clinical Virology, School of Medicine, University of Crete, Heraklion 71003, Greece

Received April 8, 2024; Accepted September 25, 2024

DOI: 10.3892/or.2024.8817

Abstract. The global obesity epidemic, attributed to sedentary lifestyles, unhealthy diets, genetics and environmental factors, has led to over 1.9 billion adults being classified as overweight and 650 million living with obesity. Despite advancements in early detection and treatment, lung cancer prognosis remains poor due to late diagnoses and limited therapies. The obesity paradox challenges conventional thinking by suggesting that individuals with obesity and certain diseases, including cancer, may have an improved prognosis compared with their counterparts of a normal weight. This observation has prompted investigations to understand protective mechanisms, including potentially favorable adipokine secretion and metabolic reserves that contribute to tolerating cancer treatments. However, understanding the association between obesity and lung cancer is complex. While smoking is the primary risk factor of lung cancer, obesity may independently impact lung cancer risk, particularly in non-smokers. Adipose tissue dysfunction, including low-grade chronic inflammation, and hormonal changes contribute to lung cancer development and progression. Obesity-related factors may also influence treatment responses and survival outcomes in patients with lung cancer. The impact of obesity on treatment modalities such as chemotherapy, radiotherapy and surgery is still under investigation. Challenges in managing patients with obesity and cancer include increased surgical complexity, higher rates of postoperative complications and limited treatment options due to comorbidities. Targeted interventions aimed at reducing obesity prevalence and promoting healthy lifestyles are crucial for lung cancer prevention. The impact of obesity on lung cancer is multifaceted and requires further research to elucidate the underlying mechanisms and develop personalized interventions for prevention and treatment.

Correspondence to: Dr Vasiliki Epameinondas Georgakopoulou, Department of Pathophysiology, Laiko General Hospital, National and Kapodistrian University of Athens, 17 Agiou Thoma Street, Athens 11527, Greece
E-mail: vaso_georgakopoulou@hotmail.com

Key words: obesity, lung cancer, cancer risk, inflammation, adipose tissue

Contents

1. Introduction

Obesity, defined by an excessive accumulation of body fat, has escalated to epidemic levels globally. Since 1980, its prevalence has more than doubled, affecting >1.9 billion adults worldwide, with 650 million categorized as living with obesity (1). Over a third of the global population is currently classed as overweight or obese, with projections suggesting that by 2030, 38% of adults will be overweight and 20% will suffer from obesity (2). In the US, obesity affects ~35% of adults and 30% of children, with even higher rates in specific subpopulations, such as Hispanic and non-Hispanic Black adults, where obesity prevalence reaches 43 and 48%, respectively (2). In Europe, obesity prevalence in adults increased from 13 to 17% between 1992 and 2005, with projections indicating it could reach 30% by 2015 (2). The economic burden is notable, with obesity-related healthcare costs in the US alone estimated at $190 billion annually, and the risk of type 2 diabetes increasing threefold for overweight individuals and sevenfold for those with obesity (2). Multiple factors, including

sedentary lifestyles, unhealthy dietary patterns, genetic predispositions and environmental conditions, influence this surge in obesity rates (2).

The rising prevalence of obesity has far-reaching implications for public health, as it is associated with an increased risk of various chronic diseases, including cardiovascular disease, diabetes and several types of cancer (2). Among the cancers linked to obesity, lung cancer is particularly concerning given its status as the leading cause of cancer-related mortality globally (3). Lung cancer comprises a diverse group of malignancies originating from the epithelial cells of the lungs, with the primary subtypes being non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC) (4). Despite advances in early detection and therapeutic strategies, lung cancer prognosis remains poor, largely due to late-stage diagnoses and limited treatment options (5).

In the context of lung cancer, the association between obesity and survival rates has produced conflicting findings. While obesity is a well-established risk factor for the development of lung cancer, some studies suggest that patients with obesity who are diagnosed with lung cancer may have improved survival rates, a phenomenon known as the obesity paradox (6-8). The obesity paradox is a term used in medical research to describe the unexpected observation that, in certain populations, being overweight or having obesity is associated with a lower risk of mortality compared with individuals of a normal weight (9). This paradoxical phenomenon challenges the traditional understanding that obesity universally leads to worse health outcomes (9). The concept first gained attention in patients with chronic diseases, particularly cardiovascular disease and chronic kidney disease (9). It has been noticed that overweight or individuals with mild obesity occasionally had improved survival rates compared with those of normal weight within these specific groups (9). The paradox has also been observed in conditions such as heart failure, stroke and diabetes (9).

Several hypotheses have been proposed to explain the mechanisms behind the obesity paradox in cancer. One theory suggests that excess adipose tissue in individuals with obesity may have protective effects through the secretion of adipokines, which possess potential anti-inflammatory and immunomodulatory properties (10). Additionally, patients with obesity may have greater metabolic reserves, allowing them to better tolerate aggressive cancer treatments and withstand the physiological stresses associated with cancer progression (11). Moreover, certain genetic and molecular alterations present in individuals with obesity, such as dysregulation in insulin-like growth factor (IGF) signaling, chronic inflammation, adipokine imbalance, alterations in the PI3K/AKT/mTOR pathway and changes in estrogen metabolism, may influence tumor biology and response to therapy, potentially contributing to observed survival benefits. Additionally, metabolic reprogramming, hypoxia-driven angiogenesis, and obesity-associated epigenetic modifications may further affect the therapeutic outcomes in obese individuals (12,13). However, the intricate interplay between obesity, cancer biology and treatment outcomes is complex and multifaceted, necessitating further research to elucidate the underlying mechanisms.

The aim of the present review is to examine the association between obesity and lung cancer. First, the epidemiological evidence will be presented and the impact of adiposity and related pathophysiological mechanisms on lung cancer development, progression and treatment outcomes will be explored. The mechanisms by which obesity influences treatment modalities and survival will be analyzed, the potential protective mechanisms underlying the obesity paradox will be assessed and the implications for clinical management will be evaluated. Finally, novel directions for future research to improve understanding and address the complexities of the obesity-lung cancer association will be proposed.

2. Impact of obesity on lung cancer

Epidemiological evidence. While the link between obesity and cancer is well-established for several malignancies, such as breast and colorectal cancer, the association with lung cancer is more complex and remains a topic of ongoing research (14).

Body mass index (BMI), a measure of obesity, and the risk of developing lung cancer have both been associated favorably in numerous meta-analyses and cohort studies (15-18). For instance, a meta-analysis found a significant positive association between excess body weight and the risk of lung cancer, particularly among non-smokers and women (15). Furthermore, evidence for an association of BMI with lung cancer was provided by a re-analysis of dose-response meta-analyses of observational studies (16).

Additionally, it appears that factors such as smoking status, sex and histological subtypes have an impact on the association between obesity and lung cancer risk. While smoking remains the primary risk factor for lung cancer, obesity may exert independent effects on lung carcinogenesis, particularly among non-smokers (17). Female ever-smokers seem to have worse outcomes at extreme BMI levels, both underweight and with obesity, compared with male ever-smokers regarding lung cancer (17). Moreover, evidence suggests that obesity may confer a higher risk of developing specific histological subtypes of lung cancer, such as adenocarcinoma, while its impact on other subtypes remains less clear (18).

By contrast, recent studies and meta-analyses have shown that a high BMI is an independent predictor of lower lung cancer risk, improved treatment outcomes and longer overall survival (OS) (17,19,20). While BMI is the most commonly used metric in the studies described in the present review, it does not differentiate between distinct types of adipose tissue with respect to metabolic activity and distribution in different anatomic locations. This is important because different adiposity patterns are associated with different biological effects. For example, visceral fat is more biologically active and is associated with poorer outcomes when compared with subcutaneous fat (21). Additionally, BMI is known to overestimate obesity when there is excess muscle mass and underestimate obesity in patients with cancer (22).

Potential pathophysiological mechanisms. The biological mechanisms underlying the association between obesity and lung cancer risk are multifaceted and presumably involve complex interactions between adipose tissue, systemic inflammation, hormonal dysregulation and metabolic alterations.

Adipose tissue is a dynamic endocrine and metabolic organ secreting various pro-inflammatory cytokines and other adipokines, such as tumor necrosis factor-α (TNF-α),

interleukin-6 (IL-6) and leptin (23). Chronic low-grade inflammation linked to obesity and dysfunctional adipose tissue leads to the promotion of tumorigenesis by creating a pro-inflammatory microenvironment, conducive to cancer initiation and progression (24). Insulin resistance, which includes impaired insulin signaling and hyperinsulinemia, are frequently associated with obesity (25). Insulin and IGF-1 play critical roles in cell proliferation, apoptosis and tumor growth, thereby promoting carcinogenesis in various tissues, including the lungs (26). Obesity impacts sex hormone metabolism, leading to alterations in estrogen and androgen levels, which may contribute to the development of hormone-related cancers, including lung cancer (27). Estrogen, in particular, has been implicated in lung cancer pathogenesis, with evidence suggesting a higher prevalence of estrogen receptor expression in lung tumors among female patients (28). Obesity-induced oxidative stress and associated DNA damage represent additional mechanisms linked to lung cancer development as excess adiposity is associated with increased production of reactive oxygen species and reduced antioxidant defenses, resulting in oxidative damage to DNA and genomic instability, predisposing to malignant transformation (29,30).

3. Obesity and survival with lung cancer

While obesity is commonly associated with an increased risk of developing lung cancer, its impact on patient survival following lung cancer diagnosis is less clear.

Survival disparities in lung cancer and obesity. Survival disparities in lung cancer among individuals with normal weight and obesity represent a complex intersection of biological, behavioral and socioeconomic factors.

One of the key mechanisms linking obesity to poor lung cancer outcomes is chronic inflammation and adipose tissue, which secretes pro-inflammatory cytokines and adipokines, creating a tumor microenvironment (TME) conducive to cancer progression and metastasis (31). This inflammatory milieu can promote tumor growth, angiogenesis and resistance to chemotherapy and immunotherapy, ultimately compromising treatment efficacy and patient survival (31). Moreover, obesity-related comorbidities, such as diabetes, cardiovascular disease and obstructive sleep apnea, further complicate lung cancer management. These conditions increase the risk of surgical complications and treatment toxicities but also contribute to poorer overall health outcomes and decreased survival rates among patients with obesity and lung cancer (32,33).

In addition to biological factors, behavioral and lifestyle factors associated with obesity may also influence lung cancer survival. Individuals with obesity are more likely to have unhealthy habits such as sedentary lifestyles, poor nutrition and smoke, all of which can exacerbate cancer-related complications and hinder treatment adherence and effectiveness (34). Furthermore, social determinants of health, including access to healthcare, socioeconomic status and healthcare disparities, may disproportionately affect individuals with obesity, limiting their ability to receive timely and appropriate cancer care (35).

Different histological subtypes and survival from lung cancer in patients with obesity

NSCLC. Barbi *et al* (12) analyzed 513 patients with stage I and II NSCLC undergoing lobectomy, revealing that a high visceral fat index (VFI) was associated with decreased recurrence-free survival (RFS) and OS. Specifically, patients in the top VFI tertile exhibited significantly worse outcomes compared with those in the bottom tertile, with hazard ratios (HR) of 1.79 for RFS and 1.84 for OS. The study also explored the TME in 159 patients with advanced-stage NSCLC, finding that high VFI was associated with a non-inflamed TME, characterized by reduced expression of immune-related genes, which likely contributed to poorer survival.

In a study by Xiong *et al* (36) involving 554 patients with advanced NSCLC from the ALTER-0302 and ALTER-0303 trials, researchers investigated the impact of obesity on outcomes in patients receiving anlotinib, a novel anti-angiogenesis drug. The patients were categorized into non-obesity (BMI <28 kg/m^2) and obesity (BMI ≥28 kg/m^2) subgroups. The results indicated a U-shaped relationship between BMI and the risk of death in patients treated with anlotinib. Specifically, patients with obesity had a trend toward worse OS compared with patients without obesity, with a HR of 2.33 (95% CI, 0.77-7.06; P=0.136). This finding suggests that obesity may predict poorer outcomes in patients receiving anlotinib for advanced NSCLC.

In a study by Nitsche *et al* (37) of 994 patients with NSCLC treated between 2008 and 2020, visceral obesity was measured using cross-sectional abdominal fat areas from computerized tomography (CT) scans. The VFI, defined as the ratio of visceral fat area to total fat area, was used to assess visceral obesity. The study found that male patients had significantly higher VFI compared with female patients, and VFI was modestly correlated with age but not with BMI. Furthermore, a subset of 175 patients had their tumors profiled for the expression of 397 cancer- and immunity-related genes, revealing that higher VFI was associated with a lower tumor immunogenicity signature score, which correlates with reduced immune response in tumors. This suggests that visceral obesity may attenuate the tumor immune environment, potentially leading to poorer outcomes in patients with NSCLC.

SCLC. In a study by Lee *et al* (38) conducted on 173 patients with SCLC, researchers investigated the impact of BMI on OS. The patients were divided into two groups based on their BMI: i) individuals with a BMI ≥23; and ii) individuals with a BMI <23. The study found that patients with a BMI ≥23 had significantly improved OS compared with those with BMI <23, with a median OS of 620.0 days vs. 311.7 days, respectively (P<0.001). Multivariate Cox analysis further indicated that a BMI ≥23 was an independent prognostic factor for OS, with a HR of 0.45 (95% CI, 0.31-0.79; P=0.004). Additionally, patients with an improved performance status (PS; ≤2) and a BMI ≥23 had the longest median OS of 17.3 months, suggesting a potential protective effect of higher BMI in SCLC.

In a retrospective study by Kwon *et al* (39) involving 1,146 Asian patients with SCLC who underwent platinum-etoposide chemotherapy, researchers investigated the prognostic significance of BMI and its association with skeletal muscle status. The study found that being underweight (BMI <18.5 kg/m^2) was associated with significantly shorter OS in both limited-disease

(LD) and extensive-disease (ED) groups, with HRs of 1.77 (95% CI, 1.01-3.09) and 1.71 (95% CI, 1.18-2.48), respectively. The negative impact of being underweight remained significant even after adjusting for skeletal muscle index and skeletal muscle attenuation, with underweight patients in the LD group having a HR of 1.96 (95% CI, 1.09-3.51) and in the ED group having a HR of 1.75 (95% CI, 1.17-2.61). This study highlights that being underweight is an independent poor prognostic factor in SCLC, irrespective of skeletal muscle status.

Obesity paradox: An intriguing phenomenon. Obesity has traditionally been viewed as a risk factor for poor prognosis in cancer, including lung cancer (40). However, emerging evidence suggests that patients with obesity may exhibit improved survival rates following a lung cancer diagnosis, a phenomenon known as the obesity paradox (9). This unexpected observation has fueled debate and led to further research into the mechanisms behind this paradox in cancer.

The mechanisms underlying the obesity paradox in lung cancer survival are likely driven by complex interactions between adipose tissue biology, systemic inflammation, metabolic alterations, treatment responses and tumor biology (41). One potential explanation is that patients with obesity often have greater metabolic reserves and nutritional stores than their normal-weight counterparts (41). These reserves may provide a survival advantage during cancer treatment (41). Specifically, the enhanced energy stores and nutrients can help patients with obesity endure the physiological stresses associated with cancer progression and aggressive treatments such as surgery, chemotherapy and radiation (431). This ability to withstand such challenges may contribute to the observed improved survival outcomes in patients with obesity (41).

Adipose tissue also plays a crucial role in modulating the TME and immune responses through the secretion of various adipokines and inflammatory mediators. For instance, adiponectin, an adipokine, exhibits anti-inflammatory and anti-tumor properties, whereas leptin, another adipokine, may promote tumor growth and metastasis (42). The regulation of these functions depends on multiple factors, including the type of adipokines secreted, the local tissue environment and systemic metabolic conditions (43). Leptin promotes cancer by enhancing cell proliferation, migration and angiogenesis, and regulation involves controlling leptin levels and signaling pathways (43). High levels of leptin can activate oncogenic pathways such as JAK/STAT, PI3K/AKT and MAPK (43). Adiponectin usually suppresses cancer by inhibiting cell proliferation and inducing apoptosis. Increasing adiponectin levels or mimicking its activity through drugs can enhance its cancer-suppressive effects (43). It works through pathways such as AMPK and PPARα, which inhibit cancer cell growth and promote apoptosis (43).

Chronic inflammation associated with obesity can promote cancer (44). Reducing systemic inflammation through lifestyle changes (such as diet and exercise) or pharmacological interventions (such as anti-inflammatory drugs) can help tilt the balance towards cancer suppression (44). In addition, obesity alters immune cell function. For example, macrophages in obese adipose tissue often exhibit a pro-inflammatory phenotype (M1) that promotes cancer (44). Promoting the anti-inflammatory (M2) phenotype of macrophages can help suppress cancer (44).

The balance between pro-inflammatory and anti-inflammatory signals within the TME may significantly impact disease progression and treatment responses, ultimately influencing survival outcomes (45). Obesity-related metabolic alterations and molecular pathways also play a role in tumor biology and treatment responses. For instance, obesity is linked to changes in insulin signaling, sex hormone metabolism and oxidative stress pathways, all of which may modulate tumor growth, angiogenesis and metastasis (45). Furthermore, obesity-related molecular alterations, such as mutations in oncogenes or tumor suppressor genes, may impart distinct biological characteristics to tumors, affecting their response to therapy and overall prognosis (46).

Insulin resistance and hyperinsulinemia, which are common in patients with obesity, are linked to cancer development through multiple mechanisms. Elevated insulin levels can directly promote cell proliferation by activating insulin and IGF receptors, leading to enhanced signaling through pathways such as PI3K/AKT and MAPK, which are critical for cancer cell growth and survival (47). Additionally, hyperinsulinemia can lower sex hormone-binding globulin (SHBG) levels, increasing free sex hormones that drive hormone-sensitive cancers such as breast and prostate cancer (47). The chronic low-grade inflammation often associated with insulin resistance further contributes to a pro-tumorigenic environment, enhancing the risk of cancer development in individuals with obesity (47).

The mechanisms underlying the obesity paradox in lung cancer are briefly illustrated in Fig. 1. Evidence from several studies indicate the existence of the obesity paradox in lung cancer. In the study by Lee *et al* (38) involving 820 Asian patients with advanced NSCLC undergoing immune checkpoint inhibitor (ICI) therapy, it was found that those with a BMI ≥25 kg/m^2 had significantly improved OS compared with those with a normal BMI. Specifically, the obesity BMI group had a HR of 0.64 for OS, indicating a 36% lower risk of death compared with those with a normal BMI, independent of clinical covariates such as skeletal muscle and visceral fat indices (38).

The study conducted by Lam *et al* (46) investigated the obesity paradox in patients with locally advanced NSCLC who were treated with definitive chemoradiotherapy. The analysis included 291 patients, stratified by BMI into underweight, normal weight, overweight and obese categories. The findings demonstrated that a higher BMI was associated with improved OS. Specifically, patients with obesity had a 34% lower risk of mortality compared with those of a normal weight, even after adjusting for multiple variables such as age, stage, smoking history and PS. The study also observed that statin use, which was more common among patients with obesity, was independently associated with improved survival (46).

Addressing potential confounding factors and biases is crucial in studies examining the obesity paradox, a phenomenon where overweight or individuals with obesity appear to have improved outcomes in certain diseases compared with those with a normal weight, as it challenges conventional understanding of the health impacts of obesity. Confounding factors such as age, smoking status, pre-existing conditions

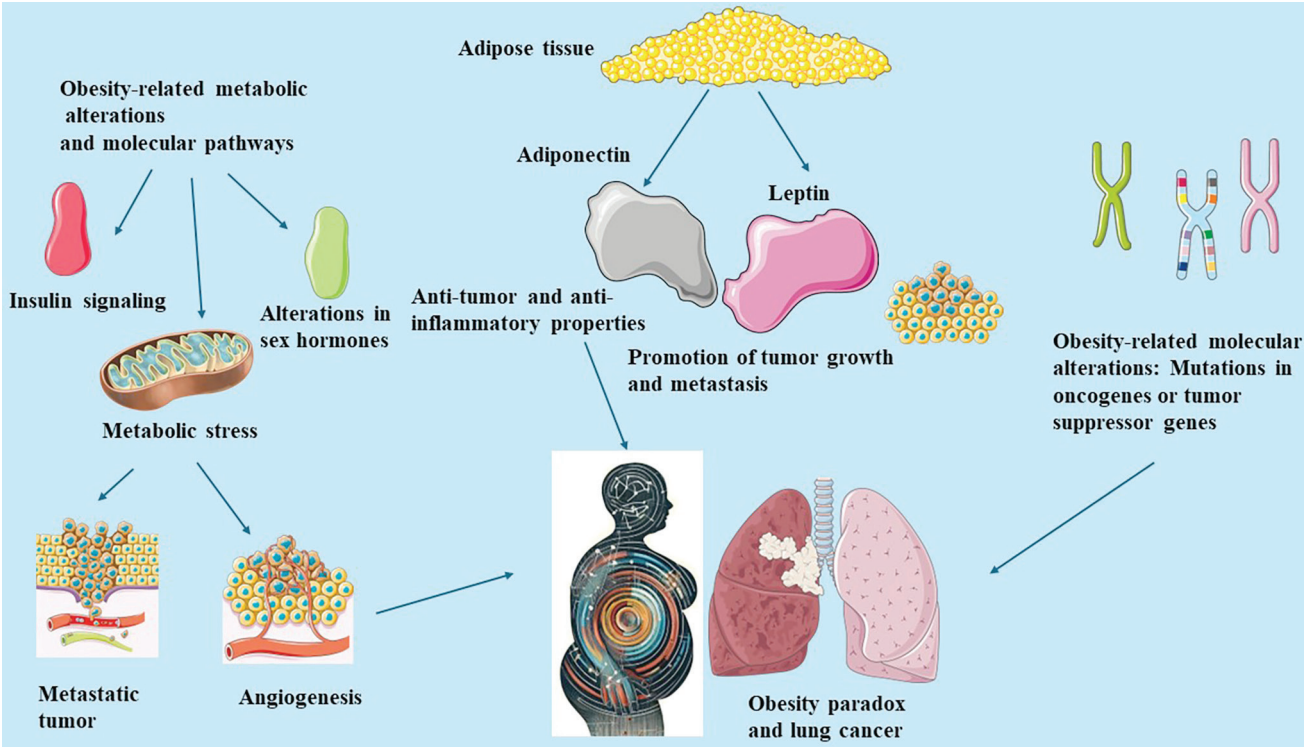

Figure 1. Mechanisms underlying the obesity paradox in lung cancer. Parts of this image derived from the free medical site, Servier (http://smart.servier.com/), licensed under a Creative Commons Attribution 3.0 Unported License.

and physical fitness play significant roles in influencing outcomes. For instance, older adults may exhibit the paradox due to survival bias, while smokers, who often have lower body weight but higher mortality rates, may skew results if not properly adjusted for (15). Additionally, chronic diseases can confound the association between obesity and outcomes, and physical fitness may independently affect health outcomes regardless of weight (15). Biases, including survivor bias, reverse causation, measurement bias and selection bias, also need to be carefully managed. Survivor bias may occur if studies only include those who have lived long enough to be part of the study, potentially excluding those who died earlier due to obesity-related complications (15). Reverse causation can mislead results when weight loss from illness is mistaken for a naturally lower weight (38). Measurement bias arises from the method by which obesity is assessed, such as using BMI, which does not distinguish between fat and muscle mass (38). Finally, selection bias can occur if studies disproportionately include certain subgroups, such as hospitalized patients, who may not represent the general population (38,48). Managing these confounders and biases is essential for accurately interpreting the obesity paradox and its implications for health outcomes (15,38,48).

There is evidence suggesting an obesity paradox in patients with renal cell carcinoma (RCC), the most prevalent type of kidney cancer, accounting for 2.4% of all adult cancers (49). While adiposity is a notable risk factor for RCC, it may also enhance prognosis (49). The increased incidence of RCC is considered to result from insulin resistance and elevated levels of IGF-1, which suppresses Bcl-2 to reduce apoptosis while promoting proliferative and angiogenic factors (50). Improved prognosis in patients with obesity may be due to similar factors as in lung cancer, such as BMI categorization and changes in the tumor immune microenvironment, with higher levels of IL-6, TNF-α and c-peptide observed in patients with obesity (51). Several studies have indicated improved OS and progression-free survival in RCC patients with obesity (52), including those with metastatic disease (53) and those who underwent nephrectomy (54,55). Patients with obesity also tend to have improved outcomes and longer OS when treated with anti-VEGF therapies such as sunitinib, sorafenib, bevacizumab and axitinib (56,57). This suggests a clear obesity paradox in RCC when patients receive immunotherapy.

Similar to NSCLC and RCC, patients with melanoma and obesity treated with immunotherapy generally experience increased survival and an improved response to checkpoint inhibitors compared with their normal-weight counterparts (58). Patients with obesity show more robust responses to ICIs and have higher OS (59). They also exhibit significantly improved responses to treatments such as dabrafenib, ipilimumab, trametinib, the BRAF inhibitor vemurafenib and PD-1 therapies (60,61). In an experimental study, mice with obesity and melanoma treated with PD-1 therapy showed improved responses than normal-weight mice (62). Thus, an obesity paradox is evident in patients with melanoma treated with immunotherapy.

Impact of timing of obesity. It has been shown that pre-diagnostic obesity can offer a metabolic reserve during cancer treatment, potentially improving outcomes (63). For instance, an early study involving 262 patients with SCLC found that obesity at the start of treatment was not associated with increased toxicity or shortened survival, suggesting that pre-diagnostic obesity may not negatively impact treatment outcomes (63).

This metabolic reserve can help patients tolerate aggressive cancer treatments better than their lean counterparts (63).

A previous retrospective study, which included 200 patients with lung cancer, found that a decrease in BMI during chemotherapy cycles was associated with poor survival (64). This indicates that weight loss and the onset of cachexia after diagnosis can significantly worsen outcomes (64).

Another study analyzed data from 25,430 patients with NSCLC and 2,787 patients with SCLC to explore the impact of BMI on lung cancer outcomes. The results revealed a U-shaped relationship between BMI and NSCLC survival, whereby underweight and morbidly obese patients had worse prognosis, while overweight and patients with obesity had improved survival. A similar but non-significant pattern was observed in SCLC. Additionally, a decrease in BMI from young adulthood to diagnosis was linked to poorer outcomes in both NSCLC and SCLC. Thus, being underweight or morbidly obese at diagnosis and a decreasing BMI from early adulthood are associated with lower survival in patients with lung cancer (65).

In addition, another study investigated the impact of pre-surgery BMI and muscle mass on survival after major lung resection for NSCLC. In a retrospective analysis of 304 patients, 7.6% were underweight, 51.6% were normal weight, 28.6% were overweight and 12.6% had obesity. Weight loss and gain were observed in 5 and 44.4% of patients, respectively. Low muscle mass was more common in patients with BMI <25 kg/m^2. Higher pre-disease and pre-surgery BMI were associated with improved OS, especially with weight gain. Low muscle mass and weight loss negatively affected outcomes. Multivariable models confirmed the prognostic value of higher pre-disease and pre-surgery BMI and the absence of low muscle mass (66).

Impact of demographics. The study by Jiang *et al* (67) evaluated the impact of sex, smoking and ethnicity on the association between BMI and OS in NSCLC using pooled data from 16 ILCCO studies. Among 20,937 patients with NSCLC, the effect of BMI on survival varied by ethnicity. Specifically, underweight white patients had poorer survival compared with black patients, and overweight/obese black patients had improved OS compared with white patients. BMI was least associated with survival in Asian patients and never-smokers. Female ever-smokers had worse outcomes at extreme BMI levels, both underweight and with obesity, compared with male ever-smokers. Thus, the association of BMI with NSCLC prognosis differs by sex, smoking status and ethnicity, with black patients having more favorable outcomes at extreme BMI levels compared with white patients, and these associations were not observed in Asian patients and never-smokers (67).

The study by Bethea *et al* (68) analyzed data from the Black Women's Health Study to investigate the association between BMI and lung cancer risk in African American women. Among 59,000 participants, 323 lung cancer cases were identified from 1995 to 2011. Higher BMI (≥30) was associated with a lower risk of lung cancer compared with normal weight individuals (BMI, 18.5-24.9), with a HR of 0.69. This inverse relationship was particularly notable among current smokers (HR, 0.62). Adjusting for smoking and other factors did not significantly alter the results. Waist circumference and waist/hip ratio were not associated with lung cancer risk. The findings suggest that high BMI may lower lung cancer risk in African American women, especially among smokers (68).

The study by Kim *et al* (69) evaluated the associations between sex-specific incidence of EGFR mutations in lung adenocarcinoma and factors such as age and obesity, using data from 1,378 cases. Obesity was categorized by BMI. In men, EGFR mutation incidence was inversely associated with age [adjusted odds ratio (OR), 0.76; P-trend=0.003] and positively associated with obesity (adjusted OR, 1.23; P-trend=0.04). In women, EGFR mutation incidence was positively associated with age (adjusted OR, 1.19; P-trend=0.02) but not significantly associated with obesity (adjusted OR, 1.03; P-trend=0.76). These findings suggest that age and obesity may influence the sex-specific incidence of EGFR mutations in lung adenocarcinoma differently (69).

Obesity and the immune system. The persistent low-grade inflammation associated with obesity and the diverse effects of adipokines on the immune system have been linked to the development of various inflammatory conditions, including rheumatic autoimmune and inflammatory diseases (70). Obesity disrupts multiple aspects of the immune system, including the integrity of lymphoid tissues, the development and function of leukocytes, the activation of the complement system, and the coordination of innate and adaptive immune responses (71). Consequently, obesity leads to a less effective immune response to infectious agents (71).

Targeting adipose tissue-tumor crosstalk mediators. Therapy resistance in tumor cells is often linked to a metabolic switch from glycolytic to lipid metabolism, highlighting the clinical importance of enzymes regulating these metabolic pathways (72-79). These enzymes are being explored as targets for novel antitumor therapies, either as standalone treatments or as chemotherapy adjuncts for therapy-resistant patients (72-79).

Fatty acid synthase (FASN) is a key focus in antitumor therapy. First-generation FASN-targeting drugs such as cerulenin, C75 and Orlistat showed promising preclinical results by reducing tumor xenograft growth but faced clinical challenges due to side effects such as anorexia and weight loss (80). Newer FASN inhibitors, such as TVB-3166 and TVB-2640, have shown effective antitumoral potential in preclinical colorectal and breast cancer models and improved tolerability in clinical trials (81). Given the link between FASN expression and HER-2 signaling, FASN-targeting therapies could help stratify patients based on their response to standard chemotherapy (82). Additionally, combining FASN inhibition with standard chemotherapy has been successful in treating therapy-resistant ovarian cancer *in vitro* and *in vivo* (82-84).

Cancer-associated adipocytes (CAAs) play an immunomodulatory role during cancer progression and are a promising therapeutic target to enhance immunotherapy (85). Strategies include directly interfering with adipocytes or blocking signals derived from CAAs (85). However, targeting CAAs is challenging due to the loss of adipocyte-specific markers and the risk of affecting healthy organs (85). Indirect targeting, such as inhibiting CD36 fatty acid transport proteins, has shown promise. In breast cancer, CD36 inhibition decreased intratumoral Tregs and increased antitumoral T cells, and combining

the CD36 monoclonal antibody with anti-PD-1 therapy enhanced antitumor activity (86). CD36, a transmembrane glycoprotein involved in fatty acid uptake and angiogenesis, is highly expressed in ovarian cancer cells co-cultured with adipocytes, leading to increased fatty acid uptake (87). CD36 inhibition reduced tumor growth *in vivo*, suggesting its potential as a therapeutic target to limit tumor aggressiveness (87).

PPARγ is a key regulator of glucose homeostasis and can upregulate tumor suppressor genes such as BRCA1 and PTEN (88,89). PPARγ antagonists, such as GW9662, have been proposed to target the crosstalk between adipocytes and cancer stem cells (88,89). GW9662 sensitized ER-responsive tumors to fulvestrant therapy in mice and inhibited bladder cell proliferation and tumor growth (88,89).

Exosomes delivering miRNA offer a promising therapeutic strategy for cancer treatment. miRNAs are stable and can regulate cell proliferation, differentiation and chemosensitivity (90). In hepatocarcinoma, downregulation of miRNA-122 is associated with poor prognosis, and miRNA-122-enriched exosomes from adipocytes can sensitize hepatocarcinoma to sorafenib treatment (90). In ovarian cancer, miRNA-121 in exosomes from CAAs induced chemoresistance to paclitaxel by downregulating APAF1. Therefore, targeting miRNA-121 or upregulating APAF-1 could reduce chemoresistance (91).

Lactate, a metabolite released in the TME, represents a therapeutic target for inhibiting CAA-mediated immunosuppression (92,93). Inhibiting lactate dehydrogenase, which converts pyruvate to lactate, has also been shown to regress NSCLC tumors and activate the immune system (92,93). Overall, targeting adipocytes, CAAs, and their adipokines and metabolites presents a promising strategy for cancer treatment.

Obesity and paraneoplastic syndromes of lung cancer. Acanthosis nigricans (AN) is a rare paraneoplastic syndrome associated with lung cancer (94). In the majority of cases, AN reflects metabolic disturbances associated with obesity, metabolic syndrome, diabetes or medications such as insulin, glucocorticoids, oral contraceptives and antipsychotics (94). The most common histologic cancer type associated with AN is adenocarcinoma, generally involving the gastrointestinal system, and less commonly, paraneoplastic AN is associated with NSCLC (94). AN is characterized by gray-brown hyperpigmented, velvety plaques that often affect the neck, flexor area, and anogenital regions (94).

4. Impact of obesity on anti-tumor therapies

Obesity is a complex metabolic condition associated with various physiological and molecular alterations that can influence the efficacy and safety of anti-tumor therapies.

Surgery. Surgery plays a critical role in the management of early-stage and operable cancers, offering the potential for curative treatment and long-term survival (95). However, obesity-related physiological changes and technical challenges can complicate surgical procedures and impact postoperative outcomes in patients with cancer and obesity (96). Obesity is associated with increased surgical complexity, longer operative times and higher rates of intraoperative complications, such as wound infections, bleeding and anastomotic leaks (97). Surgical teams may encounter technical challenges related to patient positioning, access to surgical sites and tissue manipulation, requiring specialized equipment and expertise to ensure safe and effective surgical outcomes (97). Furthermore, patients with obesity undergoing cancer surgery are at a higher risk of postoperative complications, including surgical site infections, pulmonary complications (such as atelectasis and pneumonia), venous thromboembolism (VTE) and delayed wound healing (89-100). Obesity-related factors, such as impaired tissue perfusion, compromised wound healing and reduced respiratory function, contribute to increased morbidity and mortality rates in surgical patients with obesity (98-100).

Preoperative optimization of patients with obesity undergoing cancer surgery is essential to mitigate postoperative complications, with current protocols emphasizing weight reduction, glycemic control and tailored nutritional interventions (101). Enhanced Recovery After Surgery protocols, which include strategies such as multimodal pain management, early mobilization and specific anesthetic techniques, have been particularly effective in reducing complications and shortening recovery times in this population (101). Additionally, VTE prophylaxis, incorporating both mechanical and pharmacological methods, is critical given the heightened risk in patients with obesity (101).

While obesity is generally associated with poorer long-term survival in patients with cancer, the impact of obesity on surgical outcomes and survival following cancer surgery varies across tumor types and patient populations. Studies investigating the association between obesity and long-term survival in surgically treated patients with cancer have produced conflicting results, highlighting the need for further research to clarify the association between obesity, surgery and cancer outcomes (102,103).

A study by Tong *et al* (104) examined the association between obesity and perioperative outcomes in elderly patients undergoing thoracoscopic anatomic lung cancer surgery at Shanghai Chest Hospital (Shanghai, China). Among 4,164 patients aged 65 or older, those categorized as having obesity showed higher rates of intraoperative hypoxemia (3.9 vs. 1.2%; P=0.001) and new-onset arrhythmia (4.3 vs. 2.3%; P=0.034) compared with nonobese patients. However, other perioperative outcomes, such as pulmonary complications and hospital stay, were not significantly different between the groups (P>0.05). The study supports the obesity paradox, suggesting that obesity should not preclude elderly patients from undergoing thoracoscopic anatomic lung cancer surgery (104).

The study by Guerrera *et al* (105) assessed the impact of morbid obesity on perioperative clinical and oncological outcomes following video-assisted thoracic surgery (VATS) lobectomy using data from the Italian VATS lobectomy Registry, which included 4,412 patients from 55 institutions between 2016 and 2019. Among the patients, 74 (1.7%) had morbid obesity. Multivariable-adjusted analysis indicated that morbid obesity was associated with a higher rate of complications (32.8 vs. 20.3%), but not with increased conversion to thoracotomy, surgical margin positivity, surgical time, lymph-node retrieval, intraoperative blood loss, hospital postoperative length of stay or chest tube duration. The most frequent postoperative complications in morbidly obese patients were pulmonary-related (35%). The study concluded

that VATS lobectomy can be safely and effectively performed in morbidly obese patients, maintaining equivalent short-term oncological outcomes (105).

The study by Lee *et al* (106) assessed the prognostic value of obesity and its link to skeletal muscle mass in patients with lung adenocarcinoma. Data from 636 patients (2011-2015) were analyzed. Obese patients had longer OS than non-obese patients (110.2 vs. 98.7 months; P=0.015). Multivariable Cox regression analysis showed that obesity was associated with longer survival (HR, 0.59; 95% CI, 0.40-0.86; P=0.007), even after adjusting for skeletal muscle mass (HR, 0.57; 95% CI, 0.36-0.89; P=0.014). No significant interaction was found between skeletal muscle mass and BMI on survival. Thus, obesity was linked to improved OS, independent of skeletal muscle mass (106).

The study by Tulinský *et al* (107) evaluated the effect of BMI on short-term outcomes following lung lobectomy. A retrospective comparison was made between obese and non-obese patients who underwent anatomical lung resection for cancer, ensuring both groups had similar risk factors and surgical approaches (thoracoscopy vs. thoracotomy). Among 144 patients (48 obese, 96 non-obese), the frequency of perioperative and postoperative complications did not significantly differ between groups. Non-obese patients had higher postoperative morbidity (34.4% vs. 27.1%), but this was not statistically significant (P=0.053). Hospital stay and postoperative mortality were similar in both groups, while surgery time was slightly longer for patients with obesity (P=0.133). The findings suggest that obesity does not increase the risk of complications after lung lobectomy and may even offer some protective benefits (107).

The study by Seder *et al* (108) compared robotic surgery (RTS) and video-assisted thoracoscopic surgery (VATS) for patients with obesity undergoing lung resection. Data from 8,108 patients revealed that those who underwent VATS were more than five times as likely to convert to thoracotomy than those who underwent RTS (OR, 5.33; 95% CI, 4.14-6.81; P<0.001). Patients that underwent VATS also had longer hospital stays, higher rates of respiratory failure and were less likely to be discharged home. RTS is associated with fewer conversions to thoracotomy and improved perioperative outcomes in patients with obesity (108).

The study by Leonardi *et al* (109) assessed the feasibility and safety of one-lung ventilation in patients with obesity undergoing thoracoscopic lobectomy. Among 111 patients (26 obese, 85 nonobese) treated between October 2019 and February 2022, patients with obesity more frequently used a single-lumen tube with bronchial blocker (81 vs. 19%; P=0.001). Intubation time was longer for patients with obesity (94.0 vs. 85.0 s; P=0.0004), with a higher failure rate on the first attempt (23 vs. 5%; P=0.01). Furthermore, obesity did not increase complications or mortality. The study concludes that one-lung ventilation is safe and feasible in patients with obesity, with no negative impact on outcomes (109).

Chemotherapy. Obesity can lead to changes in drug pharmacokinetics, including alterations in drug absorption, distribution, metabolism and elimination (110). These changes may affect chemotherapy dosing, drug exposure and toxicity profiles, potentially influencing treatment efficacy and tolerability (110). For instance, lipophilic chemotherapeutic agents, such as cisplatin and paclitaxel, may exhibit altered distribution and clearance in individuals with obesity due to changes in adipose tissue composition and blood flow (72). Patients with obesity may require individualized dosing strategies to achieve therapeutic drug levels while minimizing toxicity (111). However, determining optimal dosing regimens for patients with obesity can be challenging due to limited data and variability in pharmacokinetic parameters (111). Clinicians should consider factors such as ideal body weight, actual body weight, body surface area and renal function when calculating chemotherapy doses for patients with obesity, aiming to achieve a balance between efficacy and safety (112).

Obesity-related comorbidities, such as diabetes, hypertension, and cardiovascular disease, may exacerbate chemotherapy-related toxicities and complications, leading to treatment interruptions, dose reductions and poorer outcomes (113). Close monitoring and proactive management of treatment-related toxicities, including hematologic, gastrointestinal and neurotoxic effects, are essential for optimizing treatment adherence and quality of life in patients with obesity undergoing chemotherapy (113).

In the study by Kicken *et al* (114) overweight patients experienced significantly improved OS and PFS compared with normal weight patients, with adjusted HRs for OS at 0.72 (95% CI, 0.59-0.89) and for PFS at 0.74 (95% CI, 0.61-0.90). By contrast, patients with obesity did not demonstrate significant differences in OS or PFS relative to normal weight individuals. However, obesity was linked to a notably higher incidence of severe thrombocytopenia (grade ≥3), with an adjusted OR of 3.47 (95% CI, 1.75-6.90) and more frequent dose reductions due to toxicity, as evidenced by a lower relative dose intensity (RDI); 35% of patients with obesity had an RDI <80% in cycle 1 compared with 17% of normal weight patients. Despite these increased toxicity risks, higher BMI was not significantly associated with greater rates of toxicity-related hospitalization (114).

In the study by Kashiwabara *et al* (115) overweight women with lung cancer and obesity who received carboplatin-paclitaxel doublet chemotherapy were analyzed for overdosing-related toxicity and prognosis. The study found no significant difference in OS or PFS between overweight/obese patients and those with a normal BMI. Specifically, the median OS was 285 days for the BMI >25 group compared with 282 days for the BMI ≤25 group (P=0.820). However, overweight/obese patients experienced a higher incidence of Grade 4 neutropenia during the second cycle (39% in the BMI >25 group vs. 13% in the BMI ≤25 group; P=0.003), leading to more frequent dose reductions. Despite these toxicity concerns, there was no increased risk of hospitalization or other severe toxicities, suggesting that appropriate dose adjustments can mitigate the risks of overdosing in this population (115).

Immunotherapy. Immunotherapy, particularly ICIs, has revolutionized cancer treatment by harnessing the immune system to target and eliminate cancer cells (116). However, obesity-related alterations in immune function and the TME may impact the efficacy and safety of immunotherapy in patients with cancer and obesity (117).

Obesity is associated with chronic low-grade inflammation, immune dysregulation and alterations in immune cell populations, which may impair antitumor immune responses and compromise the efficacy of immunotherapy (118). Additionally, adipose tissue-derived cytokines and adipokines, such as leptin and IL-6, can modulate immune cell function and promote tumor immune evasion, potentially reducing the effectiveness of immunotherapy (118). Clinical studies investigating the impact of obesity on immunotherapy outcomes have yielded conflicting results, with some studies suggesting reduced response rates and shorter survival in patients with obesity, while others report comparable or improved outcomes (119,120).

Obesity-related comorbidities, such as metabolic syndrome and insulin resistance, may increase the risk of immune-related adverse events (irAEs) in patients with obesity receiving immunotherapy. Common irAEs, including dermatitis, colitis, pneumonitis and endocrinopathies, may be more frequent or severe in individuals with obesity, requiring close monitoring and timely intervention to prevent treatment complications and ensure patient safety (121,122).

In the study by Zhang *et al* (123) the impact of BMI on survival outcomes in patients with NSCLC treated with ICIs was investigated through a meta-analysis of nine studies encompassing 4,602 patients. The study found no significant difference in PFS (HR, 0.885; 95% CI, 0.777-1.009; P=0.068) or OS (HR, 0.947; 95% CI, 0.789-1.137; P=0.560) between patients with low BMI and those with high BMI. However, subgroup analysis revealed that overweight or obese patients had significantly prolonged PFS (HR, 0.862; 95% CI, 0.760-0.978; P=0.021) and OS (HR, 0.818; 95% CI, 0.741-0.902; P<0.0001) compared with normal-weight patients (123).

Radiotherapy. Radiotherapy plays a crucial role in the management of localized and locally advanced cancers, including lung cancer, by delivering targeted radiation doses to cancerous tissues while sparing surrounding healthy tissues (124).

Obesity-related anatomical and physiological changes can pose challenges for radiotherapy planning and delivery in patients with obesity (125,126). Obesity can alter patient anatomy and body contour, affecting target delineation, organ-at-risk (OAR) sparing and radiation dose distribution (125,126). Larger body size and increased adipose tissue thickness may result in greater tissue heterogeneity and attenuate radiation beams, potentially compromising treatment accuracy and efficacy (125,126). Advanced radiotherapy techniques, such as intensity-modulated radiotherapy and volumetric modulated arc therapy, may help optimize dose conformality and minimize radiation exposure to OARs in patients with obesity (125,126).

Obesity-related comorbidities, such as diabetes mellitus, arterial hypertension and obstructive sleep apnea, may exacerbate radiotherapy-related toxicities and complications in patients with cancer and obesity (127). Common radiation-induced toxicities, including fatigue, skin reactions, mucositis and radiation pneumonitis, may be more pronounced or occur at higher frequencies in individuals with obesity, necessitating proactive symptom management and supportive care interventions (128).

Patient-specific factors, such as tumor characteristics, treatment compliance and overall health status, may influence treatment outcomes and should be considered when assessing the impact of obesity on radiotherapy efficacy (8).

In the study by Welsh *et al* (129) the impact of obesity on the development of chest wall pain and skin toxicity following thoracic stereotactic body radiation therapy (SBRT) was examined. The study included 265 patients treated with SBRT for lung tumors located within 2.5 cm of the chest wall. It was found that patients with a BMI of 29 or higher had almost twice the risk of developing chronic chest wall pain compared with those with a lower BMI, with an OR of 2.45 (95% CI, 1.24-4.84; P=0.01). Additionally, diabetes mellitus in patients with obesity further increased the risk of severe chest wall pain (129).

5. Deciphering potential pathophysiological mechanisms connecting obesity and lung cancer

Adipose tissue dysfunction in obesity. Obesity is characterized by excess adiposity and dysregulated adipose tissue function, marked by adipocyte hypertrophy, hypoxia, inflammation and altered adipokine secretion (130-139). Adipose tissue dysfunction contributes to systemic metabolic disturbances, insulin resistance, dyslipidemia and chronic low-grade inflammation, which promote the development and progression of obesity-related diseases, including cancer (140).

Due to their presence in white adipose tissue, adipose stromal cells (ASCs) are likely significant contributors to the obesity-cancer link (141). In fact, syngeneic mouse models of melanoma, breast, prostate and lung cancer demonstrated that selectively depleting ASCs with pro-apoptotic peptides inhibits tumor vascularization and proliferation, leading to necrosis (141). Notably, this effect was more pronounced in obese mice compared with lean mice, where ASCs are more abundant (141).

Adipocyte hypertrophy. In obesity, adipocytes undergo hypertrophy and hyperplasia to accommodate excess lipid storage, leading to adipose tissue expansion (142). Enlarged adipocytes experience metabolic stress, increased lipolysis and altered adipokine secretion, contributing to adipose tissue dysfunction and systemic inflammation (142). Moreover, the increased lipolysis observed in enlarged adipocytes contributes to elevated circulating levels of free fatty acids, which can further exacerbate metabolic dysfunction and inflammation. Excess free fatty acids can impair insulin signaling pathways in various tissues, including liver, muscle and adipose tissue, promoting insulin resistance (143). Insulin resistance, a hallmark of obesity and metabolic syndrome, is associated with increased insulin and IGF levels, which can stimulate tumor cell proliferation and survival through activation of the PI3K/Akt/mTOR signaling pathway (143).

Additionally, these fatty acids serve as ligands for Toll-like receptors (TLRs) on immune cells, triggering inflammatory signaling cascades and promoting the secretion of pro-inflammatory cytokines (144). This chronic low-grade inflammation not only perpetuates adipose tissue dysfunction but also contributes to the development of insulin resistance and

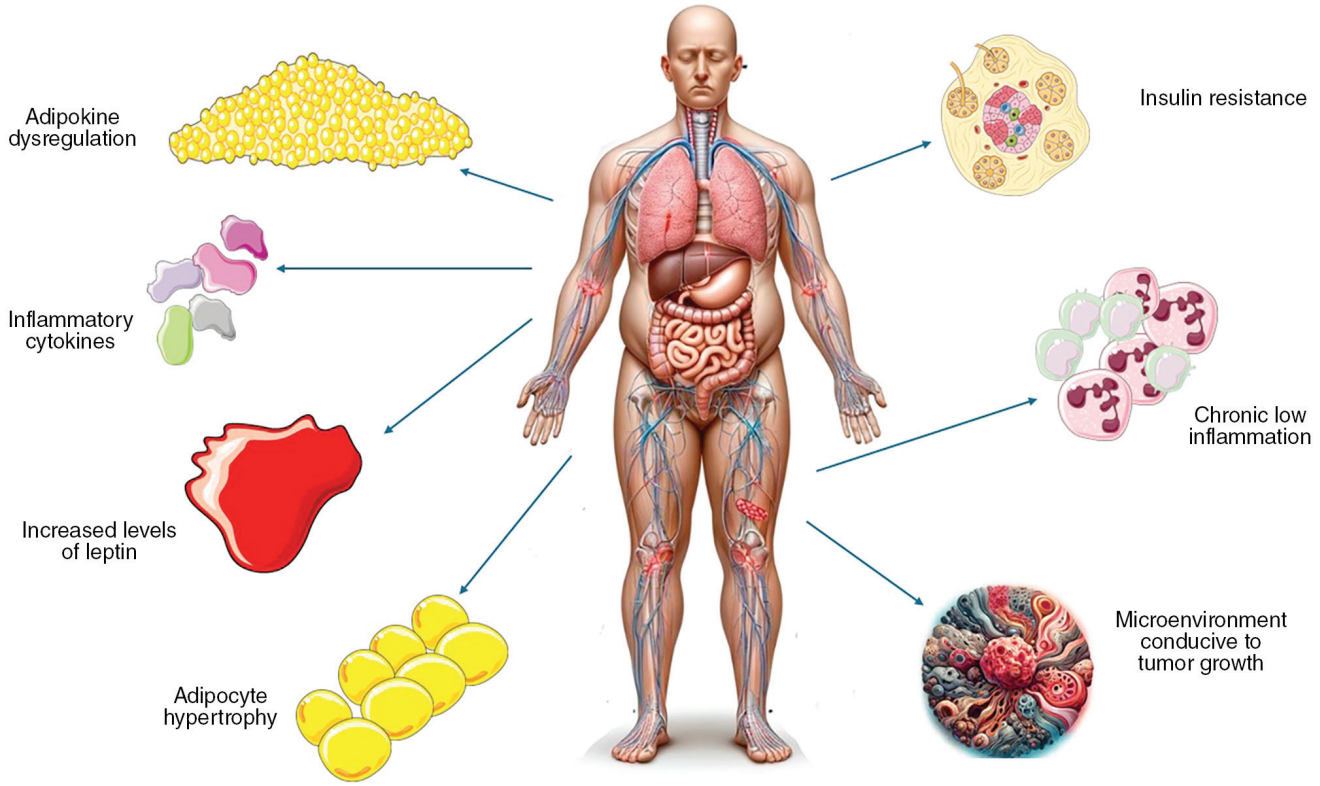

Figure 2. Potential pathophysiological mechanisms connecting obesity and lung cancer. Parts of this image derived from the free medical site, Servier (http://smart.servier.com/), licensed under a Creative Commons Attribution 3.0 Unported License.

metabolic syndrome, linking obesity to systemic metabolic complications (144,145). In lung cancer, inflammation plays a critical role in tumor initiation and promotion (144,145). Chronic inflammation of the lungs, often induced by factors such as smoking or environmental pollutants, can lead to the activation of pro-inflammatory pathways and the recruitment of immune cells to the TME (144,145). TLR activation by fatty acids released from adipose tissue in obesity further amplifies this inflammatory response, fueling tumor progression (144,145).

Hypoxia and inflammation. In the context of lung cancer, the inadequate vascularization and resultant tissue hypoxia associated with adipose tissue expansion in obesity can contribute to the development and progression of the disease (146). Adipose tissue hypoxia is apparent in rodent models of obesity but is still debatable in humans as extensively reviewed elsewhere (146,147). It potentially triggers a cascade of inflammatory responses involving the secretion of pro-inflammatory cytokines and chemokines by hypoxic adipocytes and infiltrating immune cells (147,148). These pro-inflammatory mediators, including TNF-α, IL-6 and monocyte chemoattractant protein-1 (MCP-1), create a microenvironment conducive to tumor growth, invasion and metastasis (147,148). TNF-α and IL-6, for example, are known to promote cancer cell proliferation, survival and angiogenesis, while MCP-1 facilitates the recruitment of pro-tumorigenic immune cells to the tumor site (147,148). The potential pathophysiological mechanisms connecting obesity and lung cancer are briefly illustrated in Fig. 2.

Adipokine dysregulation. Adipose tissue secretes a diverse array of adipokines, including adiponectin, leptin, resistin, visfatin and inflammatory cytokines, which regulate energy metabolism, appetite, insulin sensitivity and inflammation (148). Dysregulated adipokine secretion in obesity disrupts metabolic homeostasis, promotes insulin resistance and contributes to systemic inflammation, creating a pro-tumorigenic microenvironment conducive to cancer development and progression (31,149). Emerging evidence suggests that obesity-related alterations in adipokine secretion and chronic low-grade inflammation contribute to lung cancer development, progression and treatment outcomes (150).

Adiponectin, an adipokine with anti-inflammatory, anti-tumorigenic and insulin-sensitizing properties, is inversely associated with obesity and insulin resistance (149). Adiponectin exerts anti-proliferative and pro-apoptotic effects on lung cancer cells through AMPK activation and inhibition of the PI3K/Akt/mTOR signaling pathway, suggesting a protective role against lung tumorigenesis (149-161). Reduced circulating levels of adiponectin in obesity may contribute to increased cancer risk and poorer outcomes in patients with lung cancer (160).

Leptin, a hormone that adipocytes primarily secrete, controls inflammation, appetite and energy balance (154). Elevated circulating levels of leptin in obesity are associated with leptin resistance, chronic inflammation and increased cancer risk (154-157). Leptin promotes lung cancer cell proliferation, migration and invasion through the activation of the JAK/STAT, MAPK/ERK and PI3K/Akt signaling pathways, fostering tumor growth and metastasis (154-157).

6. Metabolically healthy obesity, sarcopenia, cachexia, unhealthy lean, body fat distribution and lung cancer

Beyond body weight alone, there are a number of other factors that affect the complex association between obesity and lung cancer.

Metabolically healthy obesity. Not all individuals with obesity are metabolically unhealthy (158). Metabolically healthy obesity (MHO) is distinguished by the lack of typical metabolic irregularities linked with obesity, including insulin resistance, dyslipidemia and hypertension (158). Despite excess adiposity, individuals with MHO have preserved insulin sensitivity, favorable lipid profiles and lower cardiovascular risk compared with metabolically unhealthy obese individuals (158,159). The presence of individuals with MHO in the obesity population adds complexity to understanding the association between obesity and lung cancer, as MHO individuals may have different cancer risk profiles and treatment responses compared with their metabolically unhealthy counterparts (160,161).

The study by Shao *et al* (160) on MHO within a cohort of 450,482 UK Biobank participants reveals that individuals with MHO have a significantly lower risk of developing lung cancer compared with metabolically unhealthy individuals. Specifically, MHO individuals were found to have a 24% reduced risk of lung cancer compared with metabolically healthy normal-weight individuals. This suggests that despite the excess body weight, metabolic health plays a protective role in cancer risk (160).

A systematic review and meta-analysis found that while obesity typically correlates with higher cancer risks and adverse outcomes, individuals with MHO exhibit a distinct risk profile. Specifically, the study observed that individuals with MHO tend to have a lower risk of metastasis and reduced rates of surgical complications compared with their metabolically unhealthy counterparts (161).

Sarcopenia. Sarcopenia, characterized by the loss of skeletal muscle mass and function, is increasingly recognized as a significant prognostic factor in patients with lung cancer (162). This condition, often associated with aging and chronic illness, can profoundly impact treatment tolerance, response to therapy and OS rates (162). Sarcopenia is frequently present in patients with lung cancer at the time of diagnosis, and cancer-related cachexia, a multifactorial syndrome characterized by involuntary weight loss, muscle wasting and systemic inflammation, exacerbates it (163-165). The presence of sarcopenia in patients with lung cancer has been linked to several adverse outcomes, including increased treatment-related toxicities, higher rates of treatment interruptions or dose reductions and poorer surgical outcomes (163-165).

Furthermore, sarcopenia can impact treatment response and tolerance in patients with lung cancer. Chemotherapy, radiation therapy and surgical interventions place significant physiological stress on the body, exacerbating muscle wasting and compromising functional status (166,167). Reduced muscle mass and strength may limit the ability of patients to tolerate aggressive treatment regimens, leading to treatment delays, dose reductions or early treatment discontinuation, which can ultimately impact survival outcomes (166,167).

Cachexia. Cachexia is a multifactorial syndrome characterized by unintentional weight loss, muscle wasting, anorexia and metabolic abnormalities commonly observed in patients with advanced cancer (168). Cachexia is associated with increased morbidity, treatment complications and reduced quality of life, contributing to poor treatment outcomes and shortened survival in patients with cancer (168,169). The presence of cachexia complicates the management of lung cancer, as it may limit treatment options, compromise treatment efficacy and exacerbate treatment-related toxicities, underscoring the need for early recognition and intervention in cachectic patients with cancer (169).

Unhealthy lean phenotype. While obesity is traditionally associated with increased cancer risk and a poor prognosis, the unhealthy lean phenotype, characterized by low muscle mass, a high body fat percentage and metabolic abnormalities, may also confer elevated cancer risk and inferior outcomes (170). Unhealthy lean individuals, particularly those with visceral adiposity and metabolic dysfunction, may exhibit similar cancer risk profiles and treatment responses to individuals with obesity, highlighting the importance of considering both adiposity and muscle mass when evaluating cancer risk and prognosis (170).

Body fat distribution. Body fat distribution, particularly abdominal obesity, plays a critical role in cancer development and progression (171). Abdominal obesity is associated with visceral adiposity and metabolic dysfunction, characterized by increased levels of pro-inflammatory cytokines, adipokines and insulin resistance (171). Visceral adipose tissue secretes bioactive molecules that promote tumor growth, angiogenesis and metastasis, contributing to the development of aggressive cancer phenotypes, including lung cancer (171). Abdominal obesity may also influence treatment responses and survival outcomes in patients with lung cancer, highlighting the importance of assessing body fat distribution in addition to overall adiposity when evaluating cancer risk and prognosis (172).

It should be noted that BMI is not an ideal indicator of obesity, as it does not accurately represent body composition (173). Consequently, studies have sought to identify body composition parameters that more accurately reflect obesity. Previous studies have investigated the association between treatment outcomes and body composition parameters obtained through CT or positron emission tomography CT in patients with NSCLC treated with ICIs (174,175). One study, for example, examined the association between measures of skeletal muscle mass and adiposity (including intramuscular, visceral and subcutaneous adipose tissue) and changes during treatment, focusing on disease progression and OS in patients with advanced lung cancer receiving immunotherapy (176). This study investigated the association between body composition, specifically skeletal muscle mass and various adipose tissue measures, with disease progression and OS in patients with advanced lung cancer receiving ICIs. The results showed that increases in intramuscular and subcutaneous adipose tissue by 10% were significantly associated

with improved disease-free survival and OS, while skeletal muscle mass and visceral adipose tissue showed no such associations. These findings suggest that changes in specific fat deposits, rather than muscle mass, may predict improved outcomes in patients with lung cancer undergoing immunotherapy. This unexpected result regarding intramuscular fat highlights the need for further research to understand its role in cancer treatment. The study emphasizes the potential for personalized treatment strategies based on body composition changes (176).

7. Other risk factors related to obesity predisposing to lung cancer

Despite the fact that obesity is a recognized major risk factor for numerous cancers, including lung cancer, there are other factors besides adiposity that play a role in this association.

Hormonal dysregulation. Obesity is associated with alterations in sex hormone metabolism, particularly increased estrogen levels and decreased levels of SHBG, leading to estrogen dominance and hormonal imbalances (177). The pivotal role of estrogen in lung cancer pathogenesis cannot be understated, as evidenced by the higher prevalence of estrogen receptor expression in lung tumors among women (178,179). The binding of excess estrogen to these receptors can activate signaling pathways that promote tumor growth and inhibit cell death, creating a conducive environment for lung cancer development (178,179). This effect is magnified by the pro-inflammatory state associated with obesity, further enhancing cancer risk (178,179). This observation underscores the significance of dysregulated sex hormone signaling in promoting the development and progression of lung cancer, especially in hormone-responsive tumors (178,179). Consequently, it is imperative to recognize and account for hormonal factors when assessing the obesity-related cancer risk (178,179).

Lifestyle factors. Obesity often coincides with unhealthy lifestyle factors such as poor diet, physical inactivity and smoking, each of which independently increases lung cancer risk but become particularly dangerous when combined (180). Diets high in calories, processed foods and sugary drinks contribute to obesity by promoting fat accumulation and metabolic dysfunction, leading to insulin resistance and chronic inflammation, which create a favorable environment for cancer development (180). Physical inactivity exacerbates these issues by reducing energy expenditure and worsening inflammation and oxidative stress, further damaging cellular structures and increasing the likelihood of mutations (180). Smoking, a well-established lung cancer risk factor, interacts with the inflammatory and metabolic disturbances caused by obesity, intensifying the effects of carcinogens in tobacco smoke and overwhelming the ability of the body to repair DNA damage (181). Together, these factors create a synergistic effect that significantly amplifies the risk of lung cancer, as the combined impact of metabolic disruption, oxidative stress and direct DNA damage from smoking creates a highly carcinogenic environment (181).

Environmental exposures. Obesity may interact with environmental exposures such as air pollution, occupational hazards and environmental toxins to significantly heighten lung cancer risk (182,183). Airborne pollutants such as particulate matter and polycyclic aromatic hydrocarbons, which are established carcinogens, exert more harmful effects in individuals with obesity because obesity is associated with chronic inflammation and impaired detoxification processes (184,185). The persistent inflammation in individuals with obesity creates a pro-carcinogenic environment, where these pollutants can more easily induce DNA damage and cellular mutations (184,185). Additionally, occupational exposures to carcinogens such as asbestos and diesel exhaust pose an even greater risk for individuals with obesity, as their excess fat tissue can store fat-soluble toxins, prolonging their presence in the body and extending their harmful effects (184,185). This prolonged exposure increases the likelihood of sustained cellular damage, ultimately fostering an environment that is highly conducive to lung cancer development (184,185).

8. Conclusions and future perspectives

Precision medicine. Advances in molecular profiling and genomic sequencing technologies offer unprecedented opportunities for personalized cancer treatment. Integrating obesity-related biomarkers, such as adipokine profiles, metabolic signatures and genetic variants, into molecular diagnostic and prognostic models may improve risk stratification and treatment selection for patients with lung cancer (186).

Immunotherapy and targeted therapies. Immunotherapy and targeted therapies like EGFR inhibitors (such as Erlotinib), ALK inhibitors (such as Crizotinib) and BRAF inhibitors (such as Dabrafenib) have transformed lung cancer treatment (116). Understanding the interplay between obesity, immune dysregulation and tumor immunogenicity is crucial for optimizing the efficacy and safety of immunotherapeutic approaches in patients with cancer and obesity (187).

Lifestyle interventions. Promoting healthy lifestyle behaviors, including weight management, physical activity and balanced nutrition, is essential for cancer prevention and control (188). Public health initiatives targeting obesity prevention and tobacco cessation can reduce modifiable cancer risk factors and improve overall health outcomes in at-risk populations (188).

Multidisciplinary care. Adopting a multidisciplinary approach to cancer care, involving oncologists, surgeons, dietitians, exercise physiologists and mental health professionals, is essential for addressing the complex needs of patients with cancer and obesity (189). Comprehensive supportive care interventions, including nutritional counseling, physical rehabilitation and psychosocial support, can optimize treatment outcomes and enhance quality of life (189,190).

Environmental health. Mitigating environmental risk factors, such as air pollution, occupational hazards and environmental toxins, is crucial for reducing the burden of cancer in high-risk

populations (191). Collaborative efforts between policymakers, healthcare providers and environmental agencies are needed to implement evidence-based interventions and regulations aimed at protecting public health and minimizing cancer risk (191).

Existing public health initiatives aim at reducing obesity and promoting healthy lifestyles, such as sugar-sweetened beverage taxes, school-based nutrition programs, and front-of-pack labeling, have shown varying degrees of effectiveness. For instance, beverage taxes have led to reduced consumption of sugary drinks, which could positively impact obesity rates over time (192). Similarly, school-based programs have improved the dietary habits and physical activity levels of children, although their long-term impact on obesity remains uncertain (193). Front-of-pack labeling has helped consumers make healthier choices, but its overall influence on reducing obesity prevalence depends on broader dietary changes (192,193),

Future perspectives. Future research should focus on identifying biomarkers that can predict how patients with lung cancer and obesity will respond to various treatments, including chemotherapy, immunotherapy and targeted therapies. These biomarkers could help in tailoring personalized treatment plans and improving outcomes. Another critical area is the development of therapeutic strategies that consider the unique pathophysiological characteristics of patients with lung cancer and obesity. This could include optimizing drug dosing to account for altered pharmacokinetics in obesity, as well as investigating how obesity-induced changes in the TME affect treatment efficacy.

Long-term studies could explore how different trajectories of obesity (such as weight loss vs. weight gain during cancer treatment) influence lung cancer progression and patient survival. Understanding these dynamics could lead to improved management strategies for patients with lung cancer and obesity. Further research could also assess the direct impact of public health interventions on reducing obesity-related lung cancer incidence and mortality. This would provide evidence for scaling up successful interventions and inform future public health policies. These aforementioned enhancements would provide a more detailed and actionable outlook on both prevention and the future direction of research in the association between obesity and lung cancer.

In conclusion, obesity represents a significant risk factor for lung cancer, profoundly impacting various aspects of the disease. It influences disease biology by contributing to tumor development and progression through mechanisms such as chronic inflammation, hormonal imbalances and metabolic dysregulation. Additionally, obesity affects treatment responses, potentially altering the efficacy and tolerability of therapies such as chemotherapy, immunotherapy and radiotherapy. Furthermore, the presence of obesity complicates patient outcomes, often leading to poorer prognoses, increased treatment-related complications and a higher likelihood of comorbid conditions. Understanding and addressing these multifaceted impacts are essential for improving the management and outcomes of lung cancer in populations with obesity.

Acknowledgements

Not applicable.

Funding

No funding was received.

Availability of data and materials

Not applicable.

Authors' contributions

DAS and VEG conceptualized the study; IGL, VEG, PS, NT, YH and DAS made a substantial contribution to data interpretation and analysis and wrote and prepared the draft of the manuscript. VEG and DAS analyzed the data and provided critical revisions. All authors contributed to manuscript revision. All authors read approved the final version of the manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

DAS is the Editor-in-Chief for the journal, but had no personal involvement in the reviewing process, or any influence in terms of adjudicating on the final decision, for this article. The other authors declare that they have no competing interests.

Use of artificial intelligence tools

During the preparation of this work, the artificial intelligence tool Chat GPT was used to improve the readability and language of the manuscript, and subsequently, the authors revised and edited the content produced by the artificial intelligence tool as necessary, taking full responsibility for the ultimate content of the present manuscript.

References

1. Chooi YC, Ding C and Magkos F: The epidemiology of obesity. Metabolism 92: 6-10, 2019.
2. Hruby A and Hu FB: The epidemiology of obesity: A big picture. Pharmacoeconomics 33: 673-689, 2015.
3. Ji X, Chen J, Ye J, Xu S, Lin B and Hou K: Epidemiological analysis of global and regional lung cancer mortality: Based on 30-year data analysis of global burden disease database. Healthcare (Basel) 11: 2920, 2023.
4. Chen Z, Fillmore CM, Hammerman PS, Kim CF and Wong KK: Non-small-cell lung cancers: A heterogeneous set of diseases. Nat Rev Cancer 14: 535-546, 2014.
5. Lemjabbar-Alaoui H, Hassan OU, Yang YW and Buchanan P: Lung cancer: Biology and treatment options. Biochim Biophys Acta 1856: 189-210, 2015.

6. Khaddour K, Gomez-Perez SL, Jain N, Patel JD and Boumber Y: Obesity, sarcopenia, and outcomes in non-small cell lung cancer patients treated with immune checkpoint inhibitors and tyrosine kinase inhibitors. Front Oncol 10: 576314, 2020.
7. Petrelli F, Cortellini A, Indini A, Tomasello G, Ghidini M, Nigro O, Salati M, Dottorini L, Iaculli A, Varricchio A, *et al*: Association of obesity with survival outcomes in patients with cancer: A systematic review and meta-analysis. JAMA Netw Open 4: e213520, 2021.
8. Zhang X, Liu Y, Shao H and Zheng X: Obesity paradox in lung cancer prognosis: Evolving biological insights and clinical implications. J Thorac Oncol 12: 1478-1488, 2017.
9. Lennon H, Sperrin M, Badrick E and Renehan AG: The obesity paradox in cancer: A review. Curr Oncol Rep 18: 56, 2016.
10. Kawai T, Autieri MV and Scalia R: Adipose tissue inflammation and metabolic dysfunction in obesity. Am J Physiol Cell Physiol 320: C375-C391, 2021.
11. Assumpção JAF, Pasquarelli-do-Nascimento G, Duarte MSV, Bonamino MH and Magalhães KG: The ambiguous role of obesity in oncology by promoting cancer but boosting antitumor immunotherapy. J Biomed Sci 29: 12, 2022.
12. Barbi J, Patnaik SK, Pabla S, Zollo R, Smith RJ Jr, Sass SN, Srinivasan A, Petrucci C, Seager R, Conroy J, *et al*: Visceral obesity promotes lung cancer progression-toward resolution of the obesity paradox in lung cancer. J Thorac Oncol 16: 1333-1348, 2021.
13. Nguyen HL, Geukens T, Maetens M, Aparicio S, Bassez A, Borg A, Brock J, Broeks A, Caldas C, Cardoso F, *et al*: Obesity-associated changes in molecular biology of primary breast cancer. Nat Commun 14: 4418, 2023.
14. Pati S, Irfan W, Jameel A, Ahmed S and Shahid RK: Obesity and cancer: A current overview of epidemiology, pathogenesis, outcomes, and management. Cancers (Basel) 15: 485, 2023.
15. Yang Y, Dong J, Sun K, Zhao L, Zhao F, Wang L and Jiao Y: Obesity and incidence of lung cancer: A meta-analysis. Int J Cancer 132: 1162-1169, 2013.
16. Choi EK, Park HB, Lee KH, Park JH, Eisenhut M, van der Vliet HJ, Kim G and Shin JI: Body mass index and 20 specific cancers: Re-analyses of dose-response meta-analyses of observational studies. Ann Oncol 29: 749-757, 2018.
17. Wu Z, Xie S, Wang F, Chen S, Su K, Li F, Cui H, Cao W, Yu Y, Qin C, *et al*: BMI changes and the risk of lung cancer in male never-smokers: A prospective cohort study. Cancer Med 11: 1336-1346, 2022.
18. Yu D, Zheng W, Johansson M, Lan Q, Park Y, White E, Matthews CE, Sawada N, Gao YT, Robien K, *et al*: Overall and central obesity and risk of lung cancer: A pooled analysis. J Natl Cancer Inst 110: 831-842, 2018.
19. Zhu H and Zhang S: Body mass index and lung cancer risk in never smokers: A meta-analysis. BMC Cancer 18: 635, 2018.
20. Wang J, Xu H, Zhou S, Wang D, Zhu L, Hou J, Tang J, Zhao J and Zhong S: Body mass index and mortality in lung cancer patients: A systematic review and meta-analysis. Eur J Clin Nutr 72: 4-17, 2018.
21. Neeland IJ, Poirier P and Després JP: Cardiovascular and metabolic heterogeneity of obesity: Clinical challenges and implications for management. Circulation 137: 1391-1406, 2018.
22. Caan BJ, Cespedes Feliciano EM and Kroenke CH: The importance of body composition in explaining the overweight paradox in cancer-counterpoint. Cancer Res 78: 1906-1912, 2018.
23. Khan M and Joseph F: Adipose tissue and adipokines: The association with and application of adipokines in obesity. Scientifica (Cairo) 2014: 328592, 2014.
24. Liu X, Yin L, Shen S and Hou Y: Inflammation and cancer: Paradoxical roles in tumorigenesis and implications in immunotherapies. Genes Dis 10: 151-164, 2021.
25. Kahn BB and Flier JS: Obesity and insulin resistance. J Clin Invest 106: 473-481, 2000.
26. Leroith D, Scheinman EJ and Bitton-Worms K: The role of insulin and insulin-like growth factors in the increased risk of cancer in diabetes. Rambam Maimonides Med J 2: e0043, 2011.
27. Zhong W, Wang X, Wang Y, Sun G, Zhang J and Li Z: Obesity and endocrine-related cancer: The important role of IGF-1. Front Endocrinol (Lausanne) 14: 1093257, 2023.
28. Rodriguez-Lara V and Avila-Costa MR: An overview of lung cancer in women and the impact of estrogen in lung carcinogenesis and lung cancer treatment. Front Med (Lausanne) 8: 600121, 2021.
29. Savini I, Catani MV, Evangelista D, Gasperi V and Avigliano L: Obesity-associated oxidative stress: Strategies finalized to improve redox state. Int J Mol Sci 14: 10497-10538, 2013.
30. Usman M and Volpi EV: DNA damage in obesity: Initiator, promoter and predictor of cancer. Mutat Res Rev Mutat Res 778: 23-37, 2018.
31. Kim JW, Kim JH and Lee YJ: The role of adipokines in tumor progression and its association with obesity. Biomedicines 12: 97, 2024.
32. Sarfati D, Koczwara B and Jackson C: The impact of comorbidity on cancer and its treatment. CA Cancer J Clin 66: 337-350, 2016.
33. Søgaard M, Thomsen RW, Bossen KS, Sørensen HT and Nørgaard M: The impact of comorbidity on cancer survival: A review. Clin Epidemiol 5 (Suppl 1): S3-S29, 2013.
34. Al-Jawaldeh A and Abbass MMS: Unhealthy dietary habits and obesity: The major risk factors beyond non-communicable diseases in the eastern mediterranean region. Front Nutr 9: 817808, 2022.
35. Washington TB, Johnson VR, Kendrick K, Ibrahim AA, Tu L, Sun K and Stanford FC: Disparities in access and quality of obesity care. Gastroenterol Clin North Am 52: 429-441, 2023.
36. Xiong A, Nie W, Cheng L, Zhong H, Chu T, Zhong R, Lu J, Wang S, Xu J, Shen Y, *et al*: Association between obesity and poor prognosis in patients receiving anlotinib for advanced non-small cell lung cancer. Front Pharmacol 13: 812555, 2022.
37. Nitsche L, Vedire Y, Kannisto E, Wang X, Seager RJ, Pabla S, Patnaik SK and Yendamuri S: Visceral Obesity in non-small cell lung cancer. Cancers (Basel) 14: 3450, 2022.
38. Lee CH, Lin C, Wang CY, Huang TC, Wu YY, Chien WC and Chen JH: Premorbid BMI as a prognostic factor in small-cell lung cancer-a single institute experience. Oncotarget 9: 24642-24652, 2018.
39. Kwon YJ, Yoon YC, Kim HS, Cha MJ, Park S and Lee JH: Prognostic significance of body mass index in small-cell lung cancer: Exploring the relationship with skeletal muscle status. J Cachexia Sarcopenia Muscle 14: 2939-2947, 2023.
40. Sutandyo N, Hanafi AR, Jayusman AM, Kurniawati SA and Hanif MA: Overweight and Obesity are associated with poorer survival among patients with advanced non-small cell lung cancer receiving platinum-based chemotherapy. Int J Gen Med 16: 85-93, 2023.
41. Tu H, McQuade JL, Davies MA, Huang M, Xie K, Ye Y, Chow WH, Rodriguez A and Wu X: Body mass index and survival after cancer diagnosis: A pan-cancer cohort study of 114 430 patients with cancer. Innovation (Camb) 3: 100344, 2022.
42. Booth A, Magnuson A, Fouts J and Foster M: Adipose tissue, obesity and adipokines: Role in cancer promotion. Horm Mol Biol Clin Investig 21: 57-74, 2015.
43. Bocian-Jastrzębska A, Malczewska-Herman A and Kos-Kudła B: Role of leptin and adiponectin in carcinogenesis. Cancers (Basel) 15: 4250, 2023.
44. Ramos-Nino ME: The role of chronic inflammation in obesity-associated cancers. ISRN Oncol 2013: 697521, 2013.
45. Wen X, Zhang B, Wu B, Xiao H, Li Z, Li R, Xu X and Li T: Signaling pathways in obesity: Mechanisms and therapeutic interventions. Signal Transduct Target Ther 7: 298, 2022.
46. Lam VK, Bentzen SM, Mohindra P, Nichols EM, Bhooshan N, Vyfhuis M, Scilla KA, Feigenberg SJ, Edelman MJ and Feliciano JL: Obesity is associated with long-term improved survival in definitively treated locally advanced non-small cell lung cancer (NSCLC). Lung Cancer 104: 52-57, 2017.
47. Gallagher EJ and LeRoith D: Insulin, insulin resistance, obesity, and cancer. Curr Diab Rep 10: 93-100, 2010.
48. Fukumoto K, Mori S, Shintani Y, Okami J, Ito H, Ohtsuka T, Toyooka S, Mori T, Watanabe SI, Asamura H, *et al*: Impact of the preoperative body mass index on the postoperative outcomes in patients with completely resected non-small cell lung cancer: A retrospective analysis of 16,503 cases in a Japanese lung cancer registry study. Lung Cancer 149: 120-129, 2020.
49. O'Rourke RW: Obesity and cancer: At the crossroads of cellular metabolism and proliferation. Surg Obes Relat Dis 10: 1208-1219, 2014.
50. Li M and Bu R: Biological support to obesity paradox in renal cell carcinoma: A review. Urol Int 104: 837-848, 2020.
51. Björndahl M, Cao R, Nissen LJ, Clasper S, Johnson LA, Xue Y, Zhou Z, Jackson D, Hansen AJ and Cao Y: Insulin-like growth factors 1 and 2 induce lymphangiogenesis in vivo. Proc Natl Acad Sci USA 102: 15593-15598, 2005.
52. Wang Q, Tu H, Zhu M, Liang D, Ye Y, Chang DW, Long Y and Wu X: Circulating obesity-driven biomarkers are associated with risk of clear cell renal cell carcinoma: A two-stage, case-control study. Carcinogenesis 40: 1191-1197, 2019.

53. Kamat AM, Shock RP, Naya Y, Rosser CJ, Slaton JW and Pisters LL: Prognostic value of body mass index in patients undergoing nephrectomy for localized renal tumors. Urology 63: 46-50, 2004.
54. Albiges L, Hakimi AA, Xie W, McKay RR, Simantov R, Lin X, Lee JL, Rini BI, Srinivas S, Bjarnason GA, *et al*: Body mass index and metastatic renal cell carcinoma: Clinical and biological correlations. J Clin Oncol 34: 3655-3663, 2016.
55. Choi Y, Park B, Jeong BC, Seo SI, Jeon SS, Choi HY, Adami HO, Lee JE and Lee HM: Body mass index and survival in patients with renal cell carcinoma: A clinical-based cohort and meta-analysis. Int J Cancer 132: 625-634, 2013.
56. Jeon HG, Jeong IG, Lee JH, Lee CJ, Kwak C, Kim HH, Lee SE and Lee E: Prognostic value of body mass index in Korean patients with renal cell carcinoma. J Urol 183: 448-454, 2010.
57. Choueiri TK, Xie W, Kollmannsberger CK, Rini BI, McDermott DF, Knox JJ and Heng DY: The impact of body mass index (BMI) and body surface area (BSA) on treatment outcome to vascular endothelial growth factor (VEGF)-targeted therapy in metastatic renal cell carcinoma: Results from a large international collaboration. J Clin Oncol 28 (15 Suppl): S4524, 2010.
58. Naik GS, Waikar SS, Johnson AEW, Buchbinder EI, Haq R, Hodi FS, Schoenfeld JD and Ott PA: Complex inter-relationship of body mass index, gender and serum creatinine on survival: Exploring the obesity paradox in melanoma patients treated with checkpoint inhibition. J Immunother Cancer 7: 89, 2019.
59. Donnelly D, Bajaj S, Yu J, Hsu M, Balar A, Pavlick A, Weber J, Osman I and Zhong J: The complex relationship between body mass index and response to immune checkpoint inhibition in metastatic melanoma patients. J Immunother Cancer 7: 222, 2019.
60. Pencheva N, Buss C, Posada J, Merghoub T and Tavazoie SF: Broad-spectrum therapeutic suppression of metastatic melanoma through nuclear hormone receptor activation. Cell 156: 986-1001, 2014.
61. McQuade JL, Daniel CR, Hess KR, Mak C, Wang DY, Rai RR, Park JJ, Haydu LE, Spencer C, Wongchenko M, *et al*: Association of body-mass index and outcomes in patients with metastatic melanoma treated with targeted therapy, immunotherapy, or chemotherapy: A retrospective, multicohort analysis. Lancet Oncol 19: 310-322, 2018.
62. Wang Z, Aguilar EG, Luna JI, Dunai C, Khuat LT, Le C, Mirsoian A, Minnar CM, Stoffel KM, Sturgill IR, *et al*: Paradoxical effects of obesity on T cell function during tumor progression and PD-1 checkpoint blockade. Nat Med 25: 141-151, 2019.
63. Georgiadis MS, Steinberg SM, Hankins LA, Ihde DC and Johnson BE: Obesity and therapy-related toxicity in patients treated for small-cell lung cancer. J Natl Cancer Inst 87: 361-366, 1995.
64. Nattenmüller J, Wochner R, Muley T, Steins M, Hummler S, Teucher B, Wiskemann J, Kauczor HU, Wielpütz MO and Heussel CP: Prognostic impact of CT-quantified muscle and fat distribution before and after first-line-chemotherapy in lung cancer patients. PLoS One 12: e0169136, 2017.
65. Shepshelovich D, Xu W, Lu L, Fares A, Yang P, Christiani D, Zhang J, Shiraishi K, Ryan BM, Chen C, *et al*: Body mass index (BMI), BMI change, and overall survival in patients with SCLC and NSCLC: A pooled analysis of the international lung cancer consortium. J Thorac Oncol 14: 1594-1607, 2019.
66. Icard P, Schussler O, Loi M, Bobbio A, Lupo AM, Wislez M, Iannelli A, Fournel L, Damotte D and Alifano M: Pre-disease and pre-surgery BMI, weight loss and sarcopenia impact survival of resected lung cancer independently of tumor stage. Cancers (Basel) 12: 266, 2020.
67. Jiang M, Fares AF, Shepshelovich D, Yang P, Christiani D, Zhang J, Shiraishi K, Ryan BM, Chen C, Schwartz AG, *et al*: The relationship between body-mass index and overall survival in non-small cell lung cancer by sex, smoking status, and race: A pooled analysis of 20,937 international lung cancer consortium (ILCCO) patients. Lung Cancer 152: 58-65, 2021.
68. Bethea TN, Rosenberg L, Charlot M, O'Connor GT, Adams-Campbell LL and Palmer JR: Obesity in relation to lung cancer incidence in African American women. Cancer Causes Control 24: 1695-1703, 2013.
69. Kim HR, Kim SY, Kim CH, Yang SH, Lee JC, Choi CM and Na II: Sex-specific incidence of EGFR mutation and its association with age and obesity in lung adenocarcinomas: A retrospective analysis. J Cancer Res Clin Oncol 143: 2283-2290, 2017.
70. Gremese E, Tolusso B, Gigante MR and Ferraccioli G: Obesity as a risk and severity factor in rheumatic diseases (autoimmune chronic inflammatory diseases). Front Immunol 5: 576, 2014.
71. Siopis G: Obesity: A comorbidity-acquired immunodeficiency syndrome (CAIDS). Int Rev Immunol 42: 415-429, 2023.
72. Cao Y: Adipocyte and lipid metabolism in cancer drug resistance. J Clin Invest 129: 3006-3017, 2019.
73. Havas KM, Milchevskaya V, Radic K, Alladin A, Kafkia E, Garcia M, Stolte J, Klaus B, Rotmensz N, Gibson TJ, *et al*: Metabolic shifts in residual breast cancer drive tumor recurrence. J Clin Invest 127: 2091-2105, 2017.
74. Iwamoto H, Abe M, Yang Y, Cui D, Seki T, Nakamura M, Hosaka K, Lim S, Wu J, He X, *et al*: Cancer lipid metabolism confers antiangiogenic drug resistance. Cell Metab 28: 104-117.e5, 2018.
75. Hoy AJ, Nagarajan SR and Butler LM: Tumour fatty acid metabolism in the context of therapy resistance and obesity. Nat Rev Cancer 21: 753-766, 2021.
76. Camarda R, Zhou AY, Kohnz RA, Balakrishnan S, Mahieu C, Anderton B, Eyob H, Kajimura S, Tward A, Krings G, *et al*: Inhibition of fatty acid oxidation as a therapy for MYC-overexpressing triple-negative breast cancer. Nat Med 22: 427-432, 2016.
77. Huang Q, Wang Q, Li D, Wei X, Jia Y, Zhang Z, Ai B, Cao X, Guo T and Liao Y: Co-administration of 20(S)-protopanaxatriol (g-PPT) and EGFR-TKI overcomes EGFR-TKI resistance by decreasing SCD1 induced lipid accumulation in non-small cell lung cancer. J Exp Clin Cancer Res 38: 129, 2019.
78. Watt MJ, Clark AK, Selth LA, Haynes VR, Lister N, Rebello R, Porter LH, Niranjan B, Whitby ST, Lo J, *et al*: Suppressing fatty acid uptake has therapeutic effects in preclinical models of prostate cancer. Sci Transl Med 11: eaau5758, 2019.
79. Pascual G, Avgustinova A, Mejetta S, Martin M, Castellanos A, Attolini CSO, Berenguer A, Prats N, Toll A, Hueto JA, *et al*: Targeting metastasis-initiating cells through the fatty acid receptor CD36. Nature 541: 41-45, 2017.
80. Buckley D, Duke G, Heuer TS, O'Farrell M, Wagman AS, McCulloch W and Kemble G: Fatty acid synthase-Modern tumor cell biology insights into a classical oncology target. Pharmacol Ther 177: 23-31, 2017.
81. Zaytseva YY, Rychahou PG, Le AT, Scott TL, Flight RM, Kim JT, Harris J, Liu J, Wang C, Morris AJ, *et al*: Preclinical evaluation of novel fatty acid synthase inhibitors in primary colorectal cancer cells and a patient-derived xenograft model of colorectal cancer. Oncotarget 9: 24787-24800, 2018.
82. Sheng X, Parmentier JH, Tucci J, Pei H, Cortez-Toledo O, Dieli-Conwright CM, Oberley MJ, Neely M, Orgel E, Louie SG and Mittelman SD: Adipocytes sequester and metabolize the chemotherapeutic daunorubicin. Mol Cancer Res 15: 1704-1713, 2017.
83. Bauerschlag DO, Maass N, Leonhardt P, Verburg FA, Pecks U, Zeppernick F, Morgenroth A, Mottaghy FM, Tolba R, Meinhold-Heerlein I and Bräutigam K: Fatty acid synthase overexpression: Target for therapy and reversal of chemoresistance in ovarian cancer. J Transl Med 13: 146, 2015.
84. Papaevangelou E, Almeida GS, Box C, deSouza NM and Chung YL: The effect of FASN inhibition on the growth and metabolism of a cisplatin-resistant ovarian carcinoma model. Int J Cancer 143: 992-1002, 2018.
85. Altieri DC: Mitochondria on the move: Emerging paradigms of organelle trafficking in tumour plasticity and metastasis. Br J Cancer 117: 301-305, 2017.
86. Wang H, Franco F, Tsui YC, Xie X, Trefny MP, Zappasodi R, Mohmood SR, Fernández-García J, Tsai CH, Schulze I, *et al*: CD36-mediated metabolic adaptation supports regulatory T cell survival and function in tumors. Nat Immunol 21: 298-308, 2020.
87. Ladanyi A, Mukherjee A, Kenny HA, Johnson A, Mitra AK, Sundaresan S, Nieman KM, Pascual G, Benitah SA, Montag A, *et al*: Adipocyte-induced CD36 expression drives ovarian cancer progression and metastasis. Oncogene 37: 2285-2301, 2018.
88. Yuan H, Kopelovich L, Yin Y, Lu J and Glazer RI: Drug-targeted inhibition of peroxisome proliferator-activated receptor-gamma enhances the chemopreventive effect of anti-estrogen therapy. Oncotarget 3: 345-356, 2012.
89. Cheng S, Qian K, Wang Y, Wang G, Liu X, Xiao Y and Wang X: PPARγ inhibition regulates the cell cycle, proliferation and motility of bladder cancer cells. J Cell Mol Med 23: 3724-3736, 2019.

90. Lou G, Song X, Yang F, Wu S, Wang J, Chen Z and Lu Y: Exosomes derived from miR-122-modified adipose tissue-derived MSCs increase chemosensitivity of hepatocellular carcinoma. J Hematol Oncol 8: 122, 2015.
91. Au Yeung CL, Co NN, Tsuruga T, Yeung TL, Kwan SY, Leung CS, Li Y, Lu ES, Kwan K, Wong KK, *et al*: Exosomal transfer of stroma-derived miR21 confers paclitaxel resistance in ovarian cancer cells through targeting APAF1. Nat Commun 7: 11150, 2016.
92. Polanski R, Hodgkinson CL, Fusi A, Nonaka D, Priest L, Kelly P, Trapani F, Bishop PW, White A, Critchlow SE, *et al*: Activity of the monocarboxylate transporter 1 inhibitor AZD3965 in small cell lung cancer. Clin Cancer Res 20: 926-937, 2014.
93. Xie H, Hanai J, Ren JG, Kats L, Burgess K, Bhargava P, Signoretti S, Billiard J, Duffy KJ, Grant A, *et al*: Targeting lactate dehydrogenase-a inhibits tumorigenesis and tumor progression in mouse models of lung cancer and impacts tumor-initiating cells. Cell Metab 19: 795-809, 2014.
94. Karakas Y, Esin E, Lacin S, Ceyhan K, Heper AO and Yalcin S: A case of acanthosis nigricans as a paraneoplastic syndrome with squamous cell lung cancer. Onco Targets Ther 9: 4815-4820, 2016.
95. Lawrenson R, Lao C, Brown L, Moosa L, Chepulis L, Keenan R, Kidd J, Middleton K, Conaglen P, de Groot C, *et al*: Management of patients with early stage lung cancer-why do some patients not receive treatment with curative intent? BMC Cancer 20: 109, 2020.
96. Plassmeier L, Hankir MK and Seyfried F: Impact of excess body weight on postsurgical complications. Visc Med 37: 287-297, 2021.
97. Tjeertes EKM, Hoeks SE, Beks SBJ, Valentijn TM, Hoofwijk AGM and Stolker RJ: Obesity-a risk factor for postoperative complications in general surgery? BMC Anesthesiol 15: 112, 2015.
98. Hodgson LE, Murphy PB and Hart N: Respiratory management of the obese patient undergoing surgery. J Thorac Dis 7: 943-952, 2015.
99. Pierpont YN, Dinh TP, Salas RE, Johnson EL, Wright TG, Robson MC and Payne WG: Obesity and surgical wound healing: A current review. ISRN Obes 2014: 638936, 2014.
100. De Camilli AR, Cadwell JB, Weiss H, Tollinche LE, McFarlane D, Broach V, Leitao MM, Kitzler R and Afonso AM: Perioperative considerations for cancer patients with obesity: A narrative review. Trends Anaesth Crit Care 46: 33-41, 2022.
101. Lang LH, Parekh K, Tsui BYK and Maze M: Perioperative management of the obese surgical patient. Br Med Bull 124: 135-155, 2017.
102. Vedire Y, Kalvapudi S and Yendamuri S: Obesity and lung cancer-a narrative review. J Thorac Dis 15: 2806-2823, 2023.
103. Alifano M, Daffré E, Iannelli A, Brouchet L, Falcoz PE, Le Pimpec Barthes F, Bernard A, Pages PB, Thomas PA, Dahan M and Porcher R: The reality of lung cancer paradox: The impact of body mass index on long-term survival of resected lung cancer. A French nationwide analysis from the epithor database. Cancers (Basel) 13: 4574, 2021.
104. Tong C, Li T, Shen Y, Zhu H, Zheng J and Wu J: Obesity does not increase perioperative outcomes in older patients undergoing thoracoscopic anatomic lung cancer surgery. Front Oncol 12: 881467, 2022.
105. Guerrera F, Lyberis P, Lausi PO, Cristofori RC, Giobbe R, Molinatti M, Filosso PL, Curcio C, Crisci R and Ruffini E; on the behalf of the Italian VATS Group: Does morbid obesity influence perioperative outcomes after video-assisted thoracic surgery (VATS) lobectomy for non-small cell lung cancer? Analysis of the Italian VATS group registry. Surg Endosc 36: 3567-3573, 2022.
106. Lee JH, Yoon YC, Kim HS, Cha MJ, Kim JH, Kim K and Kim HS: Obesity is associated with improved postoperative overall survival, independent of skeletal muscle mass in lung adenocarcinoma. J Cachexia Sarcopenia Muscle 13: 1076-1086, 2022.
107. Tulinský L, Sengul I, Ihnát P, Ostruszka P, Toman D, Guňková P, Pelikán A and Sengul D: Obesity in cases undergoing the surgical procedure of lung lobectomy: Risk or benefit? Rev Assoc Med Bras (1992) 68: 1090-1095, 2022.
108. Seder CW, Farrokhyar F, Nayak R, Baste JM, Patel Y, Agzarian J, Finley CJ, Shargall Y, Thomas PA, Dahan M, *et al*: Robotic vs thoracoscopic anatomic lung resection in obese patients: A propensity-adjusted analysis. Ann Thorac Surg 114: 1879-1885, 2022.
109. Leonardi B, Forte S, Natale G, Messina G, Rainone A, Opromolla G, Puca MA, Grande M, Martone M, Leone F, *et al*: One-lung ventilation in obese patients undergoing thoracoscopic lobectomy for lung cancer. Thorac Cancer 14: 281-288, 2023.
110. Silvestris N, Argentiero A, Natalicchio A, D'Oronzo S, Beretta GD, Acquati S, Adinolfi V, Di Bartolo P, Danesi R, Faggiano A, *et al*: Antineoplastic dosing in overweight and obese cancer patients: an associazione italiana oncologia medica (AIOM)/associazione medici diabetologi (AMD)/Società Italiana Endocrinologia (SIE)/Società Italiana Farmacologia (SIF) multidisciplinary consensus position paper. ESMO Open 6: 100153, 2021.
111. Barras M and Legg A: Drug dosing in obese adults. Aust Prescr 40: 189-193, 2017.
112. Griggs JJ, Bohlke K, Balaban EP, Dignam JJ, Hall ET, Harvey RD, Hecht DP, Klute KA, Morrison VA, Pini TM, *et al*: Appropriate systemic therapy dosing for obese adult patients with cancer: ASCO guideline update. J Clin Oncol 39: 2037-2048, 2021.
113. Dent SF, Kikuchi R, Kondapalli L, Ismail-Khan R, Brezden-Masley C, Barac A and Fradley M: Optimizing cardiovascular health in patients with cancer: A practical review of risk assessment, monitoring, and prevention of cancer treatment-related cardiovascular toxicity. Am Soc Clin Oncol Educ Book 40: 1-15, 2020.
114. Kicken MP, Kilinc HD, Cramer-van der Welle CM, Houterman S, van den Borne BEEM, Smit AAJ, van de Garde EMW and Deenen MJ; Santeon NSCLC study group: The association of body mass index with safety and effectiveness of first-line carboplatin-based chemotherapy in patients with metastatic non-small cell lung cancer. Cancer Treat Res Commun 34: 100676, 2023.
115. Kashiwabara K, Yamane H and Tanaka H: Toxicity and prognosis in overweight and obese women with lung cancer receiving carboplatin-paclitaxel doublet chemotherapy. Cancer Invest 31: 251-257, 2013.
116. Georgakopoulou VE, Garmpis N, Mermigkis D, Damaskos C, Chlapoutakis S, Mantzouranis K, Gkoufa A, Papageorgiou C, Garmpi A, Makrodimitri S, *et al*: Pulmonary adverse events due to immune checkpoint inhibitors: A literature review. Monaldi Arch Chest Dis 92, 2021.
117. Vick LV, Canter RJ, Monjazeb AM and Murphy WJ: Multifaceted effects of obesity on cancer immunotherapies: Bridging preclinical models and clinical data. Semin Cancer Biol 95: 88-102, 2023.
118. Woodall MJ, Neumann S, Campbell K, Pattison ST and Young SL: The effects of obesity on anti-cancer immunity and cancer immunotherapy. Cancers (Basel) 12: 1230, 2020.
119. Sanhueza S, Simón L, Cifuentes M and Quest AFG: The adipocyte-macrophage relationship in cancer: A potential target for antioxidant therapy. Antioxidants (Basel) 12: 126, 2023.
120. Hahn AW, Venkatesh N, Msaouel P and McQuade JL: The influence of obesity on outcomes with immune checkpoint blockade: Clinical evidence and potential biological mechanisms. Cells 12: 2551, 2023.
121. Guo H, Lin XY, Feng S, Wang C, Yuan LQ, Sheng XG and Li DP: Prognostic value of obesity in patients with cancer treated with immune checkpoint inhibitors: An updated meta-analysis and systematic review. Mol Clin Oncol 20: 5, 2023.
122. Leiter A, Carroll E, De Alwis S, Brooks D, Shimol JB, Eisenberg E, Wisnivesky JP, Galsky MD and Gallagher EJ: Metabolic disease and adverse events from immune checkpoint inhibitors. Eur J Endocrinol 184: 857-865, 2021.
123. Zhang T, Li S, Chang J, Qin Y and Li C: Impact of BMI on the survival outcomes of non-small cell lung cancer patients treated with immune checkpoint inhibitors: A meta-analysis. BMC Cancer 23: 1023, 2023.
124. Baskar R, Lee KA, Yeo R and Yeoh KW: Cancer and radiation therapy: Current advances and future directions. Int J Med Sci 9: 193-199, 2012.
125. Winters E and Poole C: Challenges and impact of patient obesity in radiation therapy practice. Radiography (Lond) 26: e158-e163, 2020.
126. Mercieca S, Belderbos JSA and van Herk M: Challenges in the target volume definition of lung cancer radiotherapy. Transl Lung Cancer Res 10: 1983-1998, 2021.
127. Ross KH, Gogineni K, Subhedar PD, Lin JY and McCullough LE: Obesity and cancer treatment efficacy: Existing challenges and opportunities. Cance 125: 1588-1592, 2019.
128. Wang K and Tepper JE: Radiation therapy-associated toxicity: Etiology, management, and prevention. CA Cancer J Clin 71: 437-454, 2021.

129. Welsh J, Thomas J, Shah D, Allen PK, Wei X, Mitchell K, Gao S, Balter P, Komaki R and Chang JY: Obesity increases the risk of chest wall pain from thoracic stereotactic body radiation therapy. Int J Radiat Oncol Biol Phys 81: 91-96, 2011.
130. Lempesis IG, Karlafti E, Papalexis P, Fotakopoulos G, Tarantinos K, Lekakis V, Papadakos SP, Cholongitas E and Georgakopoulou VE: COVID-19 and liver injury in individuals with obesity. World J Gastroenterol 29: 908-916, 2023.
131. Lempesis IG and Georgakopoulou VE: Implications of obesity and adiposopathy on respiratory infections; focus on emerging challenges. World J Clin Cases 11: 2925-2933, 2023.
132. Lempesis IG, Varrias D, Sagris M, Attaran RR, Altin ES, Bakoyiannis C, Palaiodimos L, Dalamaga M and Kokkinidis DG: Obesity and peripheral artery disease: Current evidence and controversies. Curr Obes Rep 12: 264-279, 2023.
133. Lempesis IG, Georgakopoulou VE, Papalexis P, Chrousos GP and Spandidos DA: Role of stress in the pathogenesis of cancer (Review). Int J Oncol 63: 124, 2023.
134. Lempesis IG, Hoebers N, Essers Y, Jocken JWE, Dineen R, Blaak EE, Manolopoulos KN and Goossens GH: Distinct inflammatory signatures of upper and lower body adipose tissue and adipocytes in women with normal weight or obesity. Front Endocrinol (Lausanne) 14: 1205799, 2023.
135. Lempesis IG, van Meijel RLJ, Manolopoulos KN and Goossens GH: Oxygenation of adipose tissue: A human perspective. Acta Physiol (Oxf) 228: e13298, 2020.
136. Lempesis IG and Georgakopoulou VE: Physiopathological mechanisms related to inflammation in obesity and type 2 diabetes mellitus. World J Exp Med 13: 7-16, 2023.
137. Lempesis IG, Liu J and Dalamaga M: The catcher in the gut: Tirzepatide, a dual incretin analog for the treatment of type 2 diabetes mellitus and obesity. Metabol Open 16: 100220, 2022.
138. Lempesis IG, Tsilingiris D, Liu J and Dalamaga M: Of mice and men: Considerations on adipose tissue physiology in animal models of obesity and human studies. Metabol Open 15: 100208, 2022.
139. Georgakopoulou VE, Lempesis, IG and Spandidos DA: The parallel lives of pandemics: COVID-19 and obesity. Exp Ther Med 27: 184, 2024.
140. Longo M, Zatterale F, Naderi J, Parrillo L, Formisano P, Raciti GA, Beguinot F and Miele C: Adipose tissue dysfunction as determinant of obesity-associated metabolic complications. Int J Mol Sci 20: 2358, 2019.
141. Daquinag AC, Tseng C, Zhang Y, Amaya-Manzanares F, Florez F, Dadbin A, Zhang T and Kolonin MG: Targeted proapoptotic peptides depleting adipose stromal cells inhibit tumor growth. Mol Ther 24: 34-40, 2016.
142. Jin X, Qiu T, Li L, Yu R, Chen X, Li C, Proud CG and Jiang T: Pathophysiology of obesity and its associated diseases. Acta Pharm Sin B 13: 2403-2424, 2023.
143. Capurso C and Capurso A: From excess adiposity to insulin resistance: The role of free fatty acids. Vascul Pharmacol 57: 91-97, 2012.
144. Jung UJ and Choi MS: Obesity and its metabolic complications: The role of adipokines and the relationship between obesity, inflammation, insulin resistance, dyslipidemia and nonalcoholic fatty liver disease. Int J Mol Sci 15: 6184-6223, 2014.
145. Cavaliere G, Cimmino F, Trinchese G, Catapano A, Petrella L, D'Angelo M, Lucchin L and Mollica MP: From obesity-induced low-grade inflammation to lipotoxicity and mitochondrial dysfunction: Altered multi-crosstalk between adipose tissue and metabolically active organs. Antioxidants (Basel) 12: 1172, 2023.
146. Divella R, De Luca R, Abbate I, Naglieri E and Daniele A: Obesity and cancer: The role of adipose tissue and adipocytokines-induced chronic inflammation. J Cancer 7: 2346-2359, 2016.
147. Himbert C, Delphan M, Scherer D, Bowers LW, Hursting S and Ulrich CM: Signals from the adipose microenvironment and the obesity-cancer link-a systematic review. Cancer Prev Res (Phila) 10: 494-506, 2017.
148. Fantuzzi G: Adipose tissue, adipokines, and inflammation. J Allergy Clin Immunol 115: 911-920, 2005.
149. Louie SM, Roberts LS and Nomura DK: Mechanisms linking obesity and cancer. Biochim Biophys Acta 1831: 1499-1508, 2013.
150. Dalamaga M, Diakopoulos KN and Mantzoros CS: The role of adiponectin in cancer: A review of current evidence. Endocr Rev 33: 547-594, 2012.
151. Nigro E, Scudiero O, Monaco ML, Palmieri A, Mazzarella G, Costagliola C, Bianco A and Daniele A: New insight into adiponectin role in obesity and obesity-related diseases. Biomed Res Int 2014: 658913, 2014.
152. Parida S, Siddharth S and Sharma D: Adiponectin, obesity, and cancer: Clash of the bigwigs in health and disease. Int J Mol Sci 20: 2519, 2019.
153. Dutta D, Ghosh S, Pandit K, Mukhopadhyay P and Chowdhury S: Leptin and cancer: Pathogenesis and modulation. Indian J Endocrinol Metab 16 (Suppl 3): S596-S600, 2012.
154. Lang K and Ratke J: Leptin and Adiponectin: New players in the field of tumor cell and leukocyte migration. Cell Commun Signal 7: 27, 2009.
155. Iikuni N, Lam QLK, Lu L, Matarese G and La Cava A: Leptin and inflammation. Curr Immunol Rev 4: 70-79, 2008.
156. Mullen M and Gonzalez-Perez RR: Leptin-induced JAK/STAT signaling and cancer growth. Vaccines (Basel) 4: 26, 2016.
157. Cho YK, Lee Y and Jung CH: Pathogenesis, murine models, and clinical implications of metabolically healthy obesity. Int J Mol Sci 23: 9614, 2022.
158. Blüher M: Metabolically healthy obesity. Endocr Rev 41: bnaa004, 2020.
159. Lin TY, Chen YF, Wu WT, Han DS, Tsai IC, Chang KV and Özçakar L: Impact of sarcopenia on the prognosis and treatment of lung cancer: An umbrella review. Discov Oncol 13: 115, 2022.
160. Shao F, Chen Y, Xu H, Chen X, Zhou J, Wu Y, Tang Y, Wang Z, Zhang R, Lange T, *et al*: Metabolic obesity phenotypes and risk of lung cancer: A prospective cohort study of 450,482 UK Biobank participants. Nutrients 14: 3370, 2022.
161. Malki A, Shaik RA and Sami W: Association between metabolically healthy obesity and metastasis in lung cancer patients-a systematic review and meta-analysis. Front Endocrinol (Lausanne) 14: 1238459, 2023.
162. Sørensen J: Lung cancer cachexia: Can molecular understanding guide clinical management? Integr Cancer Ther 17: 1000-1008, 2018.
163. Anjanappa M, Corden M, Green A, Roberts D, Hoskin P, McWilliam A and Choudhury A: Sarcopenia in cancer: Risking more than muscle loss. Tech Innov Patient Support Radiat Oncol 16: 50-57, 2020.
164. Peixoto da Silva S, Santos JMO, Costa E Silva MP, Gil da Costa RM and Medeiros R: Cancer cachexia and its pathophysiology: Links with sarcopenia, anorexia and asthenia. J Cachexia Sarcopenia Muscle 11: 619-635, 2020.
165. Kim EY, Lee HY, Kim KW, Lee JI, Kim YS, Choi WJ and Kim JH: Preoperative computed tomography-determined sarcopenia and postoperative outcome after surgery for non-small cell lung cancer. Scand J Surg 107: 244-251, 2018.
166. Bozzetti F: Forcing the vicious circle: Sarcopenia increases toxicity, decreases response to chemotherapy and worsens with chemotherapy. Ann Oncol 28: 2107-2118, 2017.
167. Law ML: Cancer cachexia: Pathophysiology and association with cancer-related pain. Front Pain Res (Lausanne) 3: 971295, 2022.
168. Vaughan VC, Martin P and Lewandowski PA: Cancer cachexia: Impact, mechanisms and emerging treatments. J Cachexia Sarcopenia Muscle 4: 95-109, 2013.
169. Kidd AC, Skrzypski M, Jamal-Hanjani M and Blyth KG: Cancer cachexia in thoracic malignancy: A narrative review. Curr Opin Support Palliat Care 13: 316-322, 2019.
170. Ding C, Chan Z and Magkos F: Lean, but not healthy: The 'metabolically obese, normal-weight' phenotype. Curr Opin Clin Nutr Metab Care 19: 408-417, 2016.
171. Donohoe CL, Doyle SL and Reynolds JV: Visceral adiposity, insulin resistance and cancer risk. Diabetol Metab Syndr 3: 12, 2011.
172. Crudele L, Piccinin E and Moschetta A: Visceral adiposity and cancer: Role in pathogenesis and prognosis. Nutrients 13: 2101, 2021.
173. Park JE, Jo J, Youk J, Kim M, Yoon SH, Keam B, Kim TM and Kim DW: Prognostic utility of body composition parameters based on computed tomography analysis of advanced non-small cell lung cancer treated with immune checkpoint inhibitors. Insights Imaging 14: 182, 2023.
174. Popinat G, Cousse S, Goldfarb L, Becker S, Gardin I, Salaün M, Thureau S, Vera P, Guisier F and Decazes P: Sub-cutaneous Fat Mass measured on multislice computed tomography of pretreatment PET/CT is a prognostic factor of stage IV non-small cell lung cancer treated by nivolumab. Oncoimmunology 8: e1580128, 2019.

175. Magri V, Gottfried T, Di Segni M, Urban D, Peled M, Daher S, Stoff R, Bar J and Onn A: Correlation of body composition by computerized tomography and metabolic parameters with survival of nivolumab-treated lung cancer patients. Cancer Manag Res 11: 8201-8207, 2019.
176. Khan A, Welman CJ, Abed A, O'Hanlon S, Redfern A, Azim S, Lopez P, Singh F and Khattak A: Association of computed tomography measures of muscle and adipose tissue and progressive changes throughout treatment with clinical endpoints in patients with advanced lung cancer treated with immune checkpoint inhibitors. Cancers (Basel) 15: 1382, 2023.
177. Park G, Song K, Choi Y, Oh JS, Choi HS, Suh J, Kwon A, Kim HS and Chae HW: Sex Hormone-binding globulin is associated with obesity and dyslipidemia in prepubertal children. Children (Basel) 7: 272, 2020.
178. Musial C, Zaucha R, Kuban-Jankowska A, Konieczna L, Belka M, Marino Gammazza A, Baczek T, Cappello F, Wozniak M and Gorska-Ponikowska M: Plausible role of estrogens in pathogenesis, progression and therapy of lung cancer. Int J Environ Res Public Health 18: 648, 2021.
179. Stabile LP, Davis AL, Gubish CT, Hopkins TM, Luketich JD, Christie N, Finkelstein S and Siegfried JM: Human non-small cell lung tumors and cells derived from normal lung express both estrogen receptor alpha and beta and show biological responses to estrogen. Cancer Res 62: 2141-2150, 2002.
180. McKenzie F, Biessy C, Ferrari P, Freisling H, Rinaldi S, Chajès V, Dahm CC, Overvad K, Dossus L, Lagiou P, *et al*: Healthy lifestyle and risk of cancer in the European prospective investigation into cancer and nutrition cohort study. Medicine (Baltimore) 95: e2850, 2016.
181. Rock CL, Thomson C, Gansler T, Gapstur SM, McCullough ML, Patel AV, Andrews KS, Bandera EV, Spees CK, Robien K, *et al*: American Cancer Society guideline for diet and physical activity for cancer prevention. CA Cancer J Clin 70: 245-271, 2020.
182. Khalil WJ, Akeblersane M, Khan AS, Moin ASM and Butler AE: Environmental pollution and the risk of developing metabolic disorders: obesity and diabetes. Int J Mol Sci 24: 8870, 2023.
183. Shi X, Zheng Y, Cui H, Zhang Y and Jiang M: Exposure to outdoor and indoor air pollution and risk of overweight and obesity across different life periods: A review. Ecotoxicol Environ Saf 242: 113893, 2022.
184. Holme JA, Vondráček J, Machala M, Lagadic-Gossmann D, Vogel CFA, Le Ferrec E, Sparfel L and Øvrevik J: Lung cancer associated with combustion particles and fine particulate matter ($PM_{2.5}$)-The roles of polycyclic aromatic hydrocarbons (PAHs) and the aryl hydrocarbon receptor (AhR). Biochem Pharmacol 216: 115801, 2023.
185. Bhattacharjee P, Paul S and Bhattacharjee P: Risk of occupational exposure to asbestos, silicon and arsenic on pulmonary disorders: Understanding the genetic-epigenetic interplay and future prospects. Environ Res 147: 425-434, 2016.
186. Malone ER, Oliva M, Sabatini PJB, Stockley TL and Siu LL: Molecular profiling for precision cancer therapies. Genome Med 12: 8, 2020.
187. Li MSC, Mok KKS and Mok TSK: Developments in targeted therapy & immunotherapy-how non-small cell lung cancer management will change in the next decade: A narrative review. Ann Transl Med 11: 358, 2023.
188. Rippe JM: Lifestyle medicine: The health promoting power of daily habits and practices. Am J Lifestyle Med 12: 499-512, 2018.
189. Ko C and Chaudhry S: The need for a multidisciplinary approach to cancer care. J Surg Res 105: 53-57, 2002.
190. Berardi R, Morgese F, Rinaldi S, Torniai M, Mentrasti G, Scortichini L and Giampieri R: Benefits and limitations of a multidisciplinary approach in cancer patient management. Cancer Manag Res 12: 9363-9374, 2020.
191. Manisalidis I, Stavropoulou E, Stavropoulos A and Bezirtzoglou E: Environmental and health impacts of air pollution: A review. Front Public Health 8: 14, 2020.
192. Sánchez-Romero LM, Penko J, Coxson PG, Fernández A, Mason A, Moran AE, Ávila-Burgos L, Odden M, Barquera S and Bibbins-Domingo K: Projected impact of mexico's sugar-sweetened beverage tax policy on diabetes and cardiovascular disease: A modeling study. PLoS Med 13: e1002158, 2016.
193. Cecchini M and Warin L: Impact of food labelling systems on food choices and eating behaviours: A systematic review and meta-analysis of randomized studies. Obes Rev 17: 201-210, 2016.