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The relationship between body-mass index and overall survival in non-small cell lung cancer by sex, smoking status, and race: A pooled analysis of 20,937 International lung Cancer consortium (ILCCO) patients

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Mei Jiang: Visualization, Conceptualization, Methodology, Data curation, Investigation. **Aline F. Fares:** Conceptualization, Methodology, Investigation, Visualization. **Daniel Shepshelovich:** Data curation. **Ping Yang:** Data curation. **David Christiani:** Data curation. **Jie Zhang:** Data curation. **Kouya Shiraishi:** Data curation. **Brid M. Ryan:** Data curation. **Chu Chen:** Data curation. **Ann G. Schwartz:** Data curation. **Adonina Tardon:** Data curation. **Sanjay Shete:** Data curation. **Matthew B. Schabath:** Data curation. **M. Dawn Teare:** Data curation. **Loic Le Marchand:** Data curation. **Zuo-Feng Zhang:** Data curation. **John K. Field:** Data curation. **Hermann Brenner:** Data curation. **Nancy Diao:** Data curation. **Juntao Xie:** Data curation. **Takashi Kohno:** Data curation. **Curtis C. Harris:** Data curation. **Angela S. Wenzlaff:** Data curation. **Guillermo Fernandez-Tardon:** Data curation. **Yuanqing Ye:** Data curation. **Fiona Taylor:** Data curation. **Lynne R. Wilkens:** Data curation. **Michael Davies:** Data curation. **Yi Liu:** Data curation. **Matt J. Barnett:** Data curation. **Gary E. Goodman:** Data curation. **Hal Morgenstern:** Data curation. **Bernd Holleczek:** Data curation. **Sera Thomas:** Data curation. **M. Catherine Brown:** Data curation, Supervision, Methodology. **Rayjean J. Hung:** Supervision, Project administration, Funding acquisition. **Wei Xu:** Visualization, Conceptualization, Methodology, Data curation, Investigation. **Geoffrey Liu:** Conceptualization, Methodology, Investigation, Visualization, Resources, Project administration, Funding acquisition, Supervision.

Data accessibility

The dataset from our study is held securely in coded form at the Princess Margaret Cancer Center, Toronto, Ontario, although ownership of data shared within ILCCO remain with the original investigator/studies. Data sharing agreements prohibit making the dataset publicly available, but data will be made available upon approval by the ILCCO Executive committee and individual study principal investigators with mechanisms published on its website www.ilcco.iarc.fr. The same committee and mechanism approved the present analysis. Relevant ethical and data-sharing approval must be obtained as per ILCCO policy. The underlying analysis plan and analytic code are available from the authors upon request.

Declaration of Competing Interest

The authors report no declarations of interest.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.lungcan.2020.11.029.

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Abstract

Introduction: The relationship between Body-Mass-Index (BMI) and lung cancer prognosis is heterogeneous. We evaluated the impact of sex, smoking and race on the relationship between BMI and overall survival (OS) in non-small-cell-lung-cancer (NSCLC).

Methods: Data from 16 individual ILCCO studies were pooled to assess interactions between BMI and the following factors on OS: self-reported race, smoking status and sex, using Cox models (adjusted hazard ratios; aHR) with interaction terms and adjusted penalized smoothing spline plots in stratified analyses.

Results: Among 20,937 NSCLC patients with BMI values, females = 47 %; never-smokers = 14 %; White-patients = 76 %. BMI showed differential survival according to race whereby compared to normal-BMI patients, being underweight was associated with poor survival among white patients (OS, aHR = 1.66) but not among black patients (aHR = 1.06; $p_{interaction}$ = 0.02). Comparing overweight/obese to normal weight patients, Black NSCLC patients who were overweight/obese also had relatively better OS ($p_{interaction}$ = 0.06) when compared to White-patients. BMI was least associated with survival in Asian-patients and never-smokers. The outcomes of female ever-smokers at the extremes of BMI were associated with worse outcomes in both the underweight ($p_{interaction}$<0.001) and obese categories ($p_{interaction}$ = 0.004) relative to the normal-BMI category, when compared to male ever-smokers.

Conclusion: Underweight and obese female ever-smokers were associated with worse outcomes in White-patients. These BMI associations were not observed in Asian-patients and never-smokers. Black-patients had more favorable outcomes in the extremes of BMI when compared to White-patients. Body composition in Black-patients, and NSCLC subtypes more commonly seen in Asian-patients and never-smokers, may account for differences in these BMI-OS relationships.

Keywords

Body mass index; Obesity; Lung cancer; Interaction

1. Introduction

Studies of Body Mass Index (BMI) and cancer have reported varying results. Obesity is a known risk factor for carcinogenesis [1–3]. Obesity is also a negative prognostic factor for several malignancies: The National Comprehensive Cancer Network Guidelines recommend maintaining an ideal BMI of between 20 25 kg/m^2 as part of treatment and surveillance in breast, colon and esophageal cancers [4–7]. However, lung cancer epidemiologic studies consistently demonstrated a lower risk of death among overweight/obese patients with non-small cell lung cancer (NSCLC), a phenomenon known as the “obesity paradox”, and a higher risk among the underweight, when compared with patients who have normal BMI. This is in contrast to the evidence linking obesity with poor survival in many cancer types; reasons for this inconsistency are not well understood [8–10].

Various hypotheses could explain this unexpected inverse relationship. Weight loss (as a signal of more aggressive cancer or as a result of heavy smoking) prior to cancer diagnosis can lead to reverse causation [11–15]. Alternatively, BMI does not fully account for body composition, such as differences in the ratio of muscle and different types of adiposity in patients with identical BMI, especially in chronically ill patients [11,12,14–17]. Endogenous (e.g., sex and race) and exogenous factors (e.g., tobacco consumption) also have direct associations with body habitus [18–20]. Finally, intrinsic differences in lung cancer tumor biology and carcinogenesis may confound the BMI and survival relationship. Tobacco is the number one cause of DNA damage in lung cancer, resulting in a higher tumor mutation burden and altering both innate and acquired tumor immunity and inflammation. In contrast, never smokers with lung cancer often have tumors that carry driver mutations, with lower tumor mutation burden and less immunogenicity [21–23]. As lung cancer is considered a biologically heterogenous cancer, these differences may lead to different catabolic burden, and may be associated with body composition and weight differences.

Although we previously reported on consortium results of the overall relationship between BMI and survival in NSCLC, we now investigate some of the heterogeneous results between BMI and survival [9]. We postulated that the association between BMI and survival in NSCLC, the most common form of lung cancer, varied according to sex, race and smoking status at diagnosis. However, to test this hypothesis, large datasets are required. We therefore continued to utilize the International Lung Cancer Consortium’s outcomes database, which is a consortium of international cohorts of lung cancer, to study the interactions between sex, race and smoking status with BMI for an overall survival (OS) outcome.

2. Materials and methods

2.1. Study design and population

A large pooled database was assembled consisting of 16 studies participating in the International Lung Cancer Consortium (ILCCO; //ilcco.iarc.fr). Comprehensive analyses for each study have been previously published [24–28]. Descriptions and sample sizes of individual studies included in this analysis have previously been reported [9]. To be included, patients were diagnosed with NSCLC, with available BMI at diagnosis, date of diagnosis, vital status at last follow up and/or date of death. Written informed consent was

obtained from all study subjects, and approval from ethics committees were obtained from each study center.

2.2. BMI and covariates assessments

Weight and height were collected at baseline in all studies. BMI at baseline was defined as BMI at the time of diagnosis and up to 1 year prior to diagnosis and was calculated as weight in kilograms divided by the square of the height in meters (kg/m^2). BMI was stratified according to the standard World Health Organization (WHO) classification as underweight (< 18.5 kg/m^2), normal weight (BMI 18.5 to < 25 kg/m^2), overweight (BMI 25 to < 30 kg/m^2) and obese (BMI ≥ 30 kg/m^2). Covariates evaluated included self-reported race, sex, educational level, year of diagnosis, histology, smoking status and stage at diagnosis. Race information was categorized as White patients, Black patients, Asian patients and others. Histological subtypes were defined as adenocarcinoma, squamous cell carcinoma, and others.

The primary outcome was overall survival (OS) defined as time from date of diagnosis of lung cancer until death or date of last follow-up.

2.3. Statistical analysis

The integration and quality control of epidemiological data and outcomes-related variables [9,24–28] and sensitivity analysis processes have been described previously [9]. In the present paper, we first analyzed the impact of race, sex and smoking status on the BMI-survival relationship. For each category of covariate, we assessed the association between baseline BMI and overall survival. The Kaplan-Meier (KM) curves of OS were assessed using log-rank tests. In addition, univariable analysis and multivariable analysis were conducted on OS using penalized smooth spline curves (continuous BMI variable) and Cox proportional hazard models (continuous and categorical BMI models) for each variable of interest. The multivariable survival analysis that generated the base models included all variables and was adjusted for BMI at baseline, race, stage, sex, smoking, age at diagnosis, histology, educational level and year of diagnosis. Spline curves are functions that are defined by a polynomial, allowing complex shapes of relationships with continuous variables to be modeled [9,29,30]. The association between BMI categories and categories of each clinical variable was assessed using Chi-square tests. Interactions for covariates of interest—race, sex, smoking and stage—by BMI were tested using BMI as categorical variable. Two sided tests were applied. Results were considered significant if the p-value was less than or equal to 0.05. Data quality control and statistical analyses were conducted using SAS 9.4 and R (http://CRAN.R-project.org, R Foundation, Vienna, Austria, R-3.6.1 version).

In addition to the main analysis, we performed five different sensitivity analyses to assess the impact of possible confounding factors and of data discrepancies between some patient cohorts: A) Date of BMI at diagnosis: we excluded a cohort study of 817 patients (4% of the pooled analysis) where BMI values were collected at various time-points before diagnosis (Supplementary Table 1); B) Smoking: to evaluate if smoking is a major confounding factor on the BMI-OS relationship, we incorporated smoking variables such as lifetime exposure to

tobacco (pack-years) and time since smoking cessation into the multivariable analysis (Supplementary Table 2); C) Weight loss: to assess whether recent weight loss prior to cancer diagnosis was a major confounding factor to the BMI-OS relationship, we included recent weight loss information, available in < 5000 patients, in the multivariable analysis (Supplementary Table 3); D) Lung-cancer-specific-survival (LCSS): with N = 7, 427, we included a sensitivity analysis using LCSS as outcome (Supplementary Table 4); and E) Inclusion of "study group" as a covariate in the multivariable analysis, with N = 15,202 (Supplementary Table 5).

3. Results

3.1. Patient demographics and clinical characteristics

Individual data from North America, Europe and Asia on 26,430 patients with NSCLC were assessed. Of 26,430 patients, 20,937 had BMI information at baseline. Table 1 shows patient demographics and clinical characteristics stratified by BMI at diagnosis: 44 % of patients were normal weight; 4% were underweight; 34 % were overweight, and 18 % were obese. Forty-seven percent were female. Seventy-six percent were White patients, 16 % Asian patients, 5% Black patients, and 3% others. Ever-smokers comprised 86 % of our population. Adenocarcinoma was the most frequent histology (59 %); 23 % had squamous cell carcinoma. At diagnosis, 32 % were stage I, 12 % were stage II, 25 % were stage III, and 31 % were stage IV. Overall median follow-up time was 3.3 years, and specifically follow-up time by-stage was as follows: stage I, 5.2 years; stage II, 4.1 years; stage III, 2.8 years; stage IV, 1.6 years and 66 % patients died during follow-up. BMI distribution was generally consistent across different subgroups, except that White and Black patients were more likely to be overweight or obese when compared to Asian patients, and females were more likely to be underweight, while males were more likely to be overweight or obese at the time of diagnosis. All the sensitivity analyses that were performed corroborated our primary results, with most retaining statistical significance (Supplementary Tables 1–5). However, some sensitivity analyses lacked adequate power due to low number of patients, but still demonstrated similar magnitudes and directions of relationships. As all of these sensitivity analyses were meant to demonstrate consistency of results, no multiple comparison adjustments were performed.

3.2. Marginal associations between race, sex, smoking, and BMI on OS

Compared to White patients, being of Black or Asian ancestry was associated with an adjusted hazard ratio (aHR) of death of 1.13 (95 %CI 1.03–1.23, p = 0.007) and 0.91 (95 %CI 0.8–1.04, p = 0.16), respectively. Compared to males, the aHR for females was 0.77 (95 %CI 0.74 0.8, p < 0.001). Never-smokers had an aHR of 0.84 (95 %CI 0.79 0.90 p < 0.001) compared to ever-smokers. Compared to normal-weight individuals, the marginal aHRs for underweight, overweight, and obese individuals were 1.57 (95 %CI 1.43–1.72, p < 0.001), 0.89 (95 % CI 0.85 0.93, p < 0.001), and 0.88 (95 %CI 0.83 0.92, p < 0.001), respectively.

3.3. Interactions between covariates (race, sex, smoking) and BMI on OS

Univariable (Supplementary Fig. 1) and multivariable analyses (Fig. 1) show the relationship between BMI and OS in various subgroups by race, sex and smoking. For completeness, the

relationships with stage are also presented. A subanalysis that grouped obese and overweight patients together are also presented (Supplementary Fig. 2).

3.4. Association between race and BMI on OS

Spline curves are shown in Fig. 2. Among white patients, being underweight was associated with a 66 % increased risk of dying compared to being normal weight, whereas this association did not hold for Black patients (aHR 1.66, 95 %CI 1.5–1.8, $p < 0.001$ for White patients, aHR 1.06, 95 %CI 0.8–1.5, $p = 0.74$ for Black patients); the $p_{interaction}$ comparing race (Black patients vs White patients) and BMI (underweight vs normal weight) was 0.02. In addition, being overweight/obese was associated with 11 % and 25 % relative decreased chances of dying in White and Black patients, respectively (aHR 0.89, 95 %CI 0.8 0.9, $p < 0.001$ for White patients, aHR 0.75, 95 %CI 0.6 0.9, $p < 0.001$ for Black patients), with a trend towards a stronger protective association observed among overweight and obese Black patients ($p_{interaction}$ values were 0.06 for overweight and obese patients). In contrast, there were no significant BMI-race relationships involving Asian patients or other races, relative to White patients. Next, we explored a three-way-analysis with Race, Smoking and BMI on OS (Supplementary Fig. 3); however, when including six different categories (White ever smokers, White never-smokers, Black ever-smokers, Black never-smokers, Asian ever-smokers, Asian never-smokers), the numbers in each category had no power to provide an accurate interpretation of the data.

3.5. Association between sex and BMI on OS

When considering sex and BMI on OS (Fig. 1 and Supplementary Fig. 4A), the $p_{interaction}$ between BMI (underweight vs normal weight) and sex was significant, at 0.006. In stratified analyses that compared sex to their corresponding normal weight individuals, underweight males had a 34 % increased relative risk of death (aHR of 1.34 95 %CI 1.2–1.6, $p < 0.001$) of death, while underweight females had a 76 % significantly higher relative risk of death (aHR of 1.76, 95 %CI 1.6–2.0, $p < 0.001$).

Similarly, among overweight or obese patients, the positive relationship between BMI and survival was weaker in females than males, when compared to normal weight individuals ($p_{interaction} = 0.04$ for overweight, and $p_{interaction} = 0.02$ for obese individuals). In corresponding stratified analyses, males who were overweight and obese had 14 % and 16 % reduced relative risk of dying (aHR 0.86, 95 % CI 0.8 0.9, $p < 0.001$ and aHR 0.84 95 % CI 0.8 0.9, $p < 0.001$, respectively). In contrast, the values in females were less significant and had a lower magnitude of benefit, with 6% and 7% relative risk reduction (aHRs 0.94 95 %CI 0.9–1.0, $p = 0.06$ and aHR 0.93 95 %CI 0.9–1.0, $p = 0.09$, respectively).

3.6. Association between smoking and BMI on OS

(Supplementary Fig. 4B): The $p_{interaction}$ between BMI (underweight vs. normal weight) and smoking status (ever vs. never smokers) was 0.03. Specifically, underweight never-smoking NSCLC patients had similar OS as normal-weight patients (aHR 1.15, 95 %CI 0.8–1.6; $p = 0.39$), while underweight ever-smokers had a 62 % increased relative risk of death (aHR 1.62, 95 %CI 1.5–1.8, $p < 0.001$).

Compared to associations in normal weight patients, there were no significant smoking-BMI interactions on OS observed between ever and never smokers in overweight or obese patients ($p_{interaction}$ values were not significant). Thus the protective effect associated with increased BMI was observed in both ever and never smokers.

3.7. Combined associations of sex and smoking with BMI on OS

We then explored sex and smoking status together and their combined relationships with BMI on OS (Fig. 3). The detrimental effect of BMI on OS by being underweight (relative to normal weight) was significantly greater in female ever-smokers than in male smokers ($p_{interaction}$ <0.001). Similarly, the benefit of being obese in protecting against death was weakest in female ever-smokers ($p_{interaction}$ = 0.004) relative to our reference group of male smokers. There were no other significant interactions between other subgroups.

4. Discussion

In this large multinational pooled database of NSCLC patients, we found that BMI and survival associations varied by race, sex and smoking status. Each of these relationships held true even after adjustment for stage, histology, and other clinically relevant variables, and with multiple sensitivity analyses that were designed to address potential confounders and data quality in subsets of patients.

Our first main finding involved the better outcomes in Black patients with NSCLC at the extremes of BMI relative to normal-weight Black patients, when compared to the extremes of BMI in White patients with NSCLC. Our finding that Black patients with NSCLC had worse OS when compared with White patients overall is consistent with prior studies [20,31]. However, being underweight (vs normal weight) in Black patients was not associated with poorer outcomes, whereas underweight White patients were associated with significantly worse overall survival (vs normal weight). Overweight/obese Black patients with NSCLC were also associated with significantly better survival relative to normal weight Black patients, significantly better than the overweight/obese versus normal weight relationship in White patients.

In two published studies that compared body compositions between healthy populations in African-Americans (defined similarly as our Black patients) and White patients, African-Americans had, on average, a higher BMI and higher lean mass area, while White patients had less lean mass area but higher proportions of visceral fat [17,32]. The inability of BMI to differentiate lean mass area and adiposity may explain some of the racial differences in the BMI-OS relationship: the higher BMI may be potentially hiding a higher muscularity in Black patients relative to other races, which may extend to underweight individuals. In contrast, White patients, the comparator group, may have higher rates of sarcopenic obesity, describing a body measurement end-point where individuals simultaneously are in the higher ranges of adiposity and in the lower ranges of muscle mass [33–35]. Studies have previously reported a link between sarcopenic obesity and mortality in multiple types of malignancies, including lung cancer [36]. Whether alternative explanations such as greater treatment-related toxicities, greater inflammation, differential tumor-derived catabolic

factors, or other genetically-defined explanations can explain this race-BMI relationship on OS remains to be clarified.

Our second main finding involved the relatively poorer outcomes of female ever-smokers in the extremes of BMI relative to their normal-weight counterparts. In this subgroup of patients, being underweight was associated with relatively worse survival compared with normal weight female ever-smokers, in comparison to the underweight vs normal weight relationships in male ever-smokers. Furthermore, when comparing the association between overweight/obese versus normal weight individuals, female ever-smokers had outcomes that were similar in overweight, obese and normal weight individuals whilst male ever-smokers who were overweight or obese were associated with improved survival relative to their corresponding male ever-smoking normal weight counterparts.

Female sex is a positive prognostic factor in lung cancer, even after adjusting for EGFR mutation status [37]. Estrogen receptors (ER) are present in up to 40 %–70 % of the NSCLC cells, [3,37]. Adipose tissue is known to increase estradiol concentration in men, as aromatase activity converts androgens into estrogens [2]. In a pooled analysis of 22 clinical trials of multiple primary sites of cancer, there was an overall survival benefit with BMI > 25 kg/m^2 among men (HR = 0.82; p = 0.003), but not among women (HR = 1.04; p = 0.86) [8,12]. Our study not only supports the results of this prior pooled analysis, but is also the first to study the combined association of smoking and sex on the BMI-OS relationship. Biologically, never smokers are more likely to have driver mutations (oncogenes) and less immunogenic tumors [21–23]; their prognosis may be less affected by BMI because the oncogenic mutation itself drives prognosis. In contrast, female ever-smokers may represent a uniquely-susceptible subgroup to the effects of BMI due to the confluence of several reasons. Firstly, smoking is associated with sarcopenia, which is a poor prognostic factor [38], especially as females have lower total lean mass compared to males [38–41]. Secondly, previous studies have shown that increased ERβ concentration in lung cancer cells are associated with better OS [42], and female smokers have relatively lower cytoplasmic ERβ concentration in lung cancer cells [43]. A recent study has shown that obesity can suppress ERβ expression through a HER-2 mechanism in breast cancer cells [44]; whether this applies to NSCLC cells is unknown.

Our third finding was that Asian patients and those who were never smokers had outcomes that were similar across the entire BMI range (i.e. extremes of BMI were not associated with significantly higher or lower HRs of survival relative to normal weight individuals in these subgroups). Never-smokers with NSCLC are more likely to carry driver mutations [22]. Although Asian patients have the lowest BMI and lean mass area, a larger proportion of their NSCLCs carry driver-mutations, particularly *EGFR* mutations [17,22,32]. NSCLCs with driver mutations (i.e., “oncogene-addicted” tumors) are known to have lower tumor mutation burden, lower levels of PD-L1 expression and lower CD8+ tumor infiltrating-lymphocytes [45]. In contrast, smoking-associated NSCLC without driver mutations tend to be genetically unstable and more immunogenic [46,47]. Adiposity is associated with increased inflammation, and there has been renewed interest in how adiposity affects both chronic inflammation and the tumor immune environment [48].

In our analysis, low BMI consistently was not associated with poorer overall survival in never-smokers. This raises the hypothesis that low-BMI in never-smokers is physiological and not commonly due to cancer-associated-cachexia. Antoun et al. recently reported data on oncogene-addicted NSCLC patients showing that they had significantly less cachexia than EGFR-negative patients (43 % versus 24 %), consistent with our hypothesis [49]. A second, less likely, possibility is treatment-efficacy: never-smokers with molecularly-driven tumors derive striking benefits from targeted therapies, with improved survival that is likely independent of BMI. However, there were no time-cohort and stage differences in relationships (data not presented) given that our analyses included patients from 1974 to 2015, while the availability of tyrosine-kinase-inhibitors was more recent (2000 onwards) and only applicable for Stage IV patients.

Various methodological problems, such as confounding and reverse causation, could give rise to a false association between BMI and survival [11]. Firstly, smoking is a major prognostic confounder in lung cancer patients, where just being a current and former smoker may lead to a lower BMI and worse survival. Secondly, weight loss in a yet-undiagnosed lung cancer patient could raise the issue of reverse causation. To avoid these methodological issues, we performed two separate sensitivity analyses that included smoking variables and information on recent weight loss prior to lung cancer diagnosis. In both, the results were consistent with our primary results. Though not definitive, there is little data from our sensitivity analyses to support the idea that smoking and recent weight loss are major unmeasured confounders that would account for our main results.

Our study has several limitations. For instance, we lack data on driver-mutations and treatment. Patients were diagnosed and treated over a period of 40 years, in which diagnosis, staging, and treatment guidelines had changed considerably. In addition, specific particularities of race, must be taken into consideration, such as that Black patients often receive less aggressive treatments due to social disparities [50]. We accounted for social disparity adjusting for educational level, considered to be a reasonable surrogate for social-economic status [51], but residual effects on social disparity may still be present. Moreover, we used BMI as a proxy for body measurements such as adiposity and muscle mass. The protective effect associated with increased BMI (over-weight and obese patients) was observed in both ever and never smokers separately, suggesting that reverse causation due to smoking status alone does not explain the relationship between higher BMI and improved survival in NSCLC. However, our association study will not be able tease out issues of reverse causation further.

In conclusion, our study showed that sex, smoking and race differences influence the BMI-survival relationship. In particular, female ever-smokers were the most associated with suboptimal outcomes at the extremes of BMI relative to male ever-smokers while Black patients were most associated with the best outcomes at the extremes of BMI when compared to White patients. In contrast, BMI in Asian patients and never-smokers were not significantly associated with OS in general. These differential associations of race, sex, and smoking may reflect sex and racial differences in body composition, and distinct etiological differences in NSCLC carcinogenesis. Future prospective studies involving BMI and prognosis should take into account muscle-adiposity ratios of body composition and

molecular characteristics to better understand BMI-OS relationships across the continuum of NSCLC.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations:

aHR	adjusted Hazard Ratio
BMI	Body Mass Index
CI	Confidence Interval
DNA	Deoxyribonucleic acid
EGFR	Epidermal Growth Factor Receptor
ER	Estrogen Receptor
HER2	Human Epidermal Growth Factor Receptor 2
HR	Hazard Ratio
ILCCO	International Lung Cancer Consortium
KM	Kaplan Meier
LCSS	Lung Cancer Specific Survival
MVA	Multivariable analysis
N	Number of patients
NL	normal weight
NSCLC	Non-Small-Cell-Lung-Cancer
OS	Overall Survival
OW	overweight
PD-L1	Programmed Death Ligand 1

UW	underweight
WHO	World Health Organization

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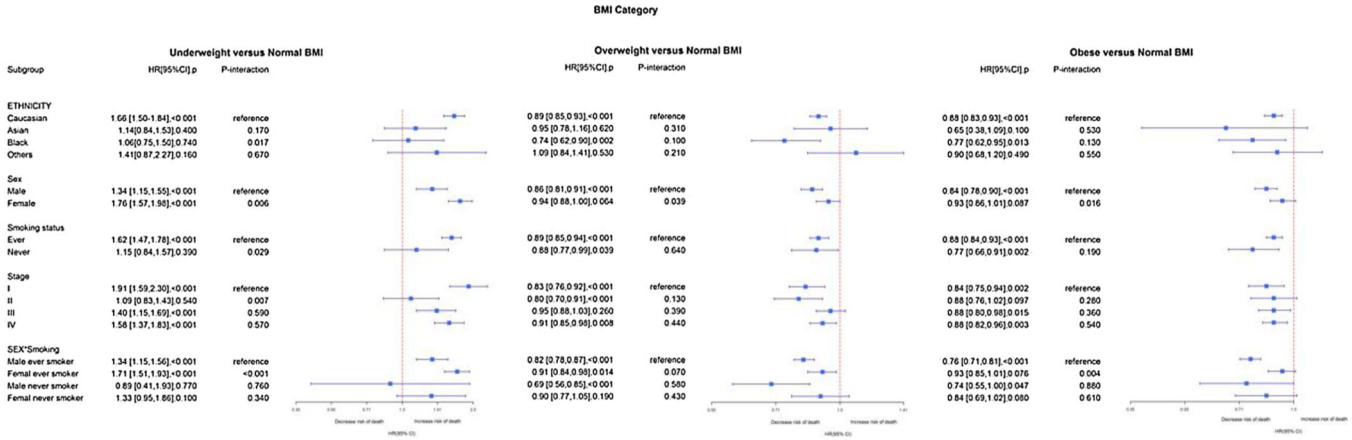

Fig. 1.

Multivariable analysis showing the association of Body Mass Index and Overall Survival stratified by specific variables (subgroups of sex, race, smoking status, stage, and combinations of sex and smoking status ("SEX*Smoking")). Models were adjusted for age, educational level, year of diagnosis, and histology. Normal weight is the reference group: between 18.5–24.9 kg/m^2; Underweight: BMI < 18.5 kg/m^2; Overweight: BMI between 25–29.9 kg/m ^{2}; Obese: BMI ≥ 30 kg/m^2. HR, hazard ratio; CI = confidence interval; p = p-value; p-interaction = p-value for interaction term of the subgroup with BMI category on overall survival.

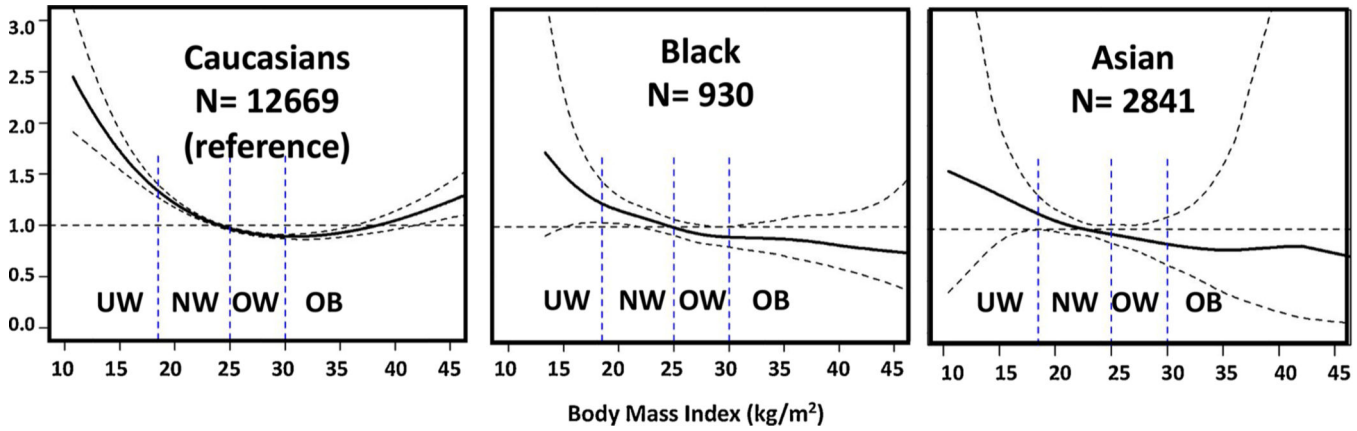

Fig. 2.

Hazard ratios of overall survival by Body Mass Index (BMI) at the time of diagnosis, using penalized smoothing spline, in specific subgroups of patients based on race. In each model, hazard ratios are adjusted for age, sex, smoking status, stage, educational level, year of diagnosis, and histology N = number of patients analyzed; NL = normal weight (BMI between 18.5–24.9 kg/m^2), UW = underweight (BMI < 18.5 kg/m^2), OW = overweight (BMI between 25–29.9 kg/m^2); OB = obese (BMI ≥ 30 kg/m^2).

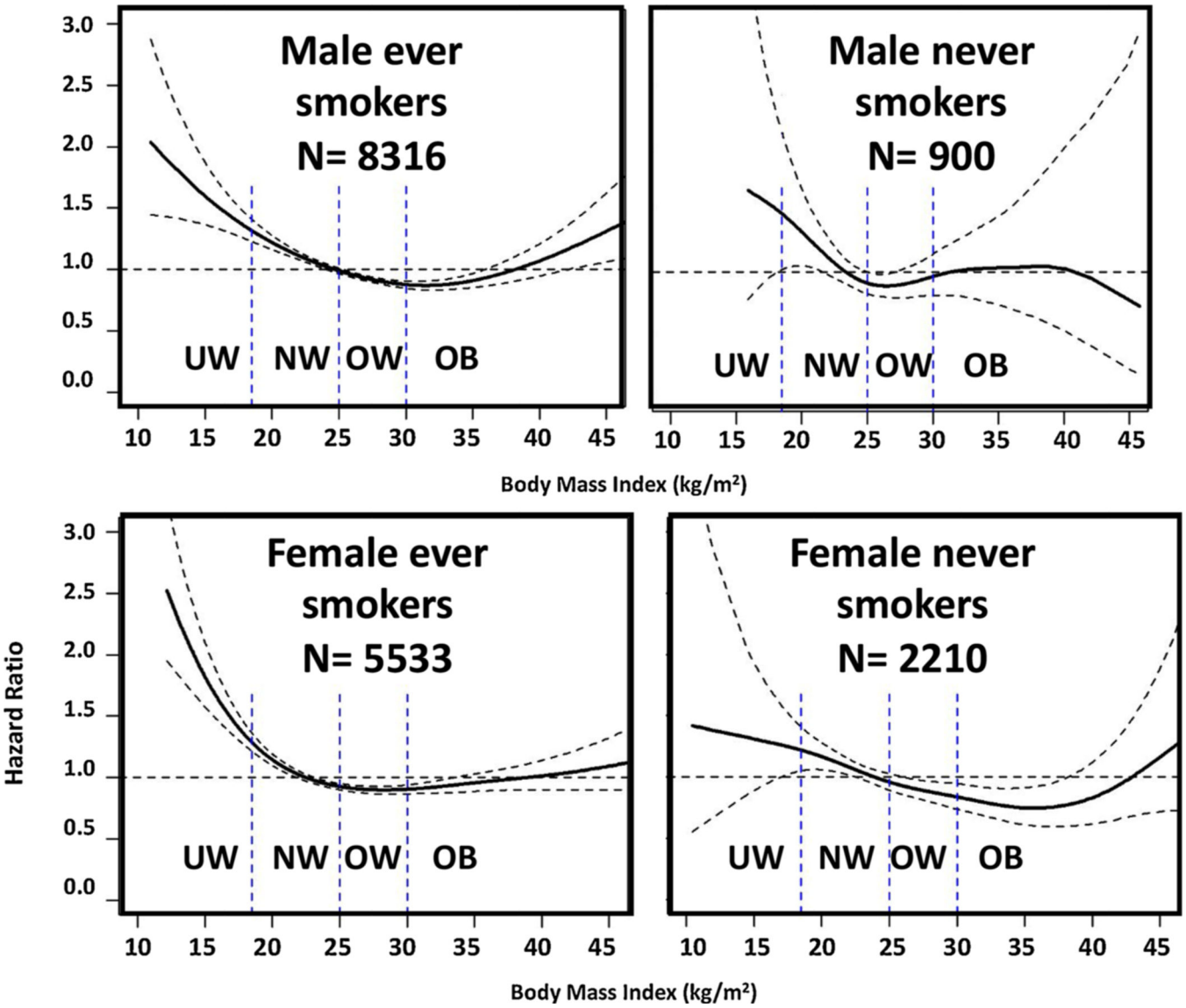

Fig. 3.

Hazard ratios of overall survival by Body Mass Index (BMI) at the time of diagnosis, using penalized smoothing spline, in specific subgroups of patients based on combinations of sex and smoking status. In each model, hazard ratios are adjusted for age, race, stage, educational level, year of diagnosis, and histology. N = number of patients analyzed; NL = normal weight (BMI between 18.5–24.9 kg/m^2); UW = underweight (BMI < 18.5 kg/m^2), OW = overweight (BMI between 25–29.9 kg/m^2); OB = obese (BMI ≥ 30 kg/m^2).

Table 1

Clinical-demographic data by BMI categories.

Variables	Number of studies providing data	Body Mass Index Categories. Unless otherwise specified: patient number, (percentage of total)				global p-value comparing across BMI categories
		Underweight (n = 906, 4%)	Normal BMI (n = 9189, 44%)	Overweight (n = 7085, 34%)	Obese (n = 3756, 18%)	
Age in years	16					<0.001
Median (range)		64 (17–91)	64 (17–95)	66 (20–97)	66 (22–95)	
Sex	16					<0.001
Male		318 (3%)	4485 (40 %)	4312 (39 %)	2060 (18 %)	
Female		588 (6%)	4704 (48 %)	2773 (28 %)	1696 (17 %)	
Race	16					<0.001
White		526 (4%)	5562 (39 %)	5158 (37 %)	2864 (20%)	
Asians		208 (7%)	2029 (68 %)	664 (22 %)	80 (3%)	
Black		48 (5%)	406 (42 %)	308 (32 %)	206 (21 %)	
Others		26 (5%)	210 (37 %)	192 (34 %)	133 (24 %)	
Missing		98	982	763	473	
Educational level	14					<0.001
Low		78 (4%)	754 (43 %)	597 (34 %)	328 (19 %)	
High		620 (4%)	6202 (42%)	5086 (35 %)	2702 (18 %)	
Missing		208 (5%)	2233 (49 %)	1402 (31 %)	726 (16 %)	
Smoking status	15					<0.001
Ever		620 (4%)	5988 (40 %)	5212 (35 %)	2975 (20 %)	
Never		91 (4%)	1162 (47 %)	825 (33 %)	396 (16 %)	
Missing		195	2039	1048	385	
Pack-years	13					<0.001
Median (range)		46 (0–274)	41 (0–219)	43 (0–240)	45 (0–208)	
Missing		356	3776	2370	1098	
Histology	16					<0.001
Squamous carcinoma		229 (5%)	1934 (40%)	1650 (34 %)	1044 (21 %)	
Adenocarcinoma		509 (4%)	5597 (46 %)	4135 (34 %)	2055 (17 %)	
Other		166 (4%)	1626 (44 %)	1280 (34 %)	651 (17 %)	
Missing		2	32	20	6	

Variables	Number of studies providing data	Body Mass Index Categories. Unless otherwise specified: patient number, (percentage of total)				global p-value comparing across BMI categories
		Underweight (n = 906, 4%)	Normal BMI (n = 9189, 44%)	Overweight (n = 7085, 34%)	Obese (n = 3756, 18%)	
Stage	16					0.002
IA		202 (4%)	2031 (44 %)	1511 (33 %)	838 (18 %)	
IB		100 (5%)	994 (46 %)	696 (32 %)	352 (16 %)	
IIA		34 (4%)	397 (44 %)	297 (33 %)	176 (19 %)	
IIB		77 (5%)	727 (45 %)	501 (31 %)	302 (19 %)	
IIIA		110 (3%)	1329 (42 %)	1175 (37 %)	580 (18 %)	
IIIB		91 (5%)	874 (45 %)	676 (35 %)	317 (16%)	
IV		292 (4%)	2837 (43 %)	2229 (34 %)	1191 (18 %)	

Underweight, BMI < 18.5 kg/m [2]; Normal weight, 18.5 ≤ BMI < 25 kg/m [2]; Overweight 25 ≤ BMI < 30 kg/m [2]; Obese BMI ≥ 30 kg/m [2].