Review Article

Obesity and lung cancer—a narrative review

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Background and Objective: A highly nuanced relationship exists between obesity and lung cancer. The association between obesity and lung cancer risk/prognosis varies depending on age, gender, race, and the metric used to quantify adiposity. Increased body mass index (BMI) is counterintuitively associated with decreased lung cancer incidence and mortality, giving rise to the term 'obesity paradox'. Potential explanations for this paradox are BMI being a poor measure of obesity, confounding by smoking and reverse causation. A literature search of this topic yields conflicting conclusions from various authors. We aim to clarify the relationship between various measures of obesity, lung cancer risk, and lung cancer prognosis.

Methods: The PubMed database was searched on 10 August 2022 to identify published research studies. Literature published in English between 2018 and 2022 were included. Sixty-nine publications were considered relevant, and their full text studied to collate information for this review.

Key Content and Findings: Lower lung cancer incidence and better prognosis was associated with increased BMI even after accounting for smoking and pre-clinical weight loss. Individuals with high BMI also responded better to treatment modalities such as immunotherapy compared to individuals with a normal BMI. However, these associations varied highly depending on age, gender, and race. Inability of BMI to measure body habitus is the main driver behind this variability. The use of anthropometric indicators and image-based techniques to quantify central obesity easily and accurately is on the rise. Increase in central adiposity is associated with increased incidence and poorer prognosis of lung cancer, contrasting BMI.

Conclusions: The obesity paradox may arise due to the improper use of BMI as a measure of body composition. Measures of central obesity better portray the deleterious effects of obesity and are more appropriate to be discussed when talking about lung cancer. The use of obesity metrics based on anthropometric measurements and imaging modalities has been shown to be feasible and practical. However, a lack of standardization makes it difficult to interpret the results of studies using these metrics. Further research must be done to understand the association between these obesity metrics and lung cancer.

Keywords: Obesity paradox; lung cancer; body mass index (BMI); obesity

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Introduction

Cancer is the second leading cause of death worldwide, with an estimated 14.1 million incident cases and 8.2 million deaths (1). Lung cancer in particular, is the leading cause of global cancer incidence and mortality (2). Besides well-established risk factors such as genetic predisposition, radiation, tobacco use and other environmental exposures, obesity has been linked to the development of many

cancers (3). This is quite concerning as the global prevalence of overweight and obesity has increased by 27% in adulthood and 47% in childhood during the last few decades (4). Excess adiposity has been hypothesized to act as a carcinogen by increasing inflammation, metastatic potential, angiogenesis, and evasion of apoptosis (5). Obesity has also been linked with increased overall cancer mortality in many cancers such as colorectal, liver, gallbladder, pancreatic, and kidney cancer (6). A nuanced relationship exists, however, between obesity and lung cancer risk/prognosis, termed the 'obesity paradox'. Multiple meta-analyses have shown that a high body mass index (BMI) is an independent predictor of lower lung cancer risk, better treatment outcomes, and longer overall survival (OS) (7-9). This goes against conventional understanding of the deleterious biological effects of excess fat.

Many researchers have further investigated to find out the underpinnings of the obesity paradox. One proposed major cause is the improper classification and quantification of obesity. The World Health Organization (WHO) considers overweight or obesity as abnormal or excess accumulation of fat in the body that poses a risk to health (10). The commonly used metric for identifying such unhealthy fat accumulation is BMI, the ratio of body weight to the square of its height (11). BMI between 18.5 and 24.99 kg/m^2 is considered normal, while BMI between 25 and 29.99 kg/m^2 is considered overweight and BMI $\geq$30 kg/m^2 a considered overweight and obese, respectively. A major drawback of BMI as an indicator of health is that it is agnostic of sex, ethnicity, age, and physiological status (12-14). BMI also 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 to subcutaneous fat (15). Additionally, BMI is known to overestimate obesity when there is excess muscle mass and underestimate obesity in cancer patients (14).

Besides BMI, other anthropometric measures of obesity include skin fold thickness, waist circumference (WC), hip circumference (HC), and the waist-hip ratio (WHR). These are easy to measure and validate. Unlike BMI, WC and WHR attempt to assess obesity at the abdominal level and are thought to be better than BMI in identifying the more harmful central adiposity (12,16). Direct and non-invasive assessment of body fat content and distribution is possible with methods such as dual energy X-ray absorptiometry (DEXA), computerized tomography (CT), and magnetic resonance imaging (MRI) (12,13,17,18). DEXA and MRI are both highly accurate measures of obesity but cannot be feasibly performed in all patients due to their high cost (3). Bioelectrical impedance analysis (BIA) is another technique to measure obesity and is convenient, fast, and inexpensive (19). However, it is limited by inaccuracy introduced during illness, dehydration, weight loss, and a BMI of 35 or higher (19). Quantifying obesity using CT allows for assessing body composition as it not only differentiates VAT (visceral adipose tissue), SAT (subcutaneous adipose tissue), and skeletal muscle mass but also identifies fat infiltration into muscle and various organs (12). Measurement of obesity using CT images is quick, highly accurate and can be done retrospectively, allowing for collection of data that can subsequently be analyzed. In all, more than three dozen measures of obesity have been used in research studies, though only very few of them, like BMI, have widely accepted cutoffs (20). A lack of standardization leads to large variations in the correlation between these measures and makes it difficult to synthesize a coherent picture of obesity and its relationship with lung cancer.

Assessing the impact of obesity on lung cancer prognosis is further complicated by treatment modality. Some studies have suggested improved survival in obese patients with a higher BMI to immune checkpoint inhibitor (ICI) therapy (21-24). This maybe because the tumor microenvironment is known to over express programmed cell death protein 1 (PD-1), and programmed death ligand 1 (PD-L1) receptors which in turn causes immune exhaustion (25). Lung cancer patients also tend to lose weight due to disease progression, which if not accounted for as reverse causation, may explain the inverse relationship between BMI and lung cancer prognosis (26). Presence of confounding factors such as tobacco, statin, and metformin use also need to be accounted for when describing the obesity paradox.

We present this article in hopes of clarifying the relationship between various measures of obesity, lung cancer risk and lung cancer prognosis. We present this article in accordance with the Narrative Review reporting checklist (available at https://jtd.amegroups.com/article/view/10.21037/jtd-22-1835/rc).

Methods

The PubMed medical literature database and search engine of the United States National Library of Medicine at the

Table 1 The search strategy summary

Items	Specification
Date of search	10 August 2022
Database	PubMed
Search string	airway[Title/Abstract] OR lung[Title/Abstract] OR nscl*[Title/Abstract] OR pulmonary[Title/Abstract]) AND (cancer[Title/Abstract] OR carcino*[Title/Abstract] OR oncol*[Title/Abstract]) AND (adipo*[Title] OR BMI[Title] OR "mass index"[Title] OR "body composition"[Title] OR fat[Title] OR fatness[Title] OR obes*[Title] OR overweight[Title] OR "waist") NOT embolism NOT stroke NOT infection NOT review[Publication Type]
Timeframe	2018–2022
Inclusion and exclusion criteria	Inclusion: full manuscripts published in English including all study designs Exclusion: reviews of existing literature, abstracts, preprints, and letters to editors
Selection process	Two authors independently read 304 publication titles to identify 159 publications that were relevant; following a reading of the abstracts of these publications, 69 full texts were included in this review

National Institutes of Health were used on 10 August 2022 to identify published research studies. Literature published in English between 2018 and 2022 which included all study designs that were possibly relevant to this review were included. Only full manuscripts were considered. Reviews of existing literature, abstracts, preprints, and letters to editors were excluded. The search string, designed to cover the primary themes of the review and optimized for high sensitivity, was: (airway[Title/Abstract] OR lung[Title/Abstract] OR nscl*[Title/Abstract] OR pulmonary[Title/Abstract]) AND (cancer[Title/Abstract] OR carcino*[Title/Abstract] OR oncol*[Title/Abstract]) AND (adipo*[Title] OR BMI[Title] OR "mass index"[Title] OR "body composition"[Title] OR fat[Title] OR fatness[Title] OR obes*[Title] OR overweight[Title] OR "waist") NOT embolism NOT stroke NOT infection NOT review[Publication Type]. Titles of the 304 publications that resulted with the search were read by two authors to identify 159 publications that were relevant to the topic of obesity's influence on lung cancer. Following a reading of the abstracts of these publications, 69 publications were considered relevant and their full text studied to collate information for this review. The search strategy is summarized in *Table 1*.

Obesity and risk of lung cancer

Obesity has been associated with increased risk of developing various cancers (27). The obesity paradox, however, puts forth the notion that obesity may be protective against the development of lung cancer. This is backed by the fact that most authors have found that a higher BMI is protective against lung cancer (8,26,28-36) (*Table 2*). Some, however, found that this association varies by race and gender. According to Zhu *et al.*, a significant inverse association between lung cancer risk and BMI only existed in women, but not in men (8). Similarly, Zhao *et al.* found that overweight and obese Caucasians had a decreased risk of lung cancer, but not African Americans (35). These differences can be explained by the heterogeneity of fat deposition across gender and race being inadequately captured by BMI (3). Most studies have used BMI as a static measure, however, the use of BMI as a dynamic measure to explore trends in change of BMI has been suggested. Accordingly, Wu *et al.* found that a major change in pre-diagnosis BMI was associated with increased lung cancer incidence (7).

Confounding by smoking and reverse causation due to pretreatment weight change are frequently used explanations to explain the obesity paradox (8,26,28). Lung cancer patients tend to lose weight on disease progression. Mohan *et al.* found that non-small cell lung cancer (NSCLC) patients had significant alteration in their body composition with decreased BMI, fat mass (FM), fat free mass (FFM), fat%, total body weight and functional status compared to healthy age matched controls (38). Thus, low pre-diagnosis BMI may be associated with increased risk of lung cancer if pre-clinical disease is not accounted for. Smoking greatly increases the risk of developing lung cancer (39). Cross sectional nationwide studies in UK and Japan have suggested that current smokers were less likely to be obese than former and never smokers (40,41). The

Table 2 Studies describing the association between risk of lung cancer and various obesity measures

Study	Sample size	Obesity measure	Results	Comment
Abe *et al.*, 2021 (32)	92,098	BMI, weight change	Decreased lung cancer risk with increase in BMI (P_{Trend}<0.001) in men	–
Ardesch *et al.*, 2020 (28)	9,869	ABSI, BMI, WC, WHR	Decreased lung cancer risk with increase in BMI (HR =0.94, 95% CI: 0.91–0.97). Increased lung cancer risk with increase in ABSI (HR =1.17, 95% CI: 1.05–1.30), WC (HR =1.03, 95% CI: 1.01–1.05) and WHR (HR =1.23, 95% CI: 1.09–1.38)	Measures of central obesity may be a better indicator of risk of lung cancer than BMI
Gao *et al.*, 2019 (37)	28,784,269	BMI, WC	Increased lung cancer risk with increase in WC (RR =1.26, 95% CI: 1.14–1.39)	No association between lung cancer incidence and BMI
Jeong *et al.*, 2019 (29)	100,985	BMI, fat mass, lean body mass	Lung cancer risk is inversely associated with BMI (HR =0.73, 95% CI: 0.61–0.88) and lean body mass (HR =0.73, 95% CI: 0.53–1)	–
Sanikini *et al.*, 2018 (30)	12,643	BMI	Decreased risk of lung cancer in obese (OR =0.69, 95% CI: 0.59–0.82) and overweight (OR =0.77, 95% CI: 0.68–0.86) patients	Decreased risk of lung cancer remained statistically significant after stratifying based on smoking history
Wood *et al.*, 2021 (31)	778,828	BMI, metabolic score[†]	Patients with low BMI and high metabolic score had increased lung cancer risk (HR =1.52, 95% CI: 1.44–1.6)	Inverse curvilinear relationship between lung cancer risk and BMI
Wu *et al.*, 2022 (7)	37,085	BMI, weight change	Both BMI gain ≥1.0 kg/m^2/year (HR =2.15, 95% CI: 1.15–4.02) and BMI loss ≤1.0 kg/m^2/year (HR =1.97, 95% CI: 1.12–3.45) associated with increased lung cancer risk	U-shaped restricted spline curve (P_{trend}=0.002) noted for association between annual BMI change and lung cancer risk
You *et al.*, 2022 (33)	138,110	BMI	Decreased risk of NSCLC with increase in BMI (HR_{trend} =0.78, P<0.001)	In GWIA, four independent genetic loci were found to be associated with BMI trajectories on NSCLC risk
Yu *et al.*, 2018 (34)	1,600,000	BMI, WC, WHR	Decreased lung cancer risk with increase in BMI (HR =0.91, 95% CI: 0.90–0.93). Increased lung cancer risk with increase in WC (HR =1.11, 95% CI: 1.08–1.14) and WHR (HR =1.14, 95% CI: 1.11–1.18)	–
Zhao *et al.*, 2022 (35)	53,452	BMI	Overweight (OR =0.83, 95% CI: 0.75–0.93) and obese (OR =0.64, 95% CI: 0.56–0.73) Caucasians had decreased risk of lung cancer, but not African Americans	–
Zhou *et al.*, 2021 (26)	85,716	BMI	Decreased risk of lung AC with increase in BMI (OR =0.86, 95% CI: 0.77–0.96). Increased risk of SCLC with increase in BMI (OR =1.28, 95% CI: 0.77–0.96)	Association persisted after adjusting for smoking using multivariable Mendelian randomization
Zhu *et al.*, 2018 (8)	15,000,000	BMI	Decreased risk of lung cancer with increase in BMI (RR =0.89, 95% CI: 0.84–0.95)	Study population consisted exclusively of never smokers

[†], metabolic score is derived from mid blood pressure, glucose, and triglycerides. BMI, body mass index; ABSI, A Body Shape Index; WC, waist circumference; WHR, waist-to-hip ratio; HR, hazard ratio; CI, confidence interval; RR, relative risk; OR, odds ratio; NSCLC, non-small cell lung cancer; GWIA, genome wide interaction analysis; AC, adenocarcinoma; SCLC, small cell lung cancer.

lower rates of obesity amongst current smokers are a widely proposed confounder in the association between lung cancer and obesity. However, studies and meta-analyses found that the inverse association between BMI and risk of lung cancer existed even after accounting for smoking and reverse causation (8,26,28,30-32,34,35) (*Table 2*). Similarly a meta-analysis by Zhu *et al.*, found an inverse association between BMI and lung cancer risk in a cohort of 15,000,000 never smokers (8). Whereas, in a meta-analysis of 28 cohort studies, Gao *et al.* found no statistically significant inverse association between BMI and lung cancer risk after stratifying for smoking status and excluding effects of pre-clinical cancer (37).

In contrast with studies using BMI, increased risk of lung cancer was found when measures of central obesity such as WC, WHR and A Body Shape Index (ABSI) were used as metrics of obesity (28,34,37). A combination of general and central obesity indicators maybe a better indicator of risk; Yu *et al.* found that low BMI and high WC/WHR was associated with a 40% increased risk of lung cancer compared to a high BMI and normal or moderate WC/WHR (34). Similarly, body composition analysis using DEXA showed that total body fat mass (BFM) was not associated with risk of lung cancer (29). However, a decrease in lean body mass (LBM) was predictive of lung cancer risk, implying that body composition is a more accurate measure of obesity than overall FM.

Studies understanding the relationship between obesity, immune system, and clinical markers of inflammation found that obesity was associated with neutrophil to lymphocyte ratio (NLR), systemic immune inflammatory index (SII) (42,43). A study exploring the risk of 17 cancers in 440,000 participants in the UK Biobank found that NLR, and SII were positively associated with risk of seven cancers including lung cancer (44). Some authors have used indices to measure metabolic dysfunction as a proxy measure of central obesity. Patients with a low BMI and a high metabolic score (calculated using blood pressure, glucose, and triglycerides) were 50% more likely to develop lung cancer than those with a high BMI and a low metabolic score (31). When non-alcoholic fatty liver disease (NAFLD) was used as a sign of metabolic dysfunction, NAFLD patients had higher odds of having lung adenocarcinoma (45). These clinical markers of inflammation and metabolic dysfunction can function as additional biomarkers to better quantify lung cancer risk in high-risk patient populations.

The increased understanding of genetics in the recent past has opened a new avenue to study the associations between obesity, risk of lung cancer development, and confounders such as smoking. A Mendelian randomization (MR) study by Zhou *et al.* found that while high BMI increased the risk of small cell lung cancer (SCLC), and it decreased the risk of adenocarcinoma when adjusted for smoking (26). In another MR study, BMI change from normal weight to overweight/obese was associated with protective effects against NSCLC development after accounting for smoking (34).

Obesity and survival outcomes of lung cancer

Obesity has been shown to be associated with worse survival in other cancers like colorectal, hepatocellular, oropharyngeal, and breast cancer (46-49). However, in lung cancer, the obesity paradox applies not only to risk of lung cancer development, but also to lung cancer survival times. Many authors have found that higher BMI is associated with increased OS in lung cancer (9,50-53) (*Table 3*). Though most studies found a higher BMI to be protective, some authors identified that the relationship between obesity and lung cancer risk is non-linear (52,61). These investigators found a U-shaped hazard ratio relationship between lung cancer OS and BMI on a spline plot. Underweight and morbidly obese (BMI ≥35 kg/m^2) patients had worse survival outcomes. According to Jiang *et al.*, the relationship between BMI and lung cancer survival is affected by race, gender, and smoking status (50). A large meta-analysis of 3,152,552 lung cancer patients found an increase in BMI decreased lung-cancer specific as well as all-cause mortality in Asians (9). Jiang *et al.* showed that the protective effect of being overweight/obese was seen best in African Americans, but not Caucasians; and being underweight was associated with poor survival only among Caucasians (50). A study exploring the interaction between gender, smoking, obesity, and lung cancer found that female ever-smokers at the extremes of BMI had worse OS when compared to male ever-smokers (50).

In the above studies, a high BMI serves as a positive prognostic factor for OS only in some groups of patients. However, other studies have reported no effect of BMI on lung cancer survival after performing multi-variable analysis to eliminate confounders (53-56,58) (*Table 3*). Due to the conflicting nature of the results obtained when BMI is used as the measure for obesity, authors have proposed a shift of focus to WC, WHR and imaging studies to better characterize obesity and body composition.

Leitzmann *et al.*, analyzed the National Institutes of

Table 3 Studies describing the association between lung cancer outcomes and various obesity measures

Study	Sample size	Obesity measure	Results	Comment
Barbi *et al.*, 2021 (54)	513	BMI, VFI	High VFI associated with worse OS (HR =1.84, 95% CI: 1.21–2.81) and worse RFS (HR =1.82, 95% CI: 1.06–3.11)	Supported by immunological data using mouse lung cancer models
Jiang *et al.*, 2021 (50)	20,937	BMI	Obese (HR =0.88, 95% CI: 0.83–0.92) and overweight (HR =0.89, 95% CI: 0.85–0.93) patients associated with better OS Underweight patients associated with worse OS (HR =1.58, 95% CI: 1.43–1.72)	OS is inversely associated with BMI but varies by sex, race, and smoking history
Lee *et al.*, 2018 (51)	173	BMI	BMI ≥23 kg/m^2 associated with better OS (HR =0.45, 95% CI: 0.31–0.79)	Association persisted after adjusting for stage, age, gender, smoking history and ECOG PS
Lee *et al.*, 2018 (55)	171	SAT, VAT volume	Improved PFS in patients with high SAT volume (HR =0.54, 95% CI: 0.3–0.9)	–
Minami *et al.*, 2020 (56)	128	BMI, IMAC, PMI, VSR	BMI, IMAC, PMI, and VSR did not predict OS on multivariable analysis	–
Morel *et al.*, 2018 (53)	7,051	BMI, pre-diagnosis weight loss	Worse OS with increase in patients' pre-diagnosis weight loss: HR =1.17, 1.23, and 1.46 with pre-diagnosis weight loss of 0–5, 5–10, and >10 kg respectively	Pre-diagnosis weight loss eliminates BMI from the multivariable regression model
Nam *et al.*, 2019 (57)	356	BMI	NSCLC patients with low BMI and high BMD have a higher risk of brain metastasis (HR =2.03, 95% CI: 1.21–3.4)	–
Oruc *et al.*, 2022 (58)	200	BMI, BFM	BFM >22% had improved OS compared to those with BFM ≤22% (P=0.01)	–
Sakai *et al.*, 2021 (59)	CRC: 74, NSCLC: 53	FFMI, FMI, SM FF	Increased length of hospital stay for NSCLC patients was associated with sarcopenia status (P=0.027) and increased SM FF% (P=0.035)	–
Shepshelovich *et al.*, 2019 (52)	NSCLC: 25,340, SCLC: 2,787	BMI, BMI change	Improved OS with increase in BMI at diagnosis (HR =0.92, 95% CI: 0.91–0.94)	BMI decrease in young adulthood associated with worse survival
Wang *et al.*, 2018 (9)	3,152,552	BMI	Each 5 kg/m^2 increase in BMI had a 12% lower risk of lung cancer specific mortality (HR =0.88, 95% CI: 0.75–1.02, P<0.01)	BMI was inversely associated with lung cancer-specific and all-cause mortality in Asians but not in Westerners
Yendamuri *et al.*, 2019 (60)	639	BMI	Better OS (HR =0.52) and DSS (HR =0.21) with metformin use in high BMI patients with stage 1 NSCLC	Metformin use improve outcomes only in those with high BMI. Supported by immunological data
Yuan *et al.*, 2022 (61)	7,547	BMI, post-diagnosis BMI change	Moderate (0.5–2: HR =2.45, 95% CI: 2.25–2.67), and large (>2: HR =4.65, 95% CI: 4.15–2.45) post-diagnosis decreases in BMI were associated with worse OS	–

BMI, body mass index; VFI, visceral fat index; OS, overall survival; HR, hazard ratio; CI, confidence interval; RFS, recurrence free survival; ECOG PS, Eastern Cooperative Oncology Group Performance Score; SAT, subcutaneous adipose tissue; VAT, visceral adipose tissue; PFS, progression free survival; IMAC, intramuscular adipose content; PMI, psoas muscle index; VSR, visceral to subcutaneous ration; NSCLC, non-small cell lung cancer; BMD, bone mineral density; BFM, body fat mass; CRC, colorectal cancer; FFMI, fat free mass index; FMI, fat mass index; SM FF, skeletal muscle fat fraction; SCLC, small cell lung cancer; DSS, disease specific survival.

Health and formerly the American Association of Retired Persons (NIH-AARP) Diet and Health study dataset with 225,712 patients and found that patients with a higher WC had a higher lung cancer-specific mortality (62). In a study conducted by our group, VFI (visceral fat index) was calculated as the proportion of total fat area which is truly visceral using CT scans. VFI was found to be an independent negative prognostic factor for recurrence free (RFS), OS and diseases specific survival (DSS) in a cohort of 513 stage I/II NSCLC patients (54). Central obesity (high VFI) was associated not only with shorter survival times, but also with accelerated tumor growth, sharply contrasting the obesity paradox (54). In similar image-based studies, a higher SAT volume was associated with better progression free survival (PFS) and BFM ratio >22% was predictive of longer OS (55,58). Sakai *et al.* reported increased length of hospital stay with increased skeletal muscle fat fraction and sarcopenia (59).

Another added advantage of using image-based studies to define body composition is the ability to identify obese cancer patients with sarcopenia. Sarcopenic obesity is a condition of combined skeletal muscle depletion in obese patients (63). While obesity is defined by WHO as accumulation of fat that negatively affects health, there is very little agreement on the definition of sarcopenia making the diagnosis of sarcopenic obesity even more challenging. Using the widely accepted sarcopenia cut-off suggested by Prado *et al*., Baracos *et al.* suggested a mean overall rate of 9.3% of sarcopenic obesity amongst all cancer patients and a rate of 17.9% in patients with a BMI >25 kg/m^2 (64,65). A meta-analysis of 14 studies exploring the implications of sarcopenic obesity on clinical outcomes in cancer patients found that sarcopenic obesity was significantly associated with dose limiting toxicity, surgical complications, and survival (63). In an observational study of 175 NSCLC patients receiving chemotherapy Gonzalez *et al.* found that sarcopenic obesity was a negative prognostic factor for survival (66).

Low BMI is associated with a higher tumor-node-metastasis (TNM) stage, increased metastasis, ECOG-PS (European Cooperative Oncology Group-Performance Status), and a low FFM which in turn are associated with poor survival (55,57,67,68). Patients presenting with a combination of a higher ECOG-PS and a lower BMI had worse OS compared to a lower ECOG-PS and a higher BMI (51). Some authors have suggested using dynamic measures of weight/BMI change rather than static measurements to better characterize obesity (52,53,61). Decrease in BMI or weight loss at the time of lung cancer diagnosis relative to early adulthood was associated with poor OS (53). Post-diagnosis weight loss (representing cachexia) was also associated with worse OS (52,61). Obesity also potentially modifies the disease progression of lung cancer. Patients with low SAT volume have the highest rate of lung cancer progression and NSCLC patients with low BMI are at a higher risk of brain metastasis than those with high BMI (55,57).

Obesity and therapeutic survival of lung cancer

The complex relationship between obesity and lung cancer outcomes has been further characterized by investigating the effects of increased adiposity on various therapeutic modalities.

Obesity is known to induce a state of 'meta-inflammation' by increasing the secretion of inflammatory cytokines (IL-6, TNF-α) through disruption of the endocrine system (increased insulin resistance, leptin, estrogen levels) (54). Elevated levels of leptin have been shown to increase the expression of PD-1, causing T-cell exhaustion and therefore a reduced immune response in the tumor microenvironment (21,23,54,60,69,70). Thus, the outcomes of ICI therapy are invariably affected by obesity. In a cohort of 61 squamous cell carcinoma patients, Wang *et al.* found a positive linear relationship between pre-treatment BMI and post-treatment blood immune cells, indicating a better response to immunotherapy in individuals with higher BMI (71). Better treatment response also correlated with better survival outcomes (71). Many studies have found that higher BMI was significantly associated with better OS and PFS in patients treated with ICI (22,24,69,71-76) (*Table 4*). This association was strengthened for tumors expressing higher levels of PD-1/PD-L1 within the tumor microenvironment (21,22,69,71,89). In addition to immunotherapy, combination of chemotherapy with immunotherapy was associated with better outcomes compared to chemotherapy alone only in patients with a higher BMI (21,23). Some authors have disputed the association between high BMI and improved immunotherapy outcomes. Liu *et al.* found that the effect of BMI on survival times was only significant in univariate analysis, but not multivariable analysis (83). Others found no association between BMI and response to immunotherapy (73,78,84,85,88) (*Table 4*). Authors have proposed using CT based measures of obesity to better explore this discrepancy. Popinat *et al.* showed that increased subcutaneous fat mass (SCFM) was an independent negative prognostic factor

Table 4 Studies describing the association of chemo and immunotherapy outcomes with various obesity measures

Study	Sample size	Obesity measure	Results	Comment
Arrieta *et al.*, 2022 (77)	133	BMI	Addition of metformin to EGFR TKI therapy was associated with improved PFS (HR =0.47, 95% CI: 0.28–0.78) in patients with BMI ≥24 kg/m^2 only	–
Baldessari *et al.*, 2021 (78)	44	BMI, SMI, VSR	BMI, SMI, and VSR did not predict OS	Inflammation rather than body composition is prognostic
Collet *et al.*, 2021 (72)	272	BMI	BMI ≥25 kg/m^2 associated with longer OS (HR =0.63, 95% CI: 0.44–0.92)	–
Cortellini *et al.*, 2019 (22)	976	BMI	Patients with BMI ≥25 kg/m^2 had longer OS (HR =0.49, 95% CI: 0.38–0.64), PFS (HR =0.71, 95% CI: 0.56–0.9), and TTF (HR =0.67, 95% CI: 0.53–0.85)	–
Cortellini *et al.*, 2020 (24)	1,067	BMI	Obese (OR =16.6, 95% CI: 10.3–26.7) and overweight patients (OR =10.6, 95% CI: 7.5–14.9) experienced more immune related adverse events	Higher BMI linearly correlated with higher grade immune related adverse events and adverse events leading to discontinuation
Cortellini *et al.*, 2020 (23)	1,388	BMI	Obesity is associated with improved ORR (OR =1.61, 95% CI: 1.04–2.5), PFS (HR =0.61, 95% CI: 0.45–0.82) and OS (HR =0.7, 95% CI: 0.49–0.99)	Obesity is associated with improved treatment response rate and survival in patients receiving immunotherapy, but not among patients treated with chemotherapy
Cortellini *et al.*, 2022 (73)	853	BMI	No association between first line chemoimmunotherapy and baseline BMI	–
Degens *et al.*, 2019 (79)	111	Radiation attenuation†, skeletal muscle mass, SAT, VAT, weight loss	Loss of skeletal muscle mass associated with poor OS (HR =0.949, 95% CI: 0.915–0.985)	Loss of muscle mass correlated with radiation attenuation (P=0.015), SAT loss (P<0.001), VAT loss (P=0.029), and weight loss (P<0.001)
Degens *et al.*, 2021 (80)	106	Skeletal muscle mass, SAT, VAT, weight loss	Weight loss >2% during treatment associated with worse OS (HR =2.39, 95% CI: 1.51–3.79)	–
Dragomir *et al.*, 2021 (81)	80	BMI	Decreased PFS with decrease in BMI (OR =0.96, 95% CI: 0.96–1.91) and NLR ≥3 (OR =1.1, 95% CI: 0.38–3.12)	–
Gelibter *et al.*, 2020 (69)	976	BMI	Prolonged OS (HR =0.33, 95% CI: 0.28–0.41), PFS (HR =0.46, 95% CI: 0.39–0.54), and TTF (HR =0.51, 95% CI: 0.44–0.6) in overweight/obese patients	–
Hirsch *et al.*, 2020 (82)	92	BMI, SMI	Sarcopenia was independently associated with increased risk of experiencing irALT (OR =3.84, 95% CI: 1.02–14.46)	BMI was not associated with increased risk of irALT
Imai *et al.*, 2022 (74)	99	BMI	BMI ≥22.1 kg/m^2 was associated with longer OS (P=0.002)	–
Kichenadasse *et al.*, 2020 (21)	2,110	BMI	Improved OS in obese (HR =0.69, 95% CI: 0.54–0.87) and overweight (HR =0.8, 95% CI: 0.67–0.96) patients	Association strengthened for PD-L1 positive tumors. No association for docetaxel treated patients

Table 4 (*continued*)

Table 4 (*continued*)

Study	Sample size	Obesity measure	Results	Comment
Liu *et al.*, 2022 (83)	66	BMI	High BMI associated with improved PFS (P=0.04) on univariate analysis only	–
Magri *et al.*, 2019 (84)	46	BMI, weight loss	Post-diagnosis weight loss of >5% associated with worse OS (HR =2.85, P<0.01)	BMI not associated with OS
Minami *et al.*, 2019 (67)	167	BMI, IMAC, PMI, VSR	Pre-treatment BMI <18.5 kg/m^2 associated with shorter OS (HR =1.7, 95% CI: 1.03–2.81) and shorter PFS (HR =1.72, 95% CI: 1.11–2,67)	Neither pretreatment sarcopenia nor visceral obesity was associated with survival prognosis of NSCLC patients treated with EGFR-TKI monotherapy
Minami *et al.*, 2020 (85)	74	BMI, IMAC, PMI, VFA, VSR	Low IMAC associated with longer OS (HR =0.43, 95% CI: 0.18–0.998)	PMI, VSR and VFA not associated with OS and PFS on NSCLC patients on ICI monotherapy
Nie *et al.*, 2021 (75)	3,768	BMI	Improved OS (HR =0.81, 95% CI: 0.71–0.92) overweight/obese NSCLC patients	–
Nishioka *et al.*, 2022 (86)	74	BMI, LSMI, TATI	Decrease in TATI associated with increased overall response rate (P<0.05) and longer PFS (P=0.03) in non-cachexic patients	No difference in ORR and PFS among cachexic patients
Popinat *et al.*, 2019 (87)	55	FBM, LBM, MBM, SCFM, VFM	Increase in SCFM associated with poor OS (HR =0.75)	–
Sakin *et al.*, 2021 (76)	233	BMI	BMI ≥25 kg/m^2 associated with longer OS (HR =0.41, 95% CI: 0.18–0.91)	–
Tateishi *et al.*, 2022 (88)	324	BMI	No difference in ORR, OS, and PFS observed between overweight and non-overweight patients	–
Wang *et al.*, 2021 (71)	61	BMI	Improved OS (HR =0.15, 95% CI: 0.07–0.32) and PFS (HR =0.23, 95% CI: 0.11–0.48) in patients with BMI >23.2 kg/m^2	Linear positive correlation between pre-treatment BMI and number of post-treatment serum immune cells (r^2>0.7)

†, radiation attenuation is a sign of increase in intramuscular adipose tissue. BMI, body mass index; EGFR TKI, epithelial growth factor receptor tyrosine kinase inhibitor; PFS, progression free survival; HR, hazard ratio; CI, confidence interval; SMI, skeletal muscle index; VSR, visceral-to-subcutaneous ratio; OS, overall survival; TTF, time to treatment failure; OR, odds ratio; ORR, objective response rate; SAT, subcutaneous adipose tissue; VAT, visceral adipose tissue; NLR, neutrophil to lymphocyte ratio; irALT, immune-related acute limiting toxicity; PD-L1, programmed death ligand 1; IMAC, intramuscular adipose content; PMI, psoas muscle index; NSCLC, non-small cell lung cancer; VFA, visceral fat area; ICI, immune checkpoint inhibitor; LSMI, lumbar skeletal muscle index; TATI, total adipose tissue index; FBM, fat body mass; LBM, lean body mass; MBM, muscle body mass; SCFM, subcutaneous fat mass; VFM, visceral fat mass.

for stage IV NSCLC treated by nivolumab (87). Similarly, Minami *et al.* found that low intra-muscular adipose content was predictive of longer OS (85). Some studies have shown that clinical indicators of inflammation such as blood albumin levels, neutrophil counts, C-reactive protein (CRP) and NLR are better prognostic factors than CT based body composition analysis for ICI therapy (78,80,81,84).

Like BMI and weight change, authors have proposed to use the change in body composition as a better prognostic indicator of ICI therapy. Nishioka *et al.* found that a decrease in the total adipose tissue index after ICI therapy was predictive of better overall response rate and PFS time in patients without cachexia (86). Pre-treatment weight loss or decrease in BMI, especially skeletal muscle related protein loss leading to sarcopenia or cachexia was associated with poor ORR, disease control rate (DCR), PFS, and OS (79,80,84,90) (*Table 4*). Body composition has been suggested to affect the pharmacokinetics of ICIs, which in turn may affect the number of immune related adverse events (70,82). Patients with sarcopenia or high BMI reported more adverse events, even though they developed these toxicities later when compared to normal or underweight patients (22,24,70,72,82).

High cholesterol levels and risk of prevalence of diabetes have been known to be associated with obesity (3). Thus, obese patients are more likely to use metformin and statins regularly. According to Patnaik *et al.*, statin use is associated with improved RFS (HR =0.46, P=0.002) in patients with a high BMI only. On tumor transcriptome profiling using RNA sequencing, high expression of tumoricidal genes and statin use were positively correlated. Endoplasmic reticulum stress, caspase induction, NF-kB blockade, and mTOR inhibition are potential routes through which statins influence tumor cell (91). Metformin has also been shown to decrease tumor proliferation and growth in preclinical studies via inhibition of the Krebs cycle and lipid synthesis (92,93). BMI modulates the protective effect of metformin; with the greatest effect seen in patients who are overweight or obese (77,94,95). Metformin use in pts with a BMI >25 is known to significantly improve OS and DSS (60).

Treatment of locally advanced NSCLC (stage III) includes platinum-based chemoradiotherapy (CRT). Success rates of CRT are dependent upon body composition of the patient during and before the start of treatment (96). In contrast to immunotherapy, loss of both fat and FFM was associated with a poor OS (96). Patients with low pre-treatment FFM and a weak handgrip (a clinical indicator of muscle mass) were found to have worse survival, especially in patients with normal BMI and a good functional status (96-98) (*Table 5*). Using malnutrition universal screening tool (MUST), modified Glasgow prognostic score (mGPS) and tumor lesional glycolysis as clinical indicators of malnutrition and inflammation, studies have shown that poor nutrition and systemic inflammation were associated with worse survival outcomes following CRT (99,100) (*Table 5*).

When undergoing surgery for lung cancer, it is expected that obese patients will experience more complications due to having lower lung volumes, less diaphragm excursion and being relatively immobile (101). Numerous studies, however, have shown that overweight and obese BMIs were not predictive of peri- or postoperative complications or length of post-operative hospital stay (102-107). Guerrera *et al.* found that only morbidly obese (BMI ≥40 kg/m^2) patients had increased postoperative morbidity (108). In 433 stage 1 NSCLC patients after surgical resection, BMI was predictive of home oxygen use but not acute post-operative morbidity or mortality (109). Contrary to conventional thought, multiple studies have found that increased pre-surgery BMI predicted better OS (104,106,110-112) (*Table 6*). In addition, other studies showed that underweight BMI was associated with compromised post-operative outcomes, with these patients experiencing more surgical and infectious complications (106). They also had poorer survival outcomes when compared to normal/overweight/obese individuals (104,110,112,113) (*Table 6*). Using abdominal fat measurements from pre-operative positron emission tomography (PET)/CT scans, Choi *et al.* found that adipopenia was associated with reduced OS in stage I lung cancer in post-lobectomy patients (103). Decreased muscle mass and FFM were also independently associated with increased risk of postoperative complications (prolonged air leak, pneumonia) and prolonged length of stay (102,114). When pericardial fat volume was used as a measure of obesity, higher fat volumes were associated with higher BMI and better RFS and OS in NSCLC patients undergoing resection (115). Using metabolic score as a measure of inflammation, Yuan *et al.* found that a combination of BMI and metabolic score was predictive of readmission in NSCLC patients after surgery (116).

A limitation of this review is that is that only English articles in the PubMed database were included. A more comprehensive search strategy including other languages and

Table 5 Studies describing the association of radiotherapy outcomes with various obesity measures

Study	Sample size	Obesity measure	Results	Comment
Abbass *et al.*, 2020 (99)	643	ECOG-PS[†], mGPS[‡], MUST[§], SAT, SMD, SMI, VAT	Higher MUST (HR =1.16), ECOG-PS >1 (HR =1.23), and elevated mGPS (HR =1.2) were independently associated with worse OS	Malnutrition is associated with poor overall survival in patients with lung cancer
Burtin *et al.*, 2020 (97)	936	FFM, handgrip weakness, WHO-PS	In patients with WHO-PS 0 or 1, low FFM combined with handgrip weakness predicted lower OS (HR =1.31, 95% CI: 1.07–1.59)	–
Dolan *et al.*, 2020 (100)	119	ECOG-PS, mGPS, MUST, NLR, SMD, SMI, tumor glucose uptake, visceral obesity[¶]	Higher MUST (HR =1.49, 95% CI: 1.12–1.98) and elevated tumor lesional glycolysis* (HR =2.02, 95% CI: 1.34–3.04) associated with worse OS	Total lesion glycolysis (tumor metabolic activity) and mGPS (systemic inflammatory response) were not associated with body composition
Willemsen *et al.*, 2020 (96)	233	FM, FFM, handgrip strength, weight loss	FFMI and HGS <10th percentile baseline reference values were prognostic for poor OS (HR =1.64, 95% CI: 1.1–2.39). FM loss during CRT was also predictive of poor OS (HR =3.8, 95% CI: 1.79–8.06)	Weight loss was associated with loss of fat and FFM

[†], ECOG-PS includes muscle mass and function; [‡], mGPS reflects systemic inflammation and nutritional status and is a combination of C-reactive protein and albumin levels; [§], MUST include weight loss, BMI, and nutritional intake; [¶], visceral obesity was measured as visceral fat area >160 and >80 cm^2 in males and females respectively; *, tumor lesional glycolysis is a measure of tumor metabolic activity and glucose uptake. ECOG-PS, Eastern Cooperative Oncology Group-Performance Status; mGPS, modified Glasgow prognostic score; MUST, malnutrition universal screening tool; SAT, subcutaneous adipose tissue; SMD, skeletal muscle density; SMI, skeletal muscle index; VAT, visceral adipose tissue; HR, hazard ratio; OS, overall survival; FFM, fat free mass; WHO-PS, World Health Organization-Performance Status; CI, confidence interval; NLR, neutrophil to lymphocyte ratio; FM, fat mass; FFMI, fat free mass index; HGS, hand grip strength; CRT, chemoradiotherapy.

Table 6 Studies describing the association of surgical outcomes with various obesity measures

Study	Sample size	Obesity measure	Results	Comments
Alifano *et al.*, 2021 (110)	54,631	BMI	Overweight (HR =0.84, 95% CI: 0.81–0.87) and obese (HR =0.80, 95% CI: 0.76–0.84) patients had improved OS, whereas underweight (HR =1.51, 95% CI: 1.41–1.63) patients had worse OS	–
Best *et al.*, 2022 (102)	958	BMI, IMAT, muscle and SAT areas at T5, T8, and T10 levels	Increasing muscle area predicted length of stay (coefficient =0.9, P=0.002) and decreased postoperative complications (OR =0.8, P=0.007)	Fat areas and BMI were not significant predictors of either outcome
Choi *et al.*, 2021 (103)	440	FVI[†] and SMI	Adipopenia was associated with reduced 5-year OS (HR =2.2, 95% CI: 1.1–3.8), but not 5-year DFS or postoperative complications	Relationship persisted after adjusting for age, sex, smoking history, surgical procedure, stage, histologic type, BMI, and sarcopenia
Fukumoto *et al.*, 2020 (104)	16,509	BMI	Compared to normal BMI group, worse OS in the underweight group (HR =1.41, 95% CI: 1.27–1.57) and better OS in the overweight group (HR =0.88, 95% CI: 0.8–0.96)	BMI was not predictive of postoperative morbidity and mortality
Guerrera *et al.*, 2022 (108)	4,412	BMI	BMI ≥40 kg/m^2 was associated with increased postoperative morbidity only (OR =2.74, 95% CI: 1.63–4.61)	No increase in conversion rate, blood loss, surgical time, hospital postoperative length of stay, and chest tube duration

Table 6 (*continued*)

Table 6 (*continued*)

Study	Sample size	Obesity measure	Results	Comments
Icard *et al.*, 2020 (111)	304	BMI, muscle mass, weight change	Increased pre-disease BMI (RR =0.66, 95% CI: 0.49–0.89) and pre-surgery BMI (RR =0.72, 95% CI: 0.54–0.98) independently predicted higher OS	–
Li *et al.*, 2019 (105)	1,091	FFM	Low FFM was predictive of prolonged air leak complicating VATS lobectomy (OR =1.98, 95% CI: 1.33–2.96)	BMI was not predictive
Matsuoka *et al.*, 2018 (113)	158	BMI	Low (<18.5 kg/m^2) and high (≥25 kg/m^2) BMI groups had poor OS (HR =1.68, 95% CI: 1.03–2.72) compared to normal BMI group	–
Nicastri *et al.*, 2022 (109)	433	BMI	Overweight (OR =4, 95% CI: 1.6–11.2) and obese (OR =6.1, 95% CI: 2.4–17.5) patients had increased risk of postoperative home oxygen use after lung resection	–
Patnaik *et al.*, 2021 (91)	613	BMI	Statin use associated with improved RFS (HR =0.46, P=0.002) in patients with a high BMI only	Tumor transcriptome profiling using RNA sequencing showed higher expression of tumoricidal genes with statin use in high BMI patients
Rizzo *et al.*, 2022 (114)	107	SAT, SMA, SMD	Decreased SMA (OR =0.8, 95% CI: 0.66–0.96) was associated with increased postpneumonectomy complications in men only	–
Shinohara *et al.*, 2020 (115)	349	Pericardial fat	Low pericardial fat volume associated with poor OS (HR =2.14, 95% CI: 1.21–3.79)	Pericardial fat volume has linear relationship with BMI
Takada *et al.*, 2019 (112)	546	BMI	Underweight BMI associated with poor DFS (HR =1.71, 95% CI: 1.1–2.55) and OS (HR =1.97, 95% CI: 1.16–3.19)	–
Tong *et al.*, 2022 (107)	4,035	BMI	1:1 propensity score matching showed no difference in rates of perioperative outcomes between obese and non-obese patients	–
Wang *et al.*, 2018 (106)	1,198	BMI	Underweight patients have increased post-operative mortality (OR =4.39, 95% CI: 1.31–14.72) and respiratory complications (OR =2.88, 95% CI: 1.27–6.50)	Obesity and overweight did not increase surgical complications or length of stay
Yuan *et al.*, 2022 (116)	115,393	BMI, metabolic score[‡]	Metabolically unhealthy normal (HR =1.10), metabolically unhealthy overweight (HR =1.28), and metabolically healthy overweight (HR =1.15) men had a higher risk of readmission than metabolically healthy normal weight men	Similar results were seen in women

[†], FVI (cm^3/m^2) is the total fat volume (cm^3) standardized to the square of the patient height (m); [‡], metabolic score is derived from mid blood pressure, glucose, and triglycerides. BMI, body mass index; HR, hazard ratio; CI, confidence interval; OS, overall survival; IMAT, intramuscular adipose tissue; SAT, subcutaneous adipose tissue; OR, odds ratio; FVI, fat volume index; SMI, skeletal muscle index; DFS, disease free survival; RR, relative risk; FFM, fat free mass; VATS, video-assisted thoracic surgery; RFS, recurrence free survival; SMA, skeletal muscle area; SMD, skeletal muscle density.

databases could have yielded more studies to incorporate.

Conclusions

The relationship between obesity and lung cancer is nuanced. The association between obesity or body composition and lung cancer risk and outcomes varies not only depending on age, gender, and race but also the metric used to define them. Obesity defined using BMI is associated with a decreased risk of lung cancer incidence and mortality, thus giving rise to the term 'obesity paradox'. When assessing the 'obesity paradox' care must be taken to account for confounding factors such as smoking and reverse causation. In addition, the inability of BMI to differentiate between different patterns of fat distribution has also been well documented. The use of CT and MRI based techniques have been recently proposed as a gold standard to define body composition. Although the use of obesity metrics based on the above imaging modalities have been shown to be feasible and practical, a lack of standardization has led to difficulty interpreting study results. Further research must be done to understand the association between these obesity metrics and lung cancer. Clarifying the association between obesity and lung cancer is important for the development of novel preventive, and possibly therapeutic strategies.

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Footnote

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