Title

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Journal

Journal of Thoracic Oncology, 14(9)

ISSN

1556-0864

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Publication Date

2019-09-01

DOI

10.1016/j.jtho.2019.05.031

Peer reviewed

HHS Public Access

Author manuscript

J Thorac Oncol. Author manuscript; available in PMC 2020 March 01.

Published in final edited form as:

J Thorac Oncol. 2019 September ; 14(9): 1594–1607. doi:10.1016/j.jtho.2019.05.031.

Body Mass Index (BMI), BMI Change, and Overall Survival in Patients With SCLC and NSCLC: A Pooled Analysis of the International Lung Cancer Consortium

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Disclosures: The authors declare no conflict of interest.

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Abstract

Introduction: The relationships between morbid obesity, changes in body mass index (BMI) before cancer diagnosis, and lung cancer outcomes by histology (SCLC and NSCLC) have not been well studied.

Methods: Individual level data analysis was performed on 25,430 patients with NSCLC and 2787 patients with SCLC from 16 studies of the International Lung Cancer Consortium evaluating the association between various BMI variables and lung cancer overall survival, reported as adjusted hazard ratios (aHRs) from Cox proportional hazards models and adjusted penalized smoothing spline plots.

Results: Overall survival of NSCLC had putative U-shaped hazard ratio relationships with BMI based on spline plots: being underweight (BMI < 18.5 kg/m^2; aHR = 1.56; 95% confidence interval [CI]:1.43–1.70) or morbidly overweight (BMI > 40 kg/m^2; aHR = 1.09; 95% CI: 0.95–1.26) at the time of diagnosis was associated with worse stage-specific prognosis, whereas being overweight (25 kg/m^2 ≤ BMI < 30 kg/m^2; aHR= 0.89; 95% CI: 0.85–0.95) or obese (30 kg/m^2 ≤ BMI ≤ 40 kg/m^2; aHR = 0.86; 95% CI: 0.82–0.91) was associated with improved survival. Although not significant, a similar pattern was seen with SCLC. Compared with an increased or stable BMI from the period between young adulthood until date of diagnosis, a decreased BMI was associated with worse outcomes in NSCLC (aHR = 1.24; 95% CI: 1.2–1.3) and SCLC patients (aHR=1.26 (95% CI: 1.0–1.6). Decreased BMI was consistently associated with worse outcome, across clinicodemographic subsets.

Conclusions: Both being underweight or morbidly obese at time of diagnosis is associated with lower stage-specific survival in independent assessments of NSCLC and SCLC patients. In addition, a decrease in BMI at lung cancer diagnosis relative to early adulthood is a consistent marker of poor survival.

Keywords

Body mass index; Lung cancer; Survival

Introduction

The relationship between weight and cancer survival is complex. Being significantly obese or underweight may impair the efficacy of and tolerance to treatment. Examples include the impact of such extreme weight on surgical comorbidities and when dosing chemotherapeutic agents.[1–5]

Obesity has long been associated with worse cancer outcomes. In the United States, being overweight was estimated to account for 14% of all cancer deaths in men and 20% in women, but this was studied in a cohort that was initially cancer-free, as opposed to a cohort of incident cancer patients; therefore, the reported mortality rates combined the effect of obesity on both cancer incidence and cancer outcomes.[6] Obesity can cause systemic physiologic alterations, such as higher insulin resistance, which has been linked to poor cancer outcomes, chronic inflammation, and abnormal nutrient homeostasis, which may lower the barrier for oncogenic transformation by driving cellular proliferation and resisting apoptosis.[7–9] The American Society of Clinical Oncology has investigated the association of obesity with cancer in one of its core initiatives in 2014, aiming to raise awareness of this relationship.[10,11] Lung cancer stands apart from other solid tumors. In previous studies, an excess mortality due to obesity was not described for lung cancer; instead, overweight and obese patients had improved outcomes.[6,12–19]

In studies covering both resectable and metastatic lung cancers, the worst outcomes were observed in underweight patients as defined by having a body mass index (BMI) less than 18.5 kg/m^2.[6,12–15,20–29] Being severely underweight may be an indicator of cancer cachexia, which is a well-described marker of poor outcome on cancer mortality.[30–35] Weight in the years before lung cancer diagnosis has also been assessed. For example, a prior case control study of 2285 patients reported no significant association between BMI at 2 years before lung cancer diagnosis and mortality, whereas a strong association was reported between BMI less than 18.5 kg/m^2 at diagnosis and death.[16] Associations with temporal changes in BMI before diagnosis were not reported.

There remain multiple key knowledge gaps in this research field, most commonly due to limited sample size and the single-site nature of many published series. Firstly, as most published reports focused on NSCLC, separate analyses of SCLC are scarce, whereas none have evaluated NSCLC and SCLC in parallel.[36–39] Secondly, past studies have not assessed the role of morbid obesity (defined as BMI > 40 kg/m^2) on survival, but have focused on complication rates in both obese and morbidly obese patients.[17,40,41] This is an important knowledge gap, as the only available data suggest that all overweight and obese patients have improved survival regardless of the magnitude of the BMI value. Thirdly, prior analyses have mostly assessed the prognostic role of BMI captured at the time of diagnosis, but have not evaluated BMI in a patients' prior healthy state. Although recent weight loss around the time of diagnosis has been associated with poor prognosis, longer-term changes in BMI (i.e., from the time of young adulthood until diagnosis) have not been studied previously.[21,32,35,42,] Evaluation of BMI changes over a longer time may reflect metabolic or biologic effects that can both impact cancer risk and prognosis.[7–9] In a large, multicenter, multinational cohort with special consideration of morbid obesity and SCLC patient subsets,

we describe the prognostic association of three main BMI measurements: BMI at diagnosis, BMI at young adulthood (a surrogate for BMI when healthy), and change in BMI (ΔBMI) from a young adulthood to the time of diagnosis.

Methods

Study Population

The International Lung Cancer Consortium was established in 2004 with the aims to share compatible data and maximize resource sharing for lung cancer epidemiology research. Full details have been provided previously and are available at http://ilcco.iarc.fr.[43–48] To be included in the present pooled analysis, studies had to have data on BMI at lung cancer diagnosis, lung cancer type (SCLC versus NSCLC), date of diagnosis, stage at diagnosis, vital status at last follow-up, and date of death. Optional variables included BMI at periods other than at diagnosis. The individual-level data across studies were then pooled and checked for inconsistency, inadmissible values, aberrant distributions, and outliers before being harmonized into a common data set. Written informed consents were obtained from all study participants, and each study was approved by its respective local institutional human subject review board.

Statistical Analysis

Harmonization of epidemiologic data elements has been previously described.[44] Harmonization of outcomes-related variables is described in the Supplemental Data. Separate analyses were performed for NSCLC and SCLC. Overall survival (OS) was assessed using Kaplan-Meier curves and log-rank tests in univariable analyses. OS was assessed using penalized smoothing spline (PSS) curves (continuous BMI variable) and Cox proportional hazards models (continuous and categorical variables) in multivariable analyses, adjusting for clinically relevant factors identified in the univariable analyses.[49,50] A detailed description of the PSS models is provided in the Supplemental Data. Spline curves are functions that are defined piecewise by a polynomial, allowing complex shapes of relationships with continuous variables to be modeled. In addition to treating each BMI variable as a continuous variable, BMI at diagnosis and BMI during young adulthood (defined as ages 18 to 25 years) were also categorized into standard clinical groupings of less than 18 kg/m^2 (underweight), 18 to less than 25 kg/m^2 (normal weight), 25 to less than 30 kg/m^2 (overweight), and 30 to less than 40 kg/m^2 (obese) with the morbidly obese defined as greater than 40 kg/m^2. Analyses were performed based on the pooled data, but subset analyses within individual studies were performed to evaluate consistency across studies. The clinical multivariable survival analysis that generated the base models included all variables with p values less than 0.05 on univariable analysis. To this base model, various definitions of BMI (BMI at diagnosis, BMI at young adulthood, ΔBMI), were added to the clinical multivariable model individually, as these variables were partially correlated. The association between BMI variables was tested using Pearson's correlation test. Change in BMI (ΔBMI) from young adulthood to the time of diagnosis was used to correct partially for

Supplementary Data
Note: To access the supplementary material accompanying this article, visit the online version of the *Journal of Thoracic Oncology* at www.jto.org and at https://doi.org/10.1016/j.jtho.2019.05.031.

heterogeneity of baseline (pre-illness) BMI across the population because it uses the same person's BMI at a prior, presumed healthy state (young adulthood) as a self-control. This study focuses on the primary relationships between BMI and survival; interaction analyses between BMI and other variables on survival will be reported in separate articles.

Sensitivity analyses were pre-planned to deal with potential issues related to study heterogeneity, including performing analyses that omitted participants/studies that had the following conditions, one at a time: the two Surveillance, Epidemiology, and End Results Program-staged studies; one study that used grade as a surrogate for stage, any single large studies that had more than 15% of the total population, and individual participants who were originally staged before the A/B substages were incorporated into the staging system (conservatively estimated to be before the year 2000, as the sixth edition of the American Joint Committee on Cancer staging manual was released in 1998). The fixed-effect model was used when evaluating the impact of different study groups. Given that BMI norms may be different by race, sensitivity analyses by ethnicity were performed that omitted any minority ethnicities that contributed more than 15% of the total sample.

Results

Patient and Characteristics

A total of 29,217 patients met the inclusion criteria from the 16 studies and were included in the base (clinical) model analysis (Supplementary Table 1). Patient characteristics of the pooled population according to lung cancer type are shown in Table 1. Studies were from North America, Europe, and Asia; median age was 65 years; 54% were males; the majority was ever-smokers; 10% had SCLC and the most common NSCLC subtype was adenocarcinoma; overall median follow-up time was 3.9 years; and 71% patients had died during follow-up.

BMI at diagnosis was available for 79% of patients, whereas BMI before diagnosis was available for 22% of patients. Median BMI at diagnosis and young adulthood was 25 kg/mg^2 and 23 kg/mg^2, respectively; the correlation between these two values was 0.46 ($p < 0.001$). Supplementary Table 2 describes the median OS and median follow-up times by stage, showing consistency with stage-specific expected median OS.

Patient Characteristics and OS

The results of the univariable analysis for OS are summarized in Table 2. Higher cancer stage, being older, being male, and not graduating from high school were each associated with lower survival rates for both NSCLC and SCLC. Cumulative smoking exposure, squamous cell histology, recent year of diagnosis, and being of African (black) ancestry were associated with lower survival rates for NSCLC. Multivariable analysis confirmed these variables as independently associated with survival (Table 2). Cumulative smoking was not included in the final multivariable model due to missing data for a large number of patients (Table 2). However, results remained unchanged in the subgroup of patients with available cumulative smoking data (Supplementary Table 3).

OS and BMI at Diagnosis, BMI in Young Adulthood, and Change in BMI Between These Two Timepoints

Univariable and multivariable analyses of the association of BMI at a young adult age, BMI at diagnosis, and change in BMI with OS are shown in Table 2.

The association of BMI at diagnosis and OS is depicted in PSS curves adjusted for the clinical base model (Figs. 1A and B, Table 2) and the unadjusted KaplanMeier survival curves (Figs. 1C and D, Table 2). For patients with NSCLC (Figs. 1A and C), there was a strong association with higher risk of death in underweight patients when compared to "normal" weight individuals; risk of death was lowest in "normal," overweight, and obese patients, but when the BMI was greater than 40 kg/mg^2 (morbid obesity), the risk of death increased again (Figs. 1A and C, Table 2). For SCLC (Figs. 1B and D), although there was no statistically significant association and the magnitude of hazard ratios (HRs) were smaller, the overall shape of HRs across different BMIs was similar to that of NSCLC with greater risks in the lowest and highest BMI groups (Fig. 1B versus A, Table 2). Analysis of the association between BMI at diagnosis and lung cancer-free survival showed similar findings (Supplementary Fig. 1), except for an attenuation of the increased risk of lung cancer-specific death in morbidly obese individuals.

The corresponding associations between BMI in young adulthood and OS are shown in the PSS curves (Figs. 2A and B), Kaplan-Meier survival curves (Figs. 2C and D), and summarized in Table 2. There was no strong association between BMI in young adulthood and OS in NSCLC (Figs. 2A and C, Table 2). However, there was a statistically significant relationship between being underweight during young adulthood and having poorer survival after diagnosis with SCLC; this relationship is revealed in the multivariable analysis (Fig. 2B, Table 2) that corrected for confounding prognostic variables than in the univariable analysis (Fig. 2D, Table 2).

The association between the change in BMI (ΔBMI) from early adulthood to the time of lung cancer diagnosis and OS is depicted in the PSS curves (Figs. 3A and B), the Kaplan-Meier survival curves (Figs. 3C and D), and summarized in Table 2. Relative to the BMI during early adulthood, a decrease in BMI at diagnosis was associated with worse OS when compared to patients who had similar or increased BMI at the time of diagnosis for patients with NSCLC. The benefit of an increase in BMI was present significantly for increases as large as ΔBMI of +12. There was a similar association in SCLC (Table 2, Figs. 3B and D), except that the benefit of a stable/increased BMI only occurred up to DBMI of +6 (an increase of 6 kg/m^2 of BMI). Fewer than 10% of patients had a ΔBMI greater than +6, suggesting that the estimates more than ΔBMI greater than +6 may be hard to interpret.

Subset Analyses and Sensitivity Analyses

Subset analyses of the individual studies confirmed that 15 of 16 individual studies reported that underweight patients had numerical HRs above unity, consistent with the pooled analysis.

When evaluating subset relationships between BMI at diagnosis and OS, BMI at young adulthood, and ΔBMI (Supplementary Figs. 2–4) by age, sex, education, smoking status,

ethnicity, histology, and stage, the most consistent relationship seen across all subsets was observed with ΔBMI. A decrease in BMI was associated with an increase in risk of death in all subsets of NSCLC and in most subsets of SCLC (where none of the subsets were associated with a decrease in risk). In contrast, both BMI at diagnosis and BMI in young adulthood showed much more heterogeneous associations.

The association between OS and BMI at diagnosis, in young adulthood, or changes in BMI before diagnosis remained similar across multiple pre-planned sensitivity analyses (Supplementary Table 3). These sensitivity analyses removed patients with data variables one-by-one and assessed whether the subsequent primary association remained similar after removal. Sensitivity studies confirmed consistency of the primary associations reported, despite minor variation in the magnitude of associations.

Discussion

This large pooled analysis identified a number of novel findings of the relationship between BMI variables measured in young adulthood, changes before diagnosis and at the time of diagnosis, and lung cancer survival outcomes. We describe that DBMI, that is, a change in BMI between early adulthood and the diagnosis date, was associated with OS in lung cancer. Specifically, a decrease in BMI when compared to a remote period at young adulthood is consistently associated with poorer lung cancer survival across age groups, sex, smoking status, stage, and histology with adjusted HRs of approximately 1.25. Its consistency in association across many subgroups suggests its potential utility as a clinically useful global marker of lung cancer prognosis.

We also report a potential U-shaped association between BMI at diagnosis and OS with greater mortality in the extreme groups of underweight and morbidly obese patients, relative to patients who are normal weight, with the best outcomes in those who are overweight or obese (but not morbidly obese). These relationships appear to be similar between NSCLC and SCLC patients, but more pronounced in the NSCLC patients. Whereas the increase in mortality in the underweight lung cancer patients is consistent across all analyses, the increase in mortality in the morbidly obese lung cancer patients is not as clear. The number of morbidly obese patients is modest, and the relationship is attenuated when evaluating lung cancer-specific mortality. Thus, the increase in mortality in the morbidly obese patients may be due to non-lung cancer-related causes, especially given the known increase in risk of death from all causes associated with morbid obesity. Our results also confirm findings in other patient cohorts that being overweight or obese at lung cancer diagnosis was associated with improved OS when compared to patients with normal BMI.[6,12–19] The association between low BMI and lower OS rates have been described for several malignancies, including lung cancer, with similar effect size.[6,12–15,20–29] However, the positive association between high BMIs between 25 and 40 kg/mg^2 and OS for NSCLC patients is contrary to the inverse association described for most other malignancies.[6,10,51–53] The reasons for such findings in lung cancer remain unclear, but several biologic explanations have been postulated.

In a meta-analysis of more than 10,000 patients, Zhu et al.[54] reported that increasing BMI is associated with lower lung cancer risk in never-smokers, especially in women, raising questions whether estrogens play a protective role in lung cancer carcinogenesis. Effects on prognosis were not studied. A sex difference in outcomes is suggested by our results. Both low BMI at diagnosis and a decrease in ΔBMI appear to adversely affect OS to a greater extent in women than in men (Supplementary Figs. 2 and 4), indirectly suggesting a potential hormonal influence on survival. In exploratory analyses, these sex differences were not found to be ethnically driven (data not reported), and are thus unlikely to be driven solely by molecular profiles (as Asian women have a much higher chance of carrying an EGFR-activating mutation).

Biologically, the finding of similar prognostic relationships between BMI at diagnosis and ΔBMI in Asians is important (Supplementary Figs. 2–4), as Asians diagnosed with NSCLC have different molecular profiles and outcomes compared to other ethnicities.[55] Thus, our results suggest that these BMI-survival relationships transcend histomolecular subtype differences, although conclusive evidence would need to be based on molecular profiling data, which we do not have access to for this project.

Dahlberg et al.[13] found a time-dependent relationship whereby obesity initially led to improved outcomes in stage IV patients treated with chemotherapy early in follow-up, but that the risk of death increased in obese patients after 16 months. A time-dependent analysis of our stage IV patients did not confirm such an association in our sample (data not reported).

In our pooled analysis, the relationships in both BMI at diagnosis and ΔBMI were consistent across different disease stages, including stage IA patients who typically undergo only surgical resection, and stage IV patients, who typically undergo only systemic therapy. Such consistency suggests that either the effects of BMI on survival are treatment-independent, or that multiple treatments interact with BMI in a similar manner on survival outcomes.

Compared to normal BMI during early adulthood, a significantly worse prognosis in patients with SCLC who were underweight during early adulthood was an unexpected finding, but must be interpreted with caution given the small numbers of patients. Further, because of missing data, we were not able to account for cumulative smoking exposure or comorbidities in this specific analysis. Where data were available, adjustment for smoking did not influence most results; the exception was a larger HR when comparing the underweight versus normal BMI patients at both diagnosis and in young adulthood, which was observed in both NSCLC and SCLC. These data suggest that it is possible that being underweight during early adulthood was also associated with heavier tobacco consumptions, which led to greater comorbidities at the time of diagnosis, and thus a worse prognosis. Future analyses could attempt to quantify directly cumulative smoking exposure, and particularly intensity of smoking in early adulthood, and compare it OS after lung cancer diagnosis.

The relatively better OS in patients with BMI from 18.5 kg/mg^2 to 40 kg/mg^2, specifically in stage II-IV patients, is reassuring from a chemotherapy dosing perspective, as the vast majority of patients will fall in this range of BMIs. Although there are data regarding the

importance and safety of full dosing based on true body weight, some overweight/obese patients are still under-dosed based on an assumed ideal body weight, or a capped body surface area of 2 m^2.[56] Although we had no dosing data for the patients included in this analysis, it is reassuring that OS for overweight patients is actually better than for those with BMI values within normal limits in patients with disease stages that are generally treated with chemotherapy. OS for patients with BMI greater than or equal to 40 kg/mg^2 were found to be worse comparable to patients with normal BMI. Whether this loss of the protective effect of high BMI represents the OS effect of comorbidities associated with higher BMI, suboptimal dosing, or other factors is unknown.

Our study has several limitations. First, the harmonization of different datasets collected in different countries and periods, with lack of treatment data, might have introduced external bias, although multiple sensitivity analyses showed similar results. Secondly, BMI data was derived from self-reported data, a method known to be highly correlated with measured height and weight, with slight overestimation of height and underestimation of weight.[57–59] Thus, reported BMI probably slightly underestimates true BMI values. Thirdly, BMI during early adulthood is also prone to recall bias and the reported changes may well have occurred recently, rendering ΔBMI a surrogate for recent weight loss. However, BMI at additional timepoints between young adulthood and at diagnosis was unavailable for this analysis. That the association between DBMI and OS was observed consistently across stages, including stages I and II NSCLCs where patients are least likely to be symptomatic from their cancer, suggests that the ΔBMI relationship is not completely attributable to recent weight loss as a symptom of the lung cancer. Fourthly, the strength of the association between BMI and OS in the morbidly obese group is not as strong as the associations with underweight patients. Thus, the finding of adverse outcomes associated with morbid obesity is more preliminary in nature. Fifthly, the analysis did not include data on different lung cancer treatments, a potential confounding factor. Some individual studies did provide treatment data, but when treatment and stage were included in the same model, there was significant collinearity such that either stage or treatment needed to be removed. Because data for stage was complete whereas treatment data was limited, stage was ultimately left in the final models. Finally, some patients were excluded from the analysis due to missing data, potentially introducing additional selection bias.

Recent data indicate that measures of body composition, capable of distinguishing muscle and fat, and a diagnosis of sarcopenia may be a better predictor for mortality in cancer.[60–64] However, in the absence of data from these markers, as our results suggest, changes in BMI from a healthy pre-morbid state may be a better prognosis surrogate than BMI at diagnosis.

In summary, we identified a U-shaped relationship between BMI at diagnosis and OS in patients with NSCLC, with the worst prognosis in underweight and morbidly obese patients. However, we also reported sex, ethnicity, and smoking heterogeneity in the prognostic relationship with BMI at diagnosis in our study. Thus, there should be caution regarding generalizing this relationship, given that each of these demographic variables can also influence baseline pre-morbid BMI. Instead, ΔBMI generated a more consistent prognostic relationship with OS across clinicodemographic groups. A decrease in ΔBMI from early

adulthood to the time of diagnosis was associated with a modest, but significant 20% to 30% increase in risk of dying.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Drs. Shepshelovich, Fares, Brown, and G. Liu were supported by funding from the Alan Brown Chair in Molecular Genomics, the Posluns Family Fund, and the Lusi Wong Fund. Drs. Schwartz and Wenzlaff and data collection at Karmanos were supported by National Institutes of Health (NIH) grants and contracts R01CA60691, R01CA87895, P30CA022453, and HHSN261201300011I. CARET is funded by the National Cancer Institute (NCI), NIH through grants U01-CA063673, UM1-CA167462, and U01-CA167462. Drs. Z. Zhang and Morgenstern were supported by DA/CA11386 and CA90833. Drs. Shirashi and Kohno were supported by the Health and Labour Sciences Research Grant. Drs. Ryan and Harris were supported by the Intramural Research Program of the Center for Cancer Research, NCI.

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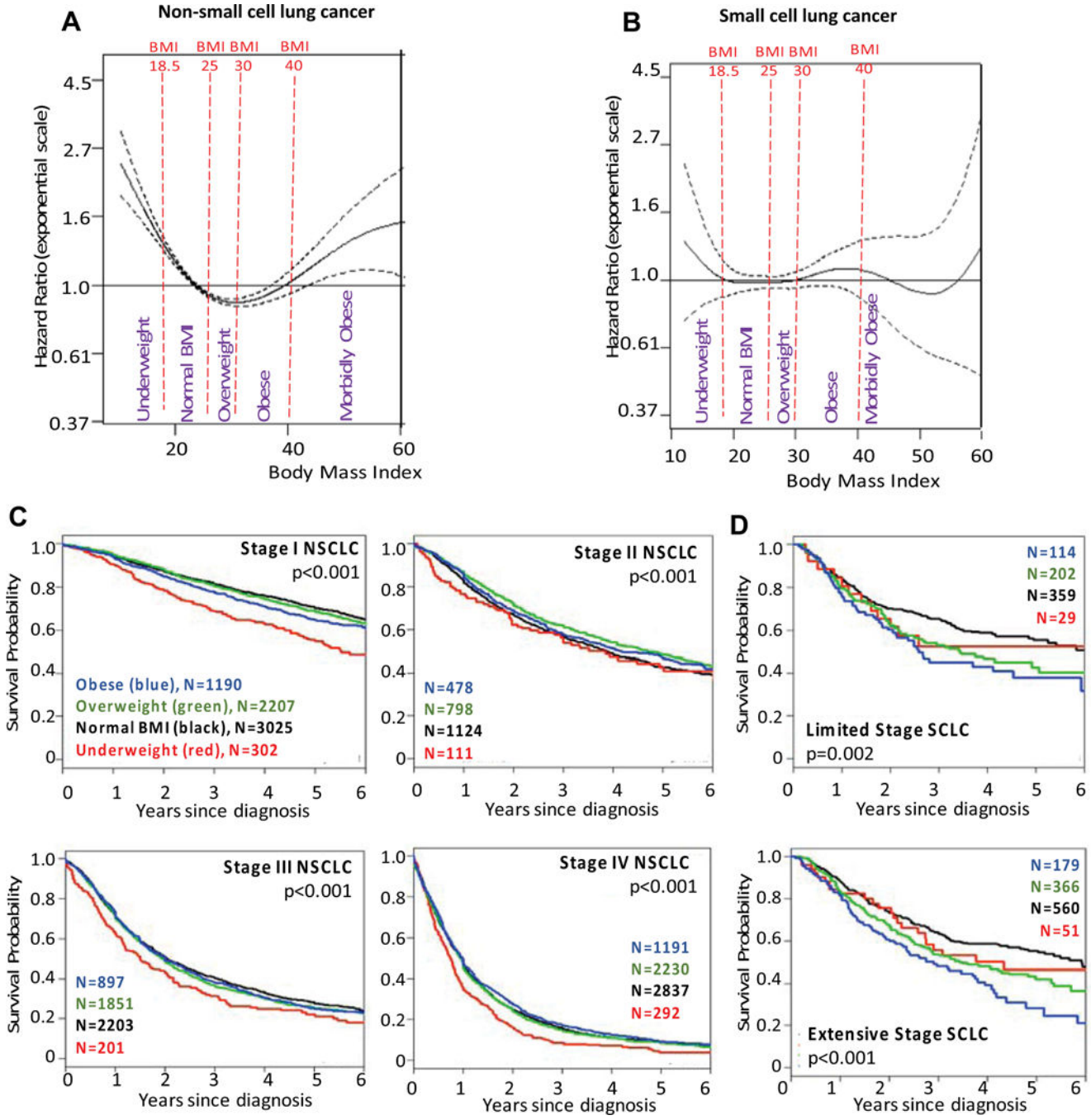

Figure 1.

The hazard ratio of overall survival based on penalized smoothing spline by body mass index (BMI [kg/m^2]) at diagnosis for (*A*) NSCLC and (*B*) SCLC, and Kaplan Meier survival curves for (*C*) NSCLC and (*D*) SCLC patients. BMI data points above 60 kg/m^2 are sparse, explaining the wide confidence intervals in *A* and B. Data are sparse when BMI is greater than 60 kg/m^2, and interpretation should be made with caution.

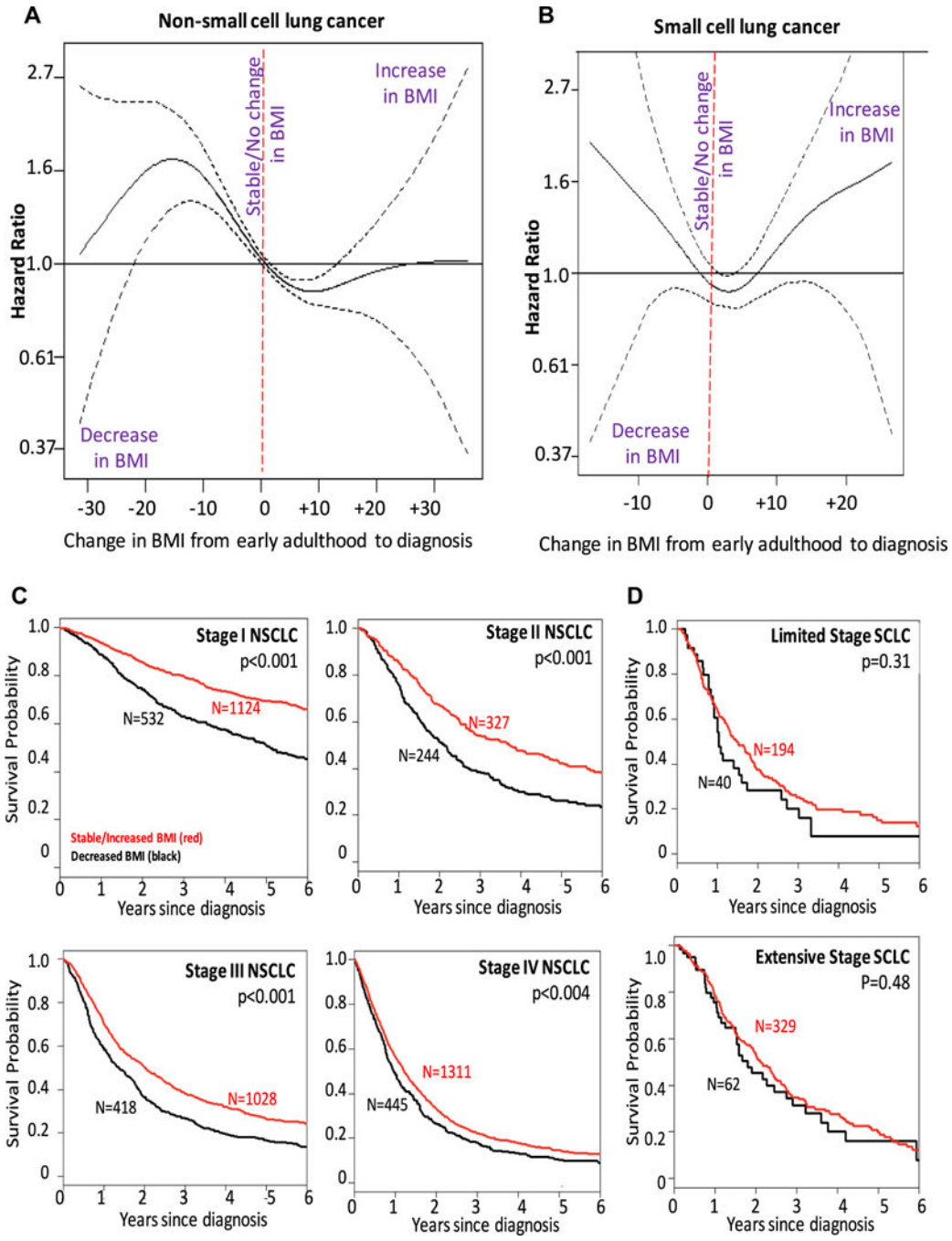

Figure 2.

The hazard ratio of overall survival based on penalized smoothing spline by body mass index at young adulthood (BMI, kg/m^2) for (*A*) NSCLC and (*B*) SCLC, and Kaplan Meier survival curves for (*C*) NSCLC patients and (*D*) SCLC patients. Young adulthood is defined as an age between 18 and 25 years, or approximately 20 years.

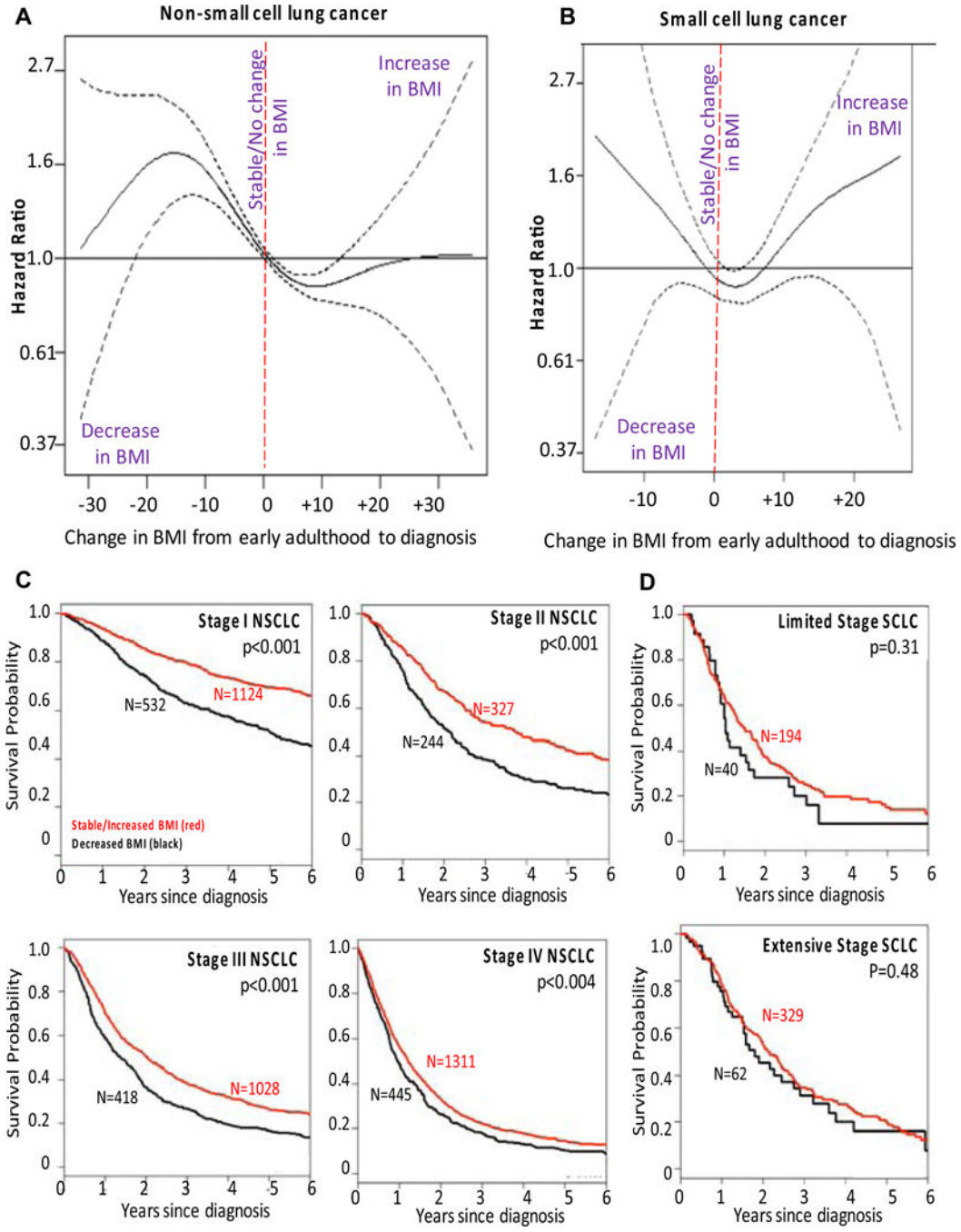

Figure 3.

The hazard ratio of overall survival based on penalized smoothing spline by change in body mass index at diagnosis (ΔBMI, kg/m^2) for (*A*) NSCLC and (*B*) SCLC, and Kaplan Meier survival curves for (*C*) NSCLC patients and (*D*) SCLC patients. The change compares the relationship between BMI at young adulthood (around 20 years of age) to the BMI at the time of the diagnosis as a means of correcting for heterogeneity of BMI in a healthy population.

Table 1.

Patients Characteristics According to Lung Cancer Type

		NSCLC		SCLC	
Variable	**Categories**	**Summary Statistics**	**No. of Studies Providing Data**	**Summary Statistics**	**No. of Studies Providing Data**
Total counts	N (%)	26,430 (100%)	16	2787 (100%)	16
Age, years	Median (range)	65 (17–97)	16	65 (22–92)	16
Year of diagnosis	Median (range)	2006 (1974–2015)	16	2005 (1987–2015)	16
Sex, n (%)	Males	14150 (54%)	16	1561 (56%)	16
High school graduate	No	1927 (11%)	14	Low: 220 (12%)	14
	Yes	15,373 (89%)		High: 1643 (88%)	
	Missing	7558		897	
Ethnicity	Caucasian	18,141 (76%)	16	2484 (93%)	16
	Asian	3938 (17%)		59 (2%)	
	Black	1020 (4%)		33 (1%)	
	Other	686 (3%)		98 (4%)	
	Missing	2645		113	
Stage	1A	5478 (21%)	16	–	16
	1B	2448 (9%)		–	
	2A	1131 (4%)		–	
	2B	1884 (7%)		–	
	3A	3905 (15%)		–	
	3B	2434 (9%)		–	
	4	9150 (35%)		–	
	Limited stage	–		1135 (41%)	
	Extensive stage			1652 (59%)	
Histology	Squamous cell	6024 (23%)	16	–	16
	Adenocarcinoma	15,812 (60%)		–	
	Other	4527 (17%)		–	
	Small cell	–		2787 (100%)	
	Missing	67		–	

Variable	Categories	NSCLC		SCLC	
		Summary Statistics	No. of Studies Providing Data	Summary Statistics	No. of Studies Providing Data
Smoking Status	Ever-smoker	17,118 (84%)	14	2389 (98%)	14
	Never-smoker	3201 (17%)		54 (2%)	
	Missing	3847		57	
Pack years among ever-smokers	Median (range)	43 (0–275)	13	50 (0.5–200)	13
	Missing	6304		748	
BMI at diagnosis, kg/mg^2	Median (range)	25.2 (11-87)	16	26.3 (12-70)	16
	BMI < 18.5 (underweight)	906 (4%)		65 (3%)	
	18.5 ≥ BMI < 25 (normal BMI)	9189 (44%)		765 (36%)	
	25 ≥ BMI < 30 (overweight)	7086 (34%)		815 (38%)	
	40 ≥ BMI ≥ 30 (obese)	3435 (16%)		487 (23%)[a]	
	BMI ≥ 40 (morbidly obese)	321 (2%)		655	
	Missing	5493			
BMI at young adult age, kg/mg^2	Median (range)	22.7 (10-71)	7	22.7 (14-43)	7
	BMI < 18.5 (underweight)	397 (7%)		31 (6%)	
	18.5 ≤ BMI <25 (normal BMI)	3518 (65%)		398 (71%)	
	25 ≤ BMI <30 (overweight)	1121 (21%)		95(17%)	
	30 ≤ BMI ≤ 40 (obese)	378 (7%)		35 (6%)[a]	
	BMI ≥ 40 (morbidly obese)	40 (1%)		134	
	Missing	943			
BMI change from young adult age to diagnosis, kg/mg^2	Decreased BMI	1639 (30%)	7	112 (20%)	7
	No change/ Increased BMI	3790 (70%)		442 (80%)	
	Missing	968		139	

[a]There were too few morbidly obese individuals to form its own category in SCLC; instead, obese and morbidly obese were grouped together. BMI, body mass index.

Table 2.

Association Between Patient Characteristics and Overall Survival: Univariable and Multivariable Analysis

Variable	Comparisons	NSCLC, HR (95%CI), *p* value		SCLC, HR (95% CI), *p* value	
		Univariable Analysis	Multivariable Analysis[a]	Univariable Analysis	Multivariable Analysis
Base (clinical) model variables					
Stage	1B vs. 1A	1.52 (1.4–1.6), <0.001	1.46 (1.35,1.58), <0.001	–	–
	2A vs. 1A	1.72 (1.6–1.9), <0.001	1.60 (1.45,1.76), <0.001	–	–
	2B vs. 1A	2.36(2.2–2.5), <0.001	2.20 (2.04,2.38), <0.001	–	–
	3A vs. 1A	3.40 (3.2–3.6), <0.001	3.15 (2.96,3.35), <0.001	–	–
	3B vs. 1A	4.60 (4.3–4.9), <0.001	4.29 (4,4.59), <0.001	–	–
	4 vs. 1A	7.79 (7.4–8.2), <0.001	7.55 (7.14,7.99), <0.001	–	–
	Extensive vs. limited	–	–	2.50 (2.3–2.7), <0.001	2.50 (2.3–27), <0.001
Age, years	Per increase in 10	1.21 (1.19–1.22), <0.001	1.20 (1.18–1.21), <0.001	1.30 (1.24–1.35) <0.001	1.28 (1.22–1.34), <0.001
Sex	Female vs. male	0.75 (0.73–0.77), <0.001	0.78 (0.75,0.8), <0.001	0.82 (0.76–0.89) <0.001	0.86 (0.79–0.93), <0.001
Secondary school	Graduate vs. not	0.77 (0.73–0.82), <0.001	0.84 (0.80–0.90), <0.001	0.72 (0.62–0.85) <0.001	0.82 (0.70–0.97), 0.02
Ethnicity	Asian vs. Caucasian	0.86 (0.78–0.96), 0.005	0.93 (0.84,1.03), 0.17	1.12 (0.79–1.60) 0.53	–
	Black vs. Caucasian	1.06 (0.97–1.20), 0.18	1.11 (1.02–1.20), 0.02	0.97 (0.63–1.50) 0.89	
	Other vs. Caucasian	0.83 (0.76–.91), <0.001	0.87 (0.80–0.96), 0.004	0.92 (0.74–1.15) 0.48	
Pack years[b]	Per increase in 10	1.04 (1.03–1.04), <0.001	–	1.01 (1.00–1.03) 0.06	–
Year of diagnosis[c]	2000 onward vs. before 2000	1.03 (0.98–1.07), 0.22	–	1.06 (0.95–1.18) 0.28	–
Histology	Adeno vs. squam	0.73 (0.70–0.76), <0.001	0.80 (0.77–0.83), <0.001	Not applicable	Not applicable
	Other vs. squam	0.95 (0.91–1.0), 0.04	1.03 (0.98–1.1), 0.24		
BMI variables, kg/mg^2 BMI at diagnosis[d]	Per increase of 5	0.95 (0.93–0.96), <0.001	0.92 (0.91–0.94), <0.001	1.00 (0.96–1.04) 0.98	1.01 (0.97–1.06), 0.53
	Underweight vs. normal	1.43 (1.32–1.55), <0.001	1.56 (1.43–1.70), <0.001	1.16 (0.89–1.51) 0.28	1.20 (0.92–1.6), 0.18
	Overweight vs. normal	0.94 (0.90–0.97), <0.001	0.89 (0.85–0.93), <0.001	0.97 (0.87–1.07) 0.51	0.93 (0.84–1.0), 0.20
	Obese vs. normal	0.92 (0.88–0.97), <0.001	0.86 (0.82–0.91), <0.001	1.05 (0.94–1.19) 0.39[e]	1.07 (0.95–1.2), 0.24[e]
	Morbidly obese vs. normal	1.04 (0.91–1.19), 0.56	1.09 (0.95–1.26), 0.22		
BMI at young adult age[d]	Per increase of 5	1.05 (1.01–1.09), 0.02	1 (0.96,1.05), 0.83	1.01 (0.89,1.14) 0.89	1.03 (0.9–1.2), 0.68
	Underweight vs. normal	1.06 (0.93–1.20), 0.38	1.15 (1–1.31), 0.04	1.70 (1.1–2.5), 0.009	1.93 (1.3–2.9), 0.001
	Overweight vs. normal	1.06 (0.97–1.15), 0.22	0.98 (0.9–1.07), 0.69	1.22 (0.95–1.6), 0.12	1.26 (0.98–1.6), 0.07

Variable	Comparisons	NSCLC, HR (95%CI), *p* value		SCLC, HR (95% CI), *p* value	
		Univariable Analysis	Multivariable Analysis[a]	Univariable Analysis	Multivariable Analysis
	Obese vs. normal	1.16 (1.02–1.32), 0.03	1.07 (0.93–1.23), 0.33	1.22 (0.83–1.8), 0.30[e]	1.39 (0.94–2.0), 0.10[e]
	Morbidly obese vs. normal	1.28 (0.88–1.85), 0.19	1.27 (0.88–1.84), 0.20		
Change in BMI from young adult age to diagnosis	Per increase of 5	0.87 (0.8–0.9), <0.001	0.89 (0.86–0.92), <0.001	1.03 (0.93–1.2), 0.55	1.03 (0.93–1.2), 0.57
	Decrease vs. increase/stable	1.31 (1.2–1.4), <0.001	1.24 (1.2–1.3), <0.001	1.25 (1.0–1.6), 0.06	1.26 (1.0–1.6), 0.06

[a]The multivariable base models included either 26,430 NSCLC or 2787 SCLC patients with data on all assessed variables in the table; for multivariable analysis of BMI at diagnosis, BMI at young adult age, and change in BMI from young adult age to time of diagnosis, each of these BMI variables was added individually to the multivariable base model. BMI at diagnosis was available for 20,937 NSCLC and 2132 SCLC patients. BMI at young adult age was available for 5454 NSCLC and 559 SCLC patients. Change in BMI was available for 5429 NSCLC and 554 SCLC patients.

[b]For every 10 pack years smoked. Not included in the base multivariable model for NSCLC due missing data for 14,359 patients.

[c]The year 2000 was chosen because it was the first full implementation year of AJCC sixth edition staging (published in 1998), which was significantly different than the fifth edition; the fourth and fifth edition are similar and the sixth and seventh edition are similar.

[d]Underweight, BMI < 18.5 kg/mg^2; normal weight 18.5 kg/mg^2 ≤ BMI < 25 kg/mg^2; overweight 25 kg/mg^2 ≤ BMI < 30 kg/mg^2; obese, 30 kg/mg^2 ≤ BMI ≤ 40 kg/mg^2; morbidly obese, BMI > 40 kg/mg^2.

[e]For SCLC cases, there were not enough morbidly obese individuals to study separately, and the obese and morbidly obese categories were combined together. HR, hazard ratio; CI, confidence interval; Adeno, adenocarcinoma; Squam, squamous cell carcinoma; BMI, body mass index; AJCC, American Joint Committee on Cancer.