Body mass index (BMI), BMI change, and overall survival in small cell and non-small cell lung cancer patients: a pooled analysis of the International Lung Cancer Consortium

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Abstract

Background: The relationships between morbid obesity, changes in body mass index (BMI) prior to cancer diagnosis, and lung cancer outcomes by histology (small-cell lung cancer (SCLC) and non-SCLC (NSCLC)) have not been well studied.

Methods: Individual level data analysis was performed on 25,430 NSCLC and 2,787 SCLC patients from sixteen studies of the International Lung Cancer Consortium (ILCCO) evaluating the association between various BMI variables and lung cancer overall survival (OS), reported as adjusted hazard ratios (aHR) from Cox proportional hazard models and adjusted penalized smoothing spline plots.

Results: OS 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%CI:1.43-1.70) or morbidly overweight (BMI>40; aHR=1.09; 95%CI:0.95-1.26) at the time of diagnosis was associated with worse stage-specific prognosis, while being overweight (25≤BMI<30; aHR=0.89; 95%CI:0.85-0.95) or obese (30≤BMI≤40; 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 time-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 clinico-demographic 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.

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 (1–3) and when dosing chemotherapeutic agents (3–5).

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 physiological alterations, such as higher insulin resistance, which has been linked to poor cancer outcomes (7), chronic inflammation (8), and abnormal nutrient homeostasis, which may lower the barrier for oncogenic transformation by driving cellular proliferation and resisting apoptosis (9). The American Society of Clinical Oncology has made investigation into the association of obesity with cancer 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 BMI<18.5, (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 prior to lung cancer diagnosis has also been assessed. For example, a prior

case control study of 2,285 patients (16) reported no significant association between BMI at two years prior to lung cancer diagnosis and mortality, while a strong association was reported between BMI<18.5 at diagnosis and death; 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 non-small cell lung cancer (NSCLC), separate analyses of small cell lung cancer (SCLC) are scarce (36–39), while none have evaluated NSCLC and SCLC in parallel. Secondly, past studies have not assessed the role of morbid obesity (defined as BMI>40) on survival (17), but have focused on complication rates in both obese and morbidly obese patients (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 (21,32,35,42), longer term changes in BMI (i.e., from the time of young adulthood until diagnosis) have not been studied previously. 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, multi-center, multi-national 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 (∆BMI) from a young adulthood to the time of diagnosis.

Methods

Study population: The International Lung Cancer Consortium (ILCCO) 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 (43) and are available at http://ilcco.iarc.fr. To be included in the present pooled analysis, studies had to have data on BMI at lung cancer diagnosis, lung cancer type (SCLC vs. NSCLC), date of diagnosis, stage at diagnosis, vital status at last follow up, and date of death. Optional variables included BMI at periods of time 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 epidemiological data elements has been previously described (44–48). Harmonization of outcomes-related variables are described in the Appendix. Separate analyses were performed for NSCLC and SCLC. 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 hazard 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 Appendix. 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 age 18-25) were also categorized into standard clinical groupings of <18 kg/m^2 (underweight), 18-<25 kg/m^2 (normal weight), 25-<30 kg/m^2 (overweight), 30-≤40kg/m^2 (obese) with the morbidly obese defined as >40kg/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 heterogeneity of baseline (pre-illness) BMI across the population, since it utilizes 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 manuscripts.

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 SEER-staged studies; one study that used grade as a surrogate for stage, any single large studies that had over 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 6th edition of the AJCC 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 over 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. 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 were 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, while BMI before diagnosis was available for 22% of patients. Median BMI at diagnosis and young adulthood was 25 and 23, 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, demonstrating 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).

Overall Survival (OS) and BMI at diagnosis, BMI in young adulthood, and change in BMI (ΔBMI) between these two time-points: 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 (Figure 1A, 1B, Table 2) and the unadjusted Kaplan-Meier survival curves (Figure 1C, 1D, Table 2). For patients with NSCLC (Figure 1A, 1C), 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 (morbid obesity), the risk of death increased again (Figure 1A, 1C, Table 2). For SCLC (Figure 1B, 1D), though there was no statistically significant association and the magnitude of 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 (Figure 1B versus 1A; Table 2). Analysis of the association between BMI at diagnosis and lung-cancer free survival showed similar findings (Supplementary Figure 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 is shown in the PSS curves (Figure 2A, 2B), Kaplan-Meier survival curves (Figure 2C, 2D), and summarized in Table 2. There was no strong association between BMI in young adulthood and OS in NSCLC (Figure 2A, 2C; 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 (Figure 2B, Table 2) that corrected for confounding prognostic variables, than in the univariable analysis (Figure 2D, Table 2).

The association between the change in BMI (∆BMI) from early adulthood to the time of lung cancer diagnosis and OS is depicted in the PSS curves (Figure 3A, 3B), the Kaplan-Meier survival curves (Figure 3C, 3D), 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 ∆BMI of +12. There was a similar association in SCLC (Table 2, Figure 3B, 3D), except that the benefit of a stable/increased BMI only occurred up to ∆BMI of +6 (an increase of 6kg/m^2 of BMI). Note that fewer than 10% of patients had a ∆BMI > +6, suggesting that the estimates above ∆BMI > +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 ∆BMI (Supplementary Figures 2-4) by age, gender, education, smoking status, ethnicity, histology, and stage, the most consistent relationship seen across all subsets was observed with ∆BMI: 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 prior to 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, change prior to diagnosis and at the time of diagnosis, and lung cancer survival outcomes. We describe that ΔBMI, that is, a change in BMI between early adulthood and the diagnosis date, was associated with overall survival in lung cancer. Specifically, a decrease in BMI when compared to a remote time period at young adulthood is consistently associated with poorer lung cancer survival across age groups, gender, smoking status, stage, and histology with adjusted hazard ratios 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 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 biological explanations have been postulated.

In a meta-analysis of over 10,000 patients, Zhu et al 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 (54). A gender difference in outcomes is suggested by our results: both low BMI at diagnosis and a decrease in ΔBMI appear to adversely affect overall survival to a greater extent in women than in men (Supplementary Figures 2 and 4), indirectly suggesting a potential hormonal influence on survival. In exploratory analyses, these gender 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 epidermal growth factor receptor activating mutation).

Biologically, the finding of similar prognostic relationships between BMI at diagnosis and ΔBMI in Asians is important (Supplementary Figures 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* 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 (13); 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 SCLC patients 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 vs 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 to 40, 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 $2m^2$ (56). While 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≥40 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 time 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-report data, a method known to be highly correlated with measured height and weight (57–59), with slight overestimation of height and underestimation of weight. 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 time-points between young adulthood and at diagnosis was unavailable for this analysis. That the association between ΔBMI and overall survival was observed consistently across stages, including Stage 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 associate with morbid obesity is more preliminary in nature. Fifthly, the analysis did not include data on different lung cancer treatments, a potential confounding factor. It should be noted that 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; since 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 indicates 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 NSCLC patients, with the worst prognosis in underweight and morbidly obese patients. However, we also reported gender, 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 clinico-demographic groups: a decrease in ΔBMI from early adulthood to the time of diagnosis was associated with a modest, but significant 20-30% increase in risk of dying.

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Figures

Figure 1: The hazard ratio of overall survival based on penalized smoothing spline by body mass index at diagnosis (BMI, kg/m^2) for (A) non-small cell lung cancer and (B) small cell lung cancer, and Kaplan Meier survival curves for (C) non-small cell lung cancers patients and (D) small cell lung cancer patients. Note that BMI data points above 60 are sparse, explaining the wide confidence intervals in panels (A) and (B). DATA ARE SPARSE WHEN BMI>60, AND INTERPRETATION SHOULD BE MADE WITH CAUTION

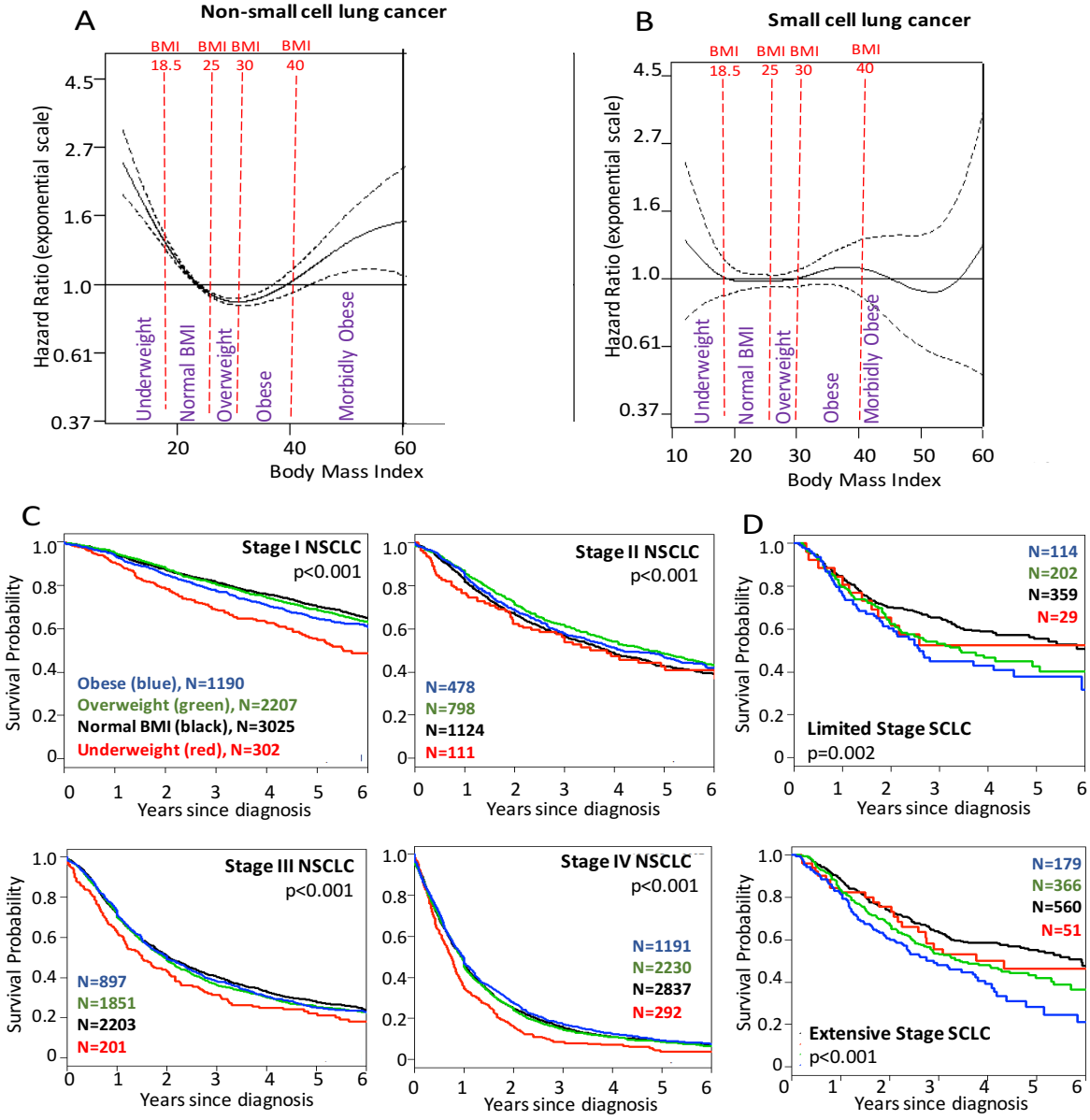


Figure 2: The hazard ratio of overall survival based on penalized smoothing spline by body mass index at young adulthood (BMI, kg/m^2) for (A) non-small cell lung cancer and (B) small cell lung cancer, and Kaplan Meier survival curves for (C) non-small cell lung cancers patients and (D) small cell lung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

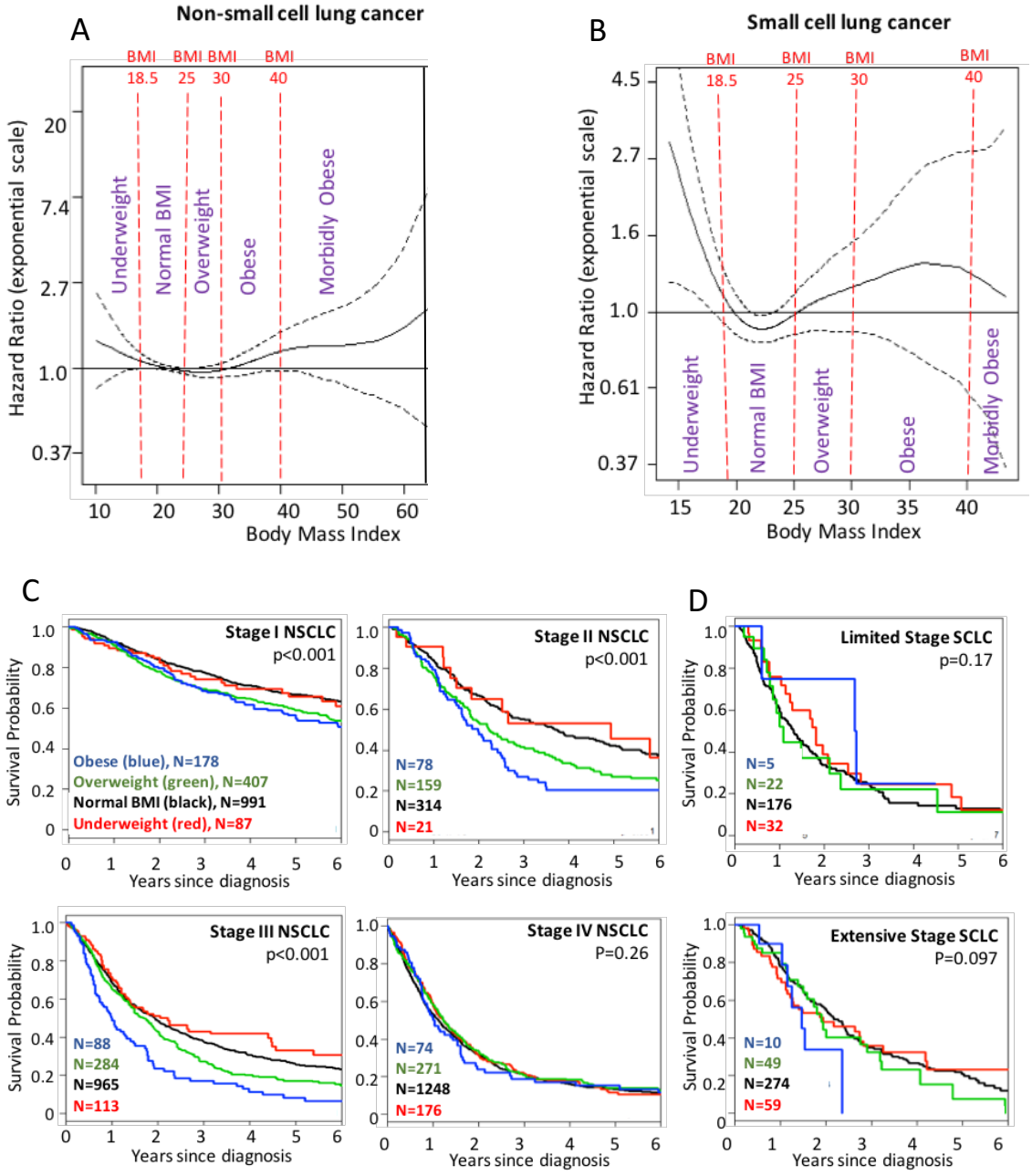


Figure 3: The hazard ratio of overall survival based on penalized smoothing spline by change in body mass index at diagnosis (ΔBMI, kg/m^2) for (A) non-small cell lung cancer and (B) small cell lung cancer, and Kaplan Meier survival curves for (C) non-small cell lung cancers patients and (D) small cell lung cancer patients. The change compares the relationship between BMI at young adulthood (around aged 20 years) to the BMI at the time of the diagnosis, as a means of correcting for heterogeneity of BMI in a healthy population.

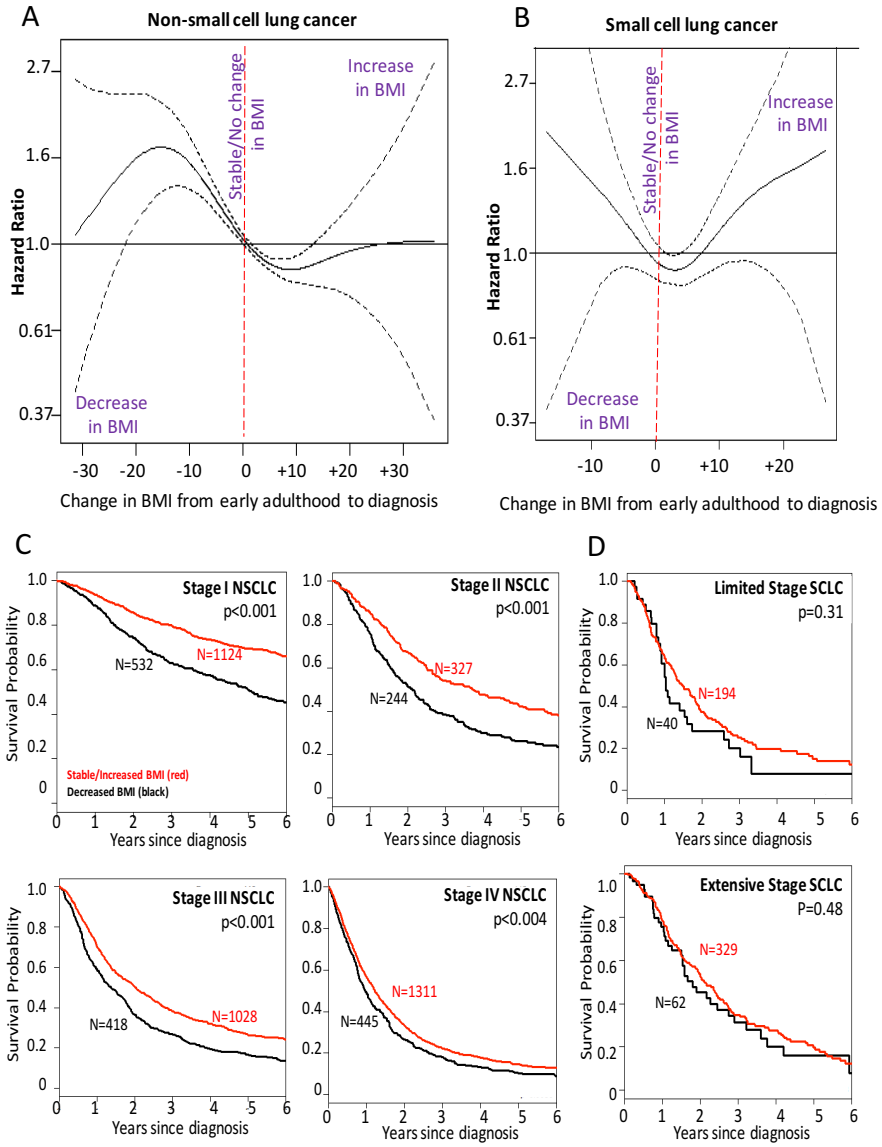


Table 1: Patients characteristics according to lung cancer type

Variable	Categories	Non-Small Cell Lung Cancer		Small cell lung cancer	
		Summary Statistics	# Studies providing data	Summary Statistics	# Studies providing data
Total Counts	N (%)	26,430 (100%)	16	2,787 (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 Yes Missing	1,927 (11%) 15,373 (89%) 7558	14	Low: 220 (12%) High: 1,643 (88%) 897	14
Ethnicity	Caucasian Asian Black Other Missing	18,141 (76%) 3,938 (17%) 1,020 (4%) 686 (3%) 2645	16	2,484 (93%) 59 (2%) 33 (1%) 98 (4%) 113	16
Stage	1A 1B 2A 2B 3A 3B 4 Limited Stage Extensive Stage	5,478 (21%) 2,448 (9%) 1,131 (4%) 1,884 (7%) 3,905 (15%) 2,434 (9%) 9,150 (35%) - -	16	- - - - - - - 1,135 (41%) 1,652 (59%)	16
Histology	Squamous cell Adenocarcinoma Other Small cell Missing	6,024 (23%) 15,812 (60%) 4,527 (17%) - 67	16	- - - 2,787 (100%) -	16
Smoking Status	Ever-smoker Never-smoker Missing	17118 (84%) 3201 (17%) 3847	14	2389 (98%) 54 (2%) 57	14
Pack years among ever-smokers	Median (range) Missing	43 (0-275) 6304	13	50 (0.5-200) 748	13
BMI at diagnosis	Median (range)	25.2 (11-87)	16	26.3 (12-70)	16
	BMI<18.5 (underweight) 18.5≥ BMI <25 (normal BMI) 25≥ BMI <30 (overweight) 40 ≥ BMI ≥30 (obese) BMI ≥ 40 (morbidly obese) Missing	906 (4%) 9,189 (44%) 7,086 (34%) 3435 (16%) 321 (2%) 5493		65 (3%) 765 (36%) 815 (38%) 487 (23%)[a] 655	
BMI at young adult age	Median (range)	22.7 (10-71)	7	22.7 (14-43)	7
	BMI<18.5 (underweight) 18.5 ≤ BMI <25 (normal BMI) 25 ≤ BMI <30 (overweight) 30 ≤ BMI ≤ 40 (obese) BMI ≥ 40 (morbidly obese) Missing	397 (7%) 3518 (65%) 1121 (21%) 378 (7%) 40 (1%) 943		31 (6%) 398 (71%) 95(17%) 35 (6%)[a] 134	
BMI change from young adult age to diagnosis	Decreased BMI No change/ Increased BMI Missing	1639 (30%) 3790 (70%) 968	7	112 (20%) 442 (80%) 139	7

[a]there were too few morbidly obese individuals to form its own category in small cell lung cancer; instead obese and morbidly obese were grouped together.

Table 2: Association between patient characteristics and overall survival: Univariable and Multivariable Analysis

Variable	Comparisons	Non-Small Cell Lung Cancer (HR (95%CI), p-value		Small Cell Lung Cancer (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	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					
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
	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 2,787 SCLC patients with data on all assessed variables in the table; for multivariable analysis of Body Mass Index (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 2,132 SCLC patients. BMI at young adult age was available for 5,454 NSCLC and 559 SCLC patients. Change in BMI was available for 5,429 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 6th edition staging (published in 1998), which was significantly different than the 5th edition; the 4th and 5th edition are similar and the 6th and 7th edition are similar; [d] underweight, BMI < 18.5; normal weight 18.5 ≤ BMI <25; overweight 25 ≤ BMI <30; obese, 30 ≤ BMI ≤ 40; morbidly obese, BMI > 40. [e] for small cell lung cancer, there were not enough morbidly obese individuals to study separately, and the obese and morbidly obese categories were combined together

Supplementary Table 1: Characteristics of the included studies

Study group	Country	Enrollment period, median (range)	Original sample size	Sample size included in analysis[1]	Participation response rates of cases (%)
CAPUA	Spain	2003 (2000-2010)	862	862	91%
CARET	USA	1991 (1985-1994)	2,236	998	80%
ESTHER	Germany	2002 (2001-2004)	201	104	50%
Fudan	China	2012 (2009-2013)	1,913	1,806	95%
Harvard	USA	2004 (1992-2011)	3,411	3,411	83%
Hawaii	USA	1994 (1991-1997)	535	535	67%
Japan	Japan	2004 (1997-2008)	1,512	1,495	98%
Karmanos	USA	2002 (1999-2005)	913	890	52%
LLP	England	2009 (1996-2013)	451	346	80%
Los Angeles	USA	2001 (1999-2003)	610	391	62%
Mayo	USA	2006 (1997-2014)	17,034	12,332	74%
MD Anderson	USA	2010 (2008-2012)	746	745	90%
NIH	USA	2006 (1993-2015)	1,699	1,479	40%
ReSoLuCENT	England	2009 (2001-2013)	545	545	33%
TLC-Moffit	USA	2011 (2001-2013)	744	744	82%
Toronto	Canada	2009 (1974-2013)	2,534	2,534	83%
Total		2006 (1974-2015)	35,946	29,217	

[1]Patients were not included in the analysis if lung cancer type (small cell/non-small cell) or survival data were missing. NA: not available; SD: standard deviation.

Supplementary Table 2: Summary of Clinical Outcomes

Type of Lung Cancer	Stage	N	Median overall survival		Median Survival Rates used for the 7th Edition AJCC[1]		Median Follow-up Time in years (months) (among censored patients)
			All patients in years (months)	Patients diagnosed since 2000 in years (months)	Pathologic Staging in years (months)	Clinical Staging in years (months)	
Non-small cell lung cancer	All stages	26,430	2.3 (28)	2.3 (28)	Not applicable	Not applicable	3.9 years (47 months)
	1A	5,478	9.2 (110)	9.3 (112)	9.0 (119)	5.0 (60)	4.3 years (52 months)
	1B	2,448	7.1 (85)	7.4 (89)	6.8 (81)	3.6 (43)	4.8 years (58 months)
	2A	1,131	5.3 (63)	5.8 (69)	4.1 (49)	2.8 (34)	3.8 years (46 months)
	2B	1,884	3.3 (40)	3.3 (40)	2.6 (31)	2.8 (18)	4.0 years (48 months)
	3A	3,905	2.3 (28)	2.3 (30)	1.8 (22)	1.2 (14)	3.4 years (41 months)
	3B	2,434	1.4 (17)	1.4 (17)	1.1 (13)	0.8 (10)	3.2 years (28 months)
	4	9,150	0.9 (11)	0.9 (11)	1.4 (17)	0.5 (6)	2.4 years (29 months)
Small cell lung cancer	All stages	2,787	1.0 (12)	1.0 (12)	Not applicable[2]	Not applicable	3.0 years (26 months)
	Limited stage	1,135	1.5 (18)	1.5 (18)	Not applicable[2]	1- 2.5 (12-30) (IIIB-IA)	3.3 years (40 months)
	Extensive stage	1,652	0.8 (9)	0.8 (9)	Not applicable[2]	0.7 (7) (IV)	1.8 years (22 months)

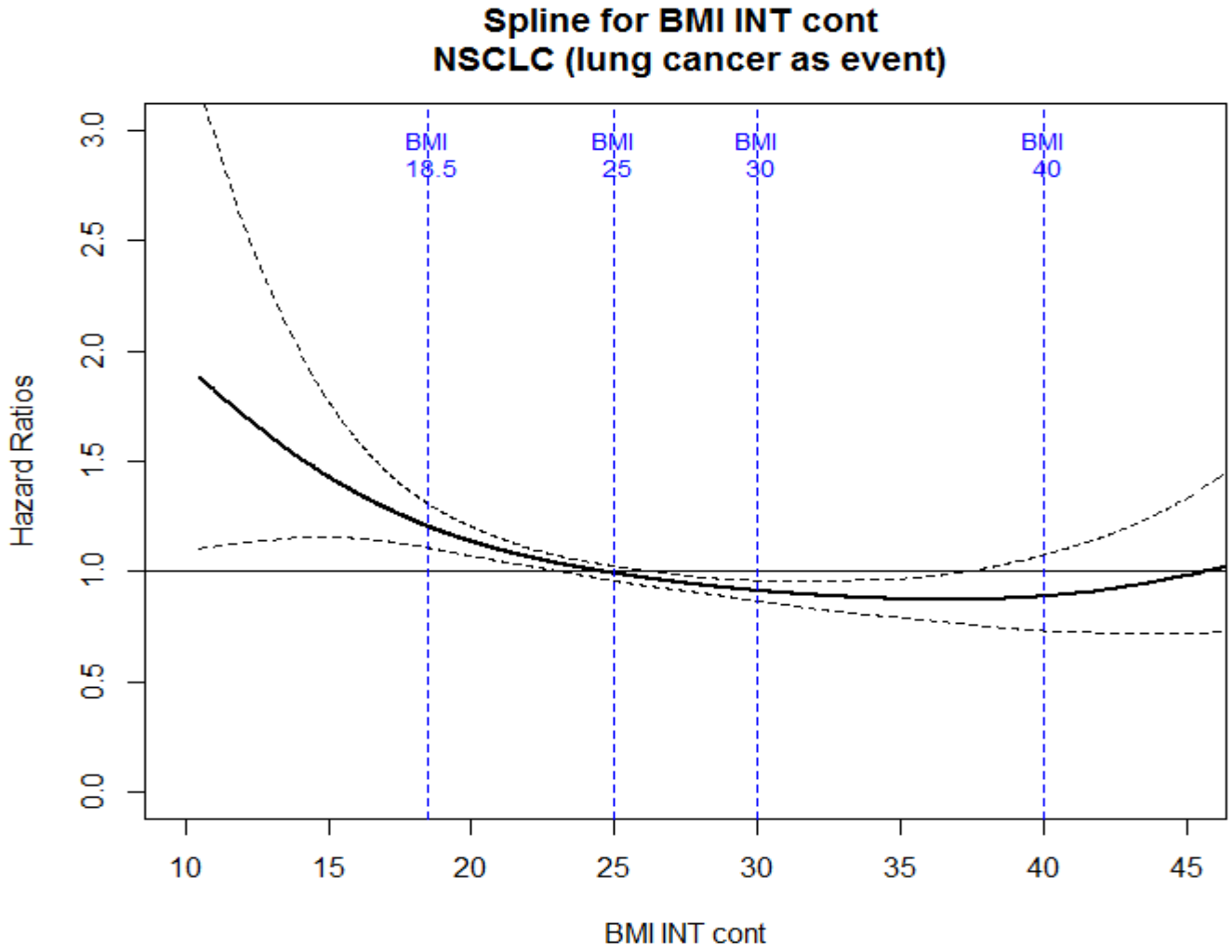
[1]Goldstraw P, Crowley J, Chansky K et al (2007) The IASLC lung cancer staging project: proposals for the revision of the TNM stage groupings in the forthcoming (seventh) edition of the TNM classification of malignant tumours. J Thoracic Oncol 2(8):706–714. [2] Small cell lung cancer patients are generally not resected; thus no pathologic staging is possible.

Supplementary Table 3: Sensitivity Analyses

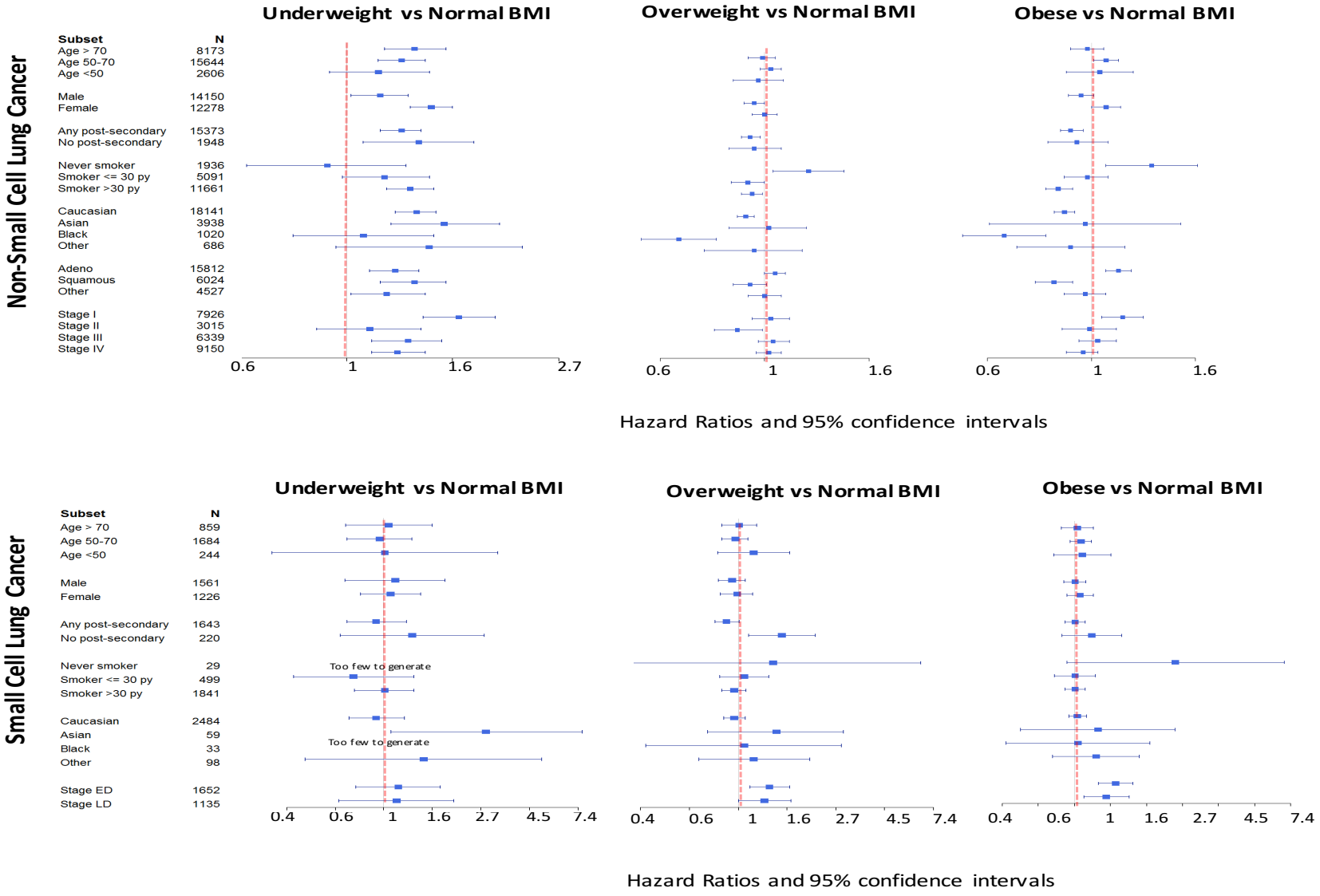
Variable		Total Study Cohort	Exclusion of trial with no staging data	Exclusion of trials with SEER staging data	Exclusion of the single largest dataset	Exclusion of Asian trials	Exclusion of patients with no cumulative smoking data[b]	Exclusion of Patients diagnosed before the year 2000
Non-Small Cell Lung Cancer								
No. of patients[a]	N	22,950	22,599	21,671	12,073	19,667	15,489	14,065
BMI at diagnosis, continuous variable	HR (95%CI); p-value	0.98 (0.98-0.99) p<0.001	0.98 (0.98-0.99) p<0.001	0.98 (0.98-0.99) p<0.001	0.98 (0.97-0.98) p<0.001	0.98 (0.98-0.99) p<0.001	0.98 (0.98-0.99) p<0.001	0.98 (0.98-0.99) p<0.001
Underweight vs Normal BMI; at diagnosis		1.56 (1.4-1.7) p<0.001	1.57 (1.4-1.7) p<0.001	1.52 (1.4-1.7) p<0.001	1.47 (1.3-1.6) p<0.001	1.58 (1.4-1.7) p<0.001	1.62 (1.5-1.8) p<0.001	1.57 (1.4-1.7) p<0.001
Overweight vs Normal BMI; at diagnosis		0.89 (0.85-0.93) p<0.001	0.89 (0.85-0.93) p<0.001	0.89 (0.85-0.93) p<0.001	0.87 (0.83-0.92) p<0.001	0.89 (0.85-0.93) p<0.001	0.89 (0.85-0.94) p<0.001	0.90 (0.85-0.94) p<0.001
Obese vs Normal BMI; at diagnosis		0.88 (0.83-0.92) p<0.001	0.88 (0.84-0.93) p<0.001	0.88 (0.83-0.93) p<0.001	0.83 (0.78-0.89) p<0.001	0.88 (0.84-0.92) p<0.001	0.89 (0.84-0.94) p<0.001	0.89 (0.84-0.95) p<0.001
BMI at young adulthood, continuous variable		1.00 (0.99-1.01) p=0.83	1.00 (0.99-1.01) p=0.73	1.00 (1.00-1.01) p=0.32	1.00 (0.99-1.01) p=0.83	1.00 (0.99-1.01) p=0.83	1.00 (0.99-1.01) p=1.00	1.00 (0.99-1.01) p=0.63
Underweight vs Normal BMI; in young adulthood		1.15 (1.0-1.31) p=0.042	1.14 (0.99-1.3) p=0.07	1.09 (0.94-1.25) p=0.25	1.15 (1.0-1.31) p=0.04	1.15 (1.0-1.31) p=0.04	1.24 (1.04-1.48) p=0.02	1.04 (0.9-1.21) p=0.59
Overweight vs Normal BMI; in young adulthood		0.98 (0.9-1.07) p=0.69	0.99 (0.91-1.08) p=0.82	0.96 (0.88-1.06) p=0.43	0.98 (0.9-1.07) p=0.69	0.98 (0.9,1.07) p=0.69	0.97 (0.87-1.07) p=0.49	0.95 (0.86-1.04) p=0.25
Obese vs Normal BMI; in young adulthood		1.09 (0.96-1.24) p=0.20	1.1 (0.96-1.25) p=0.16	1.14 (0.99-1.3) p=0.07	1.09 (0.96-1.24) p=0.20	1.09 (0.96,1.24) p=0.20	1.06 (0.92-1.22) p=0.43	1.12 (0.97-1.29) p=0.13
Increase in BMI vs Decrease in BMI		0.81 (0.75-0.87) p<0.001	0.81 (0.75-0.88) p<0.001	0.78 (0.72-0.84) p<0.001	0.81 (0.75-0.87) p<0.001	0.81 (0.75-0.87) p<0.001	0.82 (0.75-0.90) p<0.001	0.77 (0.71-0.84) p<0.001
Small Cell Lung Cancer								
No. of patients[a]	N	2,787	2,748	2,646	975	2,773	2,340	1,159
BMI at diagnosis, continuous variable	HR (95%CI); p-value	1 .00 (0.99-1.01) p=0.52	1.00 (0.99-1.01) p=0.63	1.00 (0.99-1.01) p=0.5	1.01 (0.99-1.02) p=0.43	1.00 (0.99-1.01) p=0.52	1.00 (0.99-1.01) p=0.52	1.00 (0.99-1.01) p=0.88
Underweight vs Normal BMI; at diagnosis		1.17 (0.88-1.6) p=0.27	1.17 (0.88-1.6) p=0.27	1.2 (0.88-1.6) p=0.25	1.18 (0.75-1.9) p=0.48	1.17 (0.88-1.6) p=0.27	1.17 (0.88-1.6) p=0.27	1.20 (0.85-1.7) p=0.31
Overweight vs Normal BMI; at diagnosis		0.96 (0.86-1.1) p=0.44	0.95 (0.85-1.1) p=0.44	0.95 (0.85-1.1) p=0.39	0.91 (0.76-1.1) p=0.28	0.96 (0.86-1.1) p=0.44	0.96 (0.86-1.1) p=0.44	0.96 (0.84-1.1) p=0.60
Obese vs Normal BMI; at diagnosis		1.07 (0.94-1.2) p=0.33	1.07 (0.93-1.2) p=0.40	1.07 (0.93-1.2) p=0.35	1.1 (0.88-1.4) p=0.41	1.07 (0.94-1.2) p=0.33	1.07 (0.94-1.2) p=0.33	1.02 (0.88-1.2) p=0.76
BMI at young adulthood, continuous variable		1.01 (0.98-1.03) p=0.72	1.00 (0.97-1.03) p=1	1.01 (0.98-1.04) p=0.63	1.01 (0.98-1.03) p=0.72	1.01 (0.98-1.03) p=0.72	1.01 (0.98-1.03) p=0.72	1.01 (0.97-1.04) p=0.68
Underweight vs Normal BMI; in young adulthood		1.44 (0.87-2.39) p=0.16	1.43 (0.84-2.41) p=0.18	1.15 (0.58-2.3) p=0.69	1.44 (0.87-2.39) p=0.16	1.44 (0.87-2.39) p=0.16	1.44 (0.87-2.39) p=0.16	1.14 (0.57-2.27) p=0.71
Overweight vs Normal BMI; in young adulthood		1.10 (0.82-1.49) p=0.52	1.03 (0.75-1.42) p=0.84	1.12 (0.78-1.59) p=0.54	1.10 (0.82-1.49) p=0.52	1.10 (0.82-1.49) p=0.52	1.10 (0.82-1.49) p=0.52	1.07 (0.75-1.55) p=0.70
Obese vs Normal BMI; in young adulthood		1.23 (0.80-1.91) p=0.35	1.21 (0.78-1.87) p=0.40	1.25 (0.79-1.99) p=0.34	1.23 (0.80-1.91) p=0.35	1.23 (0.80-1.91) p=0.35	1.23 (0.8-1.91) p=0.35	1.22 (0.77-1.94) p=0.39
Increased/Stable BMI vs Decreased BMI		0.86 (0.65-1.1) p=0.28	0.89 (0.66-1.2) p=0.42	0.85 (0.61-1.2) p=0.33	0.86 (0.65-1.1) p=0.28	0.86 (0.65-1.1) p=0.33	0.86 (0.65-1.1) p=0.28	0.88 (0.63-1.2) p=0.48

[a]After the exclusion of patients with missing data for the base multivariable model; [b]in this model, pack-years has been added to the model as a continuous predictor variable.

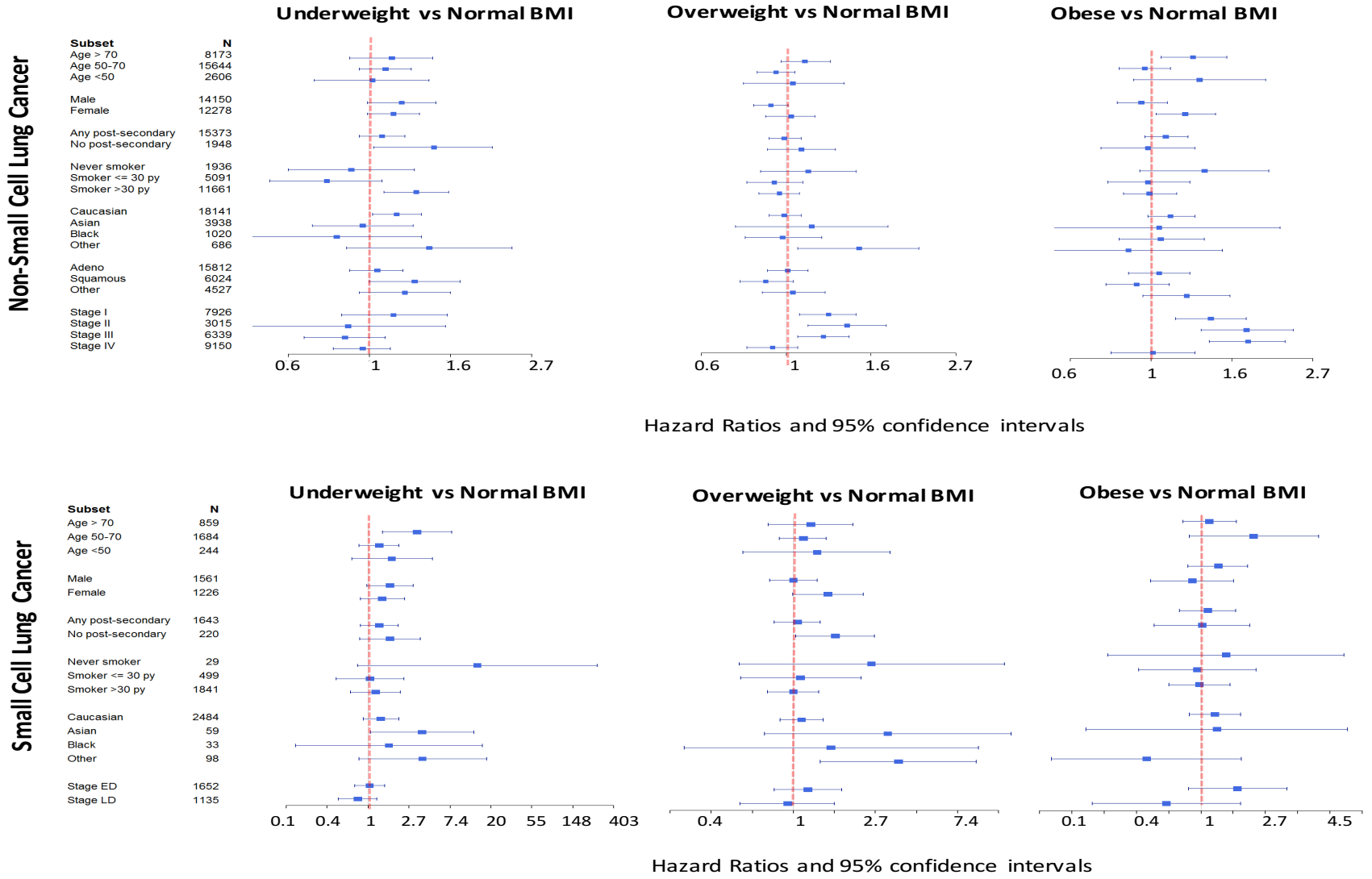
Supplementary Figure 1: Lung Cancer-Specific Survival: The hazard ratio of lung cancer free survival based on penalized smoothing spline by body mass index (BMI, kg/m^2) at lung cancer diagnosis for non-small cell lung cancer



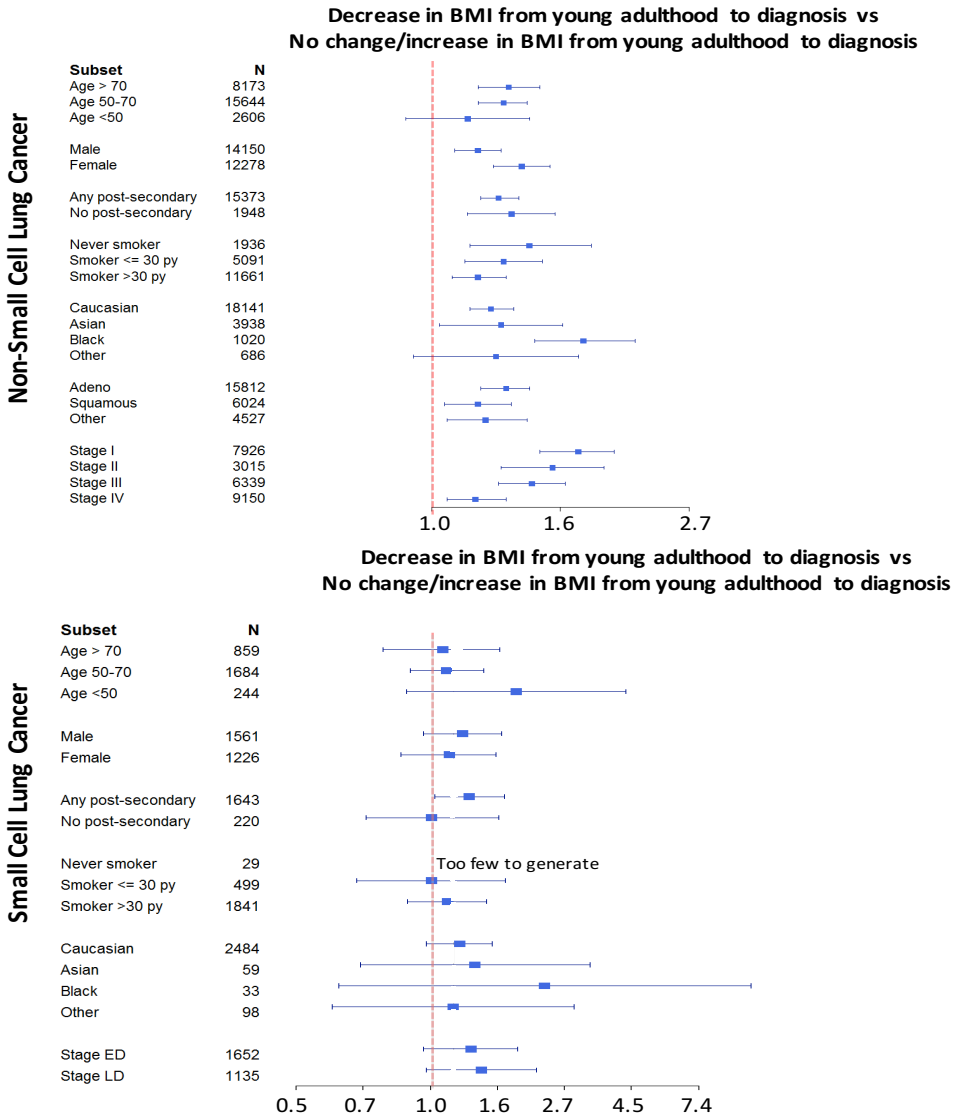
Supplementary Figure 2: BMI at diagnosis (divided into categories) versus overall survival in subsets of patients defined by clinico-demographic characteristics.



Supplementary Figure 3: BMI in young adulthood (divided into categories) versus overall survival in subsets of patients defined by clinico-demographic characteristics.



Supplementary Figure 4: Change in BMI from young adulthood until time of diagnosis versus overall survival in subsets of patients defined by clinico-demographic characteristics.



Appendix:

Harmonization process

Patient data which required harmonization included education, which was dichotomized into whether they completed high school or not; and ethnicity, which was grouped as Caucasian, Black, Asian and other. NSCLC histology was grouped as adenocarcinoma, squamous cell carcinoma and other subtypes. BMI was calculated from metric or imperial height and weight values based on the available data, and grouped into BMI<18.5, 18.5≤BMI<25, 25≤BMI<30, and BMI≥30. BMI at young adulthood was defined as BMI at approximately 20 years of age (questionnaires from different studies requested that patients recall of their height and weight at ages from 18 years through 25 years).

Cancer stage was harmonized as follows. Studies that provided TNM data were staged using the American Joint Committee on Cancer (AJCC), 7th edition, as the majority of patients were recruited when this edition was current. A sensitivity analysis according to year of diagnosis was pre-planned in order to account for any bias which might be created by using previous AJCC editions. Patients that lacked A/B substaging data were grouped with the substage "B" patients based on similarity of survival curves and proportions of patients surviving at 3- and 5-years. Two studies (Hawaii, Karmanos) provided only Surveillance, Epidemiology, and End Results Program (SEER) staging. Each SEER stage was harmonized with the AJCC stage with the most similar survival curves or proportions surviving at specific years. For NSCLC, SEER stages 1,2,3,4,7 were grouped with AJCC stages 1B, 2B, 3A, 3B and 4, respectively. For SCLC patients, SEER stages 1-4 were considered local disease (LD) while SEER stage 7 was considered extensive disease (ED). One

study (LA) provided disease grade data but had no stage data. Each grade group was combined the AJCC stage with the most similar survival curves; grades 1, 2 and 3 were harmonized with stages 1B, 3A and 4, respectively.

Penalized smoothing spline (PSS) description

The PSS models were fitted using pspline function and coxph function from survival package in R. They are penalized Cox PH models (Therneau and Grambsch, Modeling Survival Data: Extending the Cox Model, 2000, P120-123). The pspline function uses P-splines (Eilers and Marx, Statistical Science, 1981). The smoothing splines of BMI were plotted using multivariable models which included the same adjusted covariates in Table 2. The knots are determined by the degrees of freedom in this package. We tried different degrees of freedom to plot the splines and decided to use the default degrees of freedom, i.e. 4. The results were robust.