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Body mass index (BMI) has been inversely associated with lung and upper aerodigestive tract (UADT) cancers. However, only a few studies have assessed BMI change in adulthood in relation to cancer. To understand the relationship between BMI change and these cancers in both men and women, we analyzed data from a population-based case–control study conducted in Los Angeles County. Adulthood BMI change was measured as the proportional change in BMI between age 21 and 1 year before interview or diagnosis. Five categories of BMI change were included, and individuals with no more than a 5% loss or gain were defined as having a stable BMI (reference group). Adjusted odds ratios (ORs) and their 95% confidence intervals (CIs) were estimated using logistic regression models. Potential confounders included age, gender, ethnicity, education, tobacco smoking and energy intake. For UADT cancers, we also adjusted for alcohol drinking status and frequency. A BMI gain of 25% or higher in adulthood was inversely associated with lung cancer (OR 0.53, 95% CI 0.33–0.84) and UADT cancers (OR 0.44, 95% CI 0.27–0.71). In subgroup analyses, a BMI gain of ≥25% was inversely associated with lung and UADT cancers among current and former smokers, as well as among current and former alcohol drinkers. The inverse association persisted among moderate and heavy smokers (≥20 pack-years). The observed inverse associations between adulthood BMI gain and lung and UADT cancers indicate a potential role for body weight-related biological pathways in the development of lung and UADT cancers.

Body mass index (BMI) is a proxy measure for body fat and is based on body weight and height. BMI has been positively associated with cancers of the colon, kidneys, liver, pancreas, breast and uterus, as well as with melanomas and adenocarcinoma of the esophagus.[1–9] However, BMI has been inversely associated with lung cancer and squamous cell carcinoma of the upper aerodigestive tract (SCC UADT),[9–16] which suggests that low BMI (leanness) may increase the risk of these cancers.[17–19]

The use of BMI at a single time point during the lifespan, in relation to cancer development, might not be sufficient for examining the possible effect of obesity, as BMI might change over time. An informative approach would involve BMI change (either gain or loss) between at least two separate times during the lifespan. Only a few studies have examined the association between BMI change and lung or UADT cancers. For lung cancer, an inverse association was observed with BMI gain in two cohort studies.[20,21] For UADT cancers, an inverse association with BMI gain was reported in two case–control studies in Europe.[11,19] In the United States, there has been no published study in both men and women investigating the role of BMI change in the development of both lung and UADT cancers and of possible effect modification by tobacco smoking. Therefore, we conducted our analyses on the association between BMI change and lung and UADT cancers in a population-based case–control study in Los Angeles County, California, USA.

Key words: body mass index, lung cancer, upper aerodigestive tract cancer, tobacco smoking, metabolism
Abbreviations: BMI: body mass index; CI: confidence intervals; CT: computed axial tomography; OR: odds ratio; ROR: ratio of odds ratios; SCC: squamous cell carcinoma; UADT: upper aerodigestive tract
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Material and Methods

Study population

Epidemiologic data were collected in a population-based case–control study of lung and UADT cancers, in both men and women, conducted in Los Angeles County, California, USA. The detailed study design and population have been described elsewhere.[22,23] Eligible cases and controls were residents of Los Angeles County between the ages of 18–65 years. They were recruited and interviewed between 1999 and 2004. Participants who either spoke English or Spanish or had translators available at home were interviewed. Lung cancer cases ($n = 611$) and UADT cancer cases ($n = 601$) were newly diagnosed and identified by the Los Angeles County Cancer Surveillance Program.[22] UADT cancer cases included oral/pharyngeal, laryngeal and esophageal (adenocarcinoma and squamous cell) cancers. Cases were confirmed pathologically (>95%) or by magnetic resonance imaging or computed axial tomography. Controls with no history of investigated cancers were recruited from the neighborhood of the cases. Cases and controls (1:1) were individually matched by age (within 10-year categories) and gender. Controls were residents of Los Angeles County at the time of diagnosis for cases or at study entry for controls, 18–65 years of age during the enrollment period, and spoke English or Spanish or had translators available at home. As we could not identify sufficient eligible controls for all cases during the study period and to increase power of the study, we decided to analyze the data by breaking the individual matching and using all controls for both lung and UADT cancers as a common control group in an unconditional logistic regression model.

Among contacted and eligible participants, recruitment rates were 79% for controls, 39% for lung cancer cases and 46% for UADT cancer cases. Informed consent and research protocols were approved by the Institutional Review Boards of the University of California, Los Angeles and University of Southern California. Written informed consent was obtained from individual study participants. A standardized questionnaire was administered to all participants by trained interviewers with individual interview sessions of 40–60 min. The standardized questionnaire was used to collect data on participant demographics, occupational history, tobacco and alcohol use, family history of cancer and passive smoke exposures. Dietary information was collected using a food frequency questionnaire based on the Brief Block FFQ developed by the National Cancer Institute.[24]

Definition of anthropometric variables

BMI (kg/m^2) at 1 year before interview and BMI at age 21 were calculated from self-reported height and weight measures collected during the in-person interview. We based cut-off points for BMI at 1 year before interview according to categories defined by the World Health Organization. There was a lower prevalence of individuals with BMIs greater than 25 kg/m^2 in the United States before 1990s, when most study participants would have been 21 years of age.[25,26] Therefore, to avoid sparse data issues in higher BMI categories for the BMI at age 21 variable, we used cut-off points based on quartiles of the control population for the main analyses (<20.34, 20.34 to <22.15, 22.15 to <24.34, ≥24.34 kg/m^2) and on tertiles for the stratified analyses (<20.96, 20.96 to <23.56, ≥23.56 kg/m^2). Proportional change in BMI was defined as [(BMI at 1 year before interview − BMI at age 21)/BMI at age 21]×100. The median time between BMI measurements was 32 years for lung cancer cases, 30 years for SCC UADT cancer cases and 30 years for controls. In the main analyses, we used fine categories of BMI change that include a <−5% BMI change (loss), −5% ≤ BMI change <5% (stable), 5 to <15% (gain), 15 to <25% (gain), 25 to <35% (gain) and ≥35% (gain). Given the observed similarity of associations across the moderate and high categories of BMI change, in our stratified analyses, we collapsed strata to these following categories: <−5% BMI change (loss), −5% ≤ BMI change <5% (stable), 5 to <25% (gain) and ≥25% (gain).

Definition of tobacco smoking characteristics

Ever smokers were defined as having smoked at least 100 cigarettes in their lifetime. Former and current smokers were defined according to smoking pack-years as light (<20), moderate (20 to <40) or heavy (40+) smokers.[27,28] Smoking pack-years were derived from participants' self-reported tobacco use over the lifespan. Cessation was defined as sustained/long term (>3 years of quit time) or recent (≤3 years of quit time).[29] The duration of cessation (quit time) was quantified by subtracting participants' self-reported age at cessation from self-reported age at interview.

Statistical analyses

The primary analyses included all lung cancer cases ($n = 611$) and all squamous cell UADT cancer cases ($n = 527$). The subsite and histologic analyses included lung cancer (small cell, adenocarcinoma, large cell and squamous cell) and SCC UADT cancer sites (oral and pharyngeal, laryngeal and esophageal), as well as adenocarcinoma of the esophagus ($n = 74$). Controls more than 3 years younger than the youngest lung cancer case or more than 3 years older than the oldest lung cancer case ($n = 11$) were excluded from all analyses, and the remaining 1,029 controls were a common control group for lung and UADT cancer cases. Crude and adjusted odds ratios (ORs) and their 95% confidence intervals (CIs) were estimated using unconditional logistic regression models with stable BMI (no more than a 5% loss or gain over time) as the reference group. For all tests of trend, the three BMI variables (BMI at 21, BMI at 1 year before interview/diagnosis and BMI change) were treated as ordinal variables and for the test of trend with BMI change, we excluded the negative BMI change (weight loss) category. In addition to primary and stratified analyses, we also included a product term (BMI gain × pack-years) in our logistic model to check for departures from the multiplicative relationship assumed

under the null hypothesis (H_o: no change in the relation of BMI gain to cancer, across strata of pack-years). The antilog of the coefficient estimated for the product term was interpreted as the ratio of ORs (ROR) with a ROR $\neq$ 1 indicating a departure from multiplicativity and the null hypothesis. The RORs and their 95% CIs were estimated using unconditional logistic regression.

As cases and controls were matched using 10-year categories, we adjusted age using fine categories (<34, 35–36, 37–38, 39–40, 41–42, 43–44, 45–46, 47–48, 49–50, 51–52, 53–54, 55–56, 57–58 and 59–62). We also included gender, ethnicity (White, Asian-American, African-American and Hispanic), education (years, continuous), tobacco smoking status (never, former, current), tobacco smoking frequency (pack-years, continuous) and daily caloric intake (kcal, continuous) as covariates. For UADT cancers, we adjusted for alcohol drinking status (never, former, current) and frequency of alcohol drinking (years of drinking multiplied by number of drinks per day, continuous) in addition to the aforementioned variables. Fruit and vegetable intake and caloric intake were computed using methods previously described.[30] In brief, to calculate fruit and vegetable consumption, we multiplied the portion size (in grams) and number of servings per day of a given fruit or vegetable. Quartiles of total fruit and vegetable intake were based on the distribution of total fruit and vegetable intake in the control population. Total daily energy intake (calories) less than 500 or >4,500 were considered extreme values and were replaced with the mean total energy intake of the control population. Missing total energy intakes were imputed with the mean total energy intake of the control population. Our findings were consistent when we used either multiple imputation (with SAS PROC IMPUTATION) or the method of excluding all subjects with missing calorie intakes. All statistical analyses were performed using SAS v.9.1 (SAS Institute, Cary, NC).

Results

Demographic characteristics are presented in Table 1. Lung cancer cases differed from controls in BMI at age 21 (p = 0.005), but there was little difference between SCC UADT cancer cases and controls (p = 0.13). Lung (p < 0.001) and SCC UADT (p = 0.008) cancer cases differed from controls in BMI at 1 year before interview. Lung and SCC UADT cancer cases were more likely than controls to be smokers (p < 0.001) or drinkers (p < 0.001). Fruit and vegetable consumption differed between lung (p < 0.001) and UADT (p = 0.03) cancer cases and controls.

The associations between BMI and BMI change and lung and SCC UADT cancers are presented in Table 2. BMI at age 21 was not associated with either lung or SCC UADT cancers, adjusting for potential confounders. BMI at 1 year before interview was inversely related to lung (p_{trend} = 0.001) and SCC UADT (p_{trend} = 0.013) cancers. BMI gain was inversely related to lung (p_{trend} = 0.001) and SCC UADT cancers (p_{trend} = 0.002), with a ≥25% gain associated with lung (OR 0.53, 95% CI 0.33–0.84) and SCC UADT (OR 0.44, 95% CI 0.27–0.71) cancers. These inverse associations persisted across fine (10% width) strata of BMI gain for both lung (p_{trend} = 0.001) and SCC UADT (p_{trend} = 0.002) cancers. An inverse association with BMI gain was also observed for different lung-cancer histologies (data not shown) and different UADT cancer subsites (data not shown).

The results of stratified analyses are presented in Tables 3 and 4 for the relations between BMI change and lung and SCC UADT cancers by categories of BMI at age 21, tobacco smoking and alcohol drinking. Little variation was observed in the relation of BMI change to lung and SCC UADT cancers, across strata of BMI at age 21. In current smokers, a ≥25% gain in BMI was inversely associated with lung (OR 0.28, 95% CI 0.13–0.57) and SCC UADT (OR 0.23, 95% CI 0.09–0.58) cancers. In former smokers, a ≥25% gain in BMI was inversely associated with lung (OR 0.54, 95% CI 0.33–0.90) and SCC UADT (OR 0.41, 95% CI 0.23–0.76) cancers. The inverse associations persisted in moderate and heavy smokers (≥20 pack-years) for both lung and SCC UADT cancers (p_{trend} < 0.001). A ≥25% gain in BMI was associated with lung cancer in current (OR 0.48, 95% CI 0.26–0.88) and former (OR 0.43, 95% CI 0.21–0.89) drinkers and with UADT cancer in current drinkers (OR 0.26, 95% CI 0.14–0.49). However, such an inverse association was not observed among never smokers or never drinkers.

The analysis of joint associations between BMI gain and pack-years among subjects with a BMI gain (Table 5) yields results consistent with those of the stratified analyses (Tables 3 and 4). Among all study participants with BMI gain, those light and moderate smokers with a <25% BMI gain have almost six times the odds of lung cancer (95% CI 2.98, 10.5) and three times the odds of UADT cancers (95% CI 1.56, 5.86), compared to nonsmokers with a ≥25% gain in BMI in adulthood. Heavy smokers with a <25% BMI gain have almost 85 times the odds of lung cancer (95% CI 41.8, 173) and 12 times the odds of SCC UADT cancer (95% CI 5.70, 26.1), compared to nonsmokers with a ≥25% gain in BMI in adulthood. These findings, in addition to estimated RORs of 1.66 for lung cancer (p = 0.059) and 1.47 for SCC UADT cancer (p = 0.204), suggest that smoking pack-years may modify the OR for the effect of BMI gain on both lung and UADT cancers.

Discussion

The main finding of our analyses is that proportional gain in BMI in adulthood was inversely associated with lung cancer and SCC UADT cancers in middle-aged adults in Los Angeles County. Monotonic dose–response associations were observed for both cancer outcomes with adult BMI gain. Two prospective cohort studies of lung cancer and two case–control studies of UADT cancers reported similar observations.[11,19–21] A cohort study of lung cancer reported that BMI loss is strongly associated with increased risk of lung cancer, which also supports our finding.[31]

When stratifying by smoking status, we found that the inverse associations were strongest among former and

Table 1. Study population characteristics

	Lung cancer cases		SCC UADT cancer cases		Controls	
	$n = 611$		$n = 527$		$n = 1{,}040$	
Variable						
Ethnicity		%		%		%
White	359	(58.8)	289	(54.8)	634	(61.0)
Hispanic	53	(8.7)	62	(11.8)	150	(14.4)
Black	96	(15.7)	68	(12.9)	102	(9.8)
Asian	70	(11.5)	59	(11.2)	62	(6.0)
Other	32	(5.2)	47	(8.9)	91	(8.8)
Missing	1	(0.16)	2	(0.4)	1	(0.1)
p-Value*	<0.001		<0.001			
Sex						
Male	303	(49.6)	391	(74.2)	623	(59.9)
Female	308	(50.4)	136	(25.8)	417	(40.1)
Missing		(0)	0	(0)	0	(0)
p-Value*	<0.001		<0.001			
Age, mean ± SD	52.2 ± 5.4		50.3 ± 7.6		49.9 ± 7.3	
missing	0	(0)	0	(0)	0	(0)
p-Value**	<0.001		0.32			
Age, mean ± SD (excluding extreme values)[1]					50.1 ± 6.8	
Missing					11	(1.1)
BMI 1 year before interview, mean ± SD, kg/m^2	26.3 ± 5.7		26.7 ± 5.8		27.5 ± 5.7	
Missing	2	(0.3)	2	(0.4)	2	(0.2)
p-Value**	<0.001		0.008			
BMI at age 21, mean ± SD, kg/m^2	22.1 ± 3.4		22.9 ± 3.7		22.6 ± 3.7	
Missing	13	(2.1)	14	(2.6)	8	(0.8)
p-Value**	0.005		0.13			
Years between BMI time points, median (range)	32 (10–37)		30 (1–37)		30 (7–40)	
p-Value**	<0.001		0.724			
Histology or subsite						
Large cell	115	(18.8)				
Small cell	75	(12.3)				
Squamous cell	95	(15.6)				
Adenocarcinoma	297	(48.6)				
Missing	29	(4.7)				
Oral and pharyngeal			403	(76.5)		
Laryngeal			90	(17.0)		
Esophageal			34	(6.5)		
Education Level						
0–12	265	(43.4)	240	(45.5)	300	(28.9)
12–16	275	(45.0)	230	(43.6)	481	(46.3)
>16	71	(11.6)	57	(10.8)	258	(24.8)
Missing	0	(0)	0	(0)	1	(0.1)
p-Value*	<0.001		<0.001			

Table 1. Study population characteristics (Continued)

	Lung cancer cases		SCC UADT cancer cases		Controls	
	$n = 611$		$n = 527$		$n = 1{,}040$	
Variable						
Tobacco smoking status		%		%		%
Never	110	(18.0)	164	(31.1)	492	(47.3)
Former	360	(58.9)	272	(51.6)	362	(34.8)
Current	141	(23.1)	91	(17.3)	186	(17.9)
Missing	0	(0)	0	(0)	0	(0)
p-Value*	<0.001		<0.001			
Alcohol drinking status						
Never	170	(27.8)	104	(19.7)	264	(25.4)
Former	250	(40.9)	272	(51.6)	199	(19.1)
Current	190	(31.1)	149	(28.3)	573	(55.1)
Missing	1	(0.16)	2	(0.4)	4	(0.4)
p-Value*	<0.001		<0.001			
Calories	1,526.2 ± 700.0		1,797.1 ± 1,040.9		1,478.7 ± 628.4	
Missing	44	(7.2)	123	(23.3)	191	(18.3)
Calories (Number of extreme values excluded)[2]	1,529 ± 667.1 (9)		1,750.5 ± 864.5 (14)		1,483.8 ± 602 (12)	
p-Value**	0.190		<0.001			
Fruit and vegetable intake[3]						
Quartile 1	209	(34.2)	170	(32.3)	260	(25.0)
Quartile 2	145	(23.7)	119	(22.6)	259	(24.9)
Quartile 3	133	(21.8)	114	(21.6)	257	(24.7)
Quartile 4	115	(18.8)	117	(22.2)	258	(24.8)
Missing	9	(1.5)	7	(1.3)	6	(0.6)
p-Value*	<0.001		0.030			

[1]Controls >3 years younger than the youngest case or >3 years older than the oldest case were considered extreme. [2]Self-reported daily calorie intakes <500 and >4,500 were considered extreme. [3]Quartile 1 <2.33 servings, Quartile 2 from 2.33 to 3.67, Quartile 3 from 3.67 to 5.50 and Quartile 4 >5.50. **p*-Value calculated between cases and controls using a chi-square test. ***p*-Value calculated between mean values of cases and controls using a *t*-test.
Abbreviations: BMI: body mass index; SCC: squamous cell carcinoma.

current smokers. Similar effect modification by smoking was previously reported in two pooled case–control analyses of head and neck cancers[11,32] in a prospective cohort study of lung cancer in women[21] and in a prospective cohort study of esophageal cancer.[9] Because of the relatively small sample size of nonsmokers, we did not have sufficient power to detect similar association. Residual confounding by tobacco smoking may distort the observed associations because smoking is the strongest risk factor for both lung and UADT cancers. Tobacco smoking may contribute to a reduction in body weight through appetite suppression as shown in animal studies.[33] However, no correlation was observed between pack-years of smoking and adulthood BMI change among controls in our study (all controls: $r = -0.007$, p-value = 0.807; ever-smoking controls: $r = 0.010$, p-value = 0.810), among current smoking controls ($r = -0.042$, p-value = 0.566) or former smoking controls ($r = 0.075$, p-value = 0.157). Additionally, if tobacco smoking confounds the associations between adulthood BMI change and lung and UADT cancers, we should have observed positive associations between BMI loss and lung and UADT cancers among smokers. However, no apparent associations were observed with BMI loss in our study among all participants, current smokers or moderate and heavy smokers. Another possibility is that the observed association may reflect the association among tobacco quitters, who have reduced their risk of cancer through cessation[34–37] and who might also have increased their body weight.[38–41] Therefore, one might expect an inverse relationship among former smokers that should be stronger than the association observed among current smokers. However, we observed stronger inverse associations among current smokers in comparison to former smokers,

Table 2. BMI change and lung and SCC UADT cancers

Variables	Lung cancer			SCC UADT cancer		
	Ca/Co	Crude OR (95% CI)	Adjusted OR[1] (95% CI)	Ca/Co	Crude OR (95% CI)	Adjusted OR[2] (95% CI)
BMI at age 21 (kg/m^2)						
<20.34	187/255	1.00	1.00	111/255	1.00	1.00
20.34 to <22.15	148/259	0.77 (0.59, 1.02)	0.97 (0.69, 1.35)	108/259	0.95 (0.69, 1.31)	0.93 (0.64, 1.34)
22.15 to <24.34	129/262	0.67 (0.50, 0.89)	0.89 (0.63, 1.27)	153/262	1.34 (0.99, 1.80)	1.19 (0.83, 1.72)
≥24.34	134/248	0.73 (0.55, 0.97)	0.93 (0.64, 1.34)	141/248	1.30 (0.96, 1.77)	1.25 (0.86, 1.81)
p_{trend}		0.015	0.611		0.019	0.110
BMI 1 year before interview (kg/m^2)						
<18.5	18/13	1.89 (0.91, 3.93)	1.31 (0.55, 3.14)	13/13	1.76 (0.80, 3.87)	2.37 (0.95, 5.92)
18.5 to <25	263/360	1.00	1.00	204/360	1.00	1.00
25 to <30	214/397	0.73 (0.58, 0.92)	0.87 (0.66, 1.16)	199/397	0.88 (0.69, 1.12)	0.90 (0.68, 1.20)
≥30	114/257	0.60 (0.46, 0.79)	0.58 (0.41, 0.81)	109/257	0.74 (0.56, 0.99)	0.70 (0.50, 0.98)
p_{trend}		<0.001	0.001		0.014	0.013
BMI change						
<−5% (weight loss)	51/39	1.60 (0.99, 2.61)	1.09 (0.60, 1.98)	51/39	1.69 (1.04, 2.76)	1.32 (0.75, 2.31)
−5 to <+5%	113/139	1.00	1.00	107/139	1.00	1.00
5 to <15%	132/256	0.63 (0.45, 0.87)	0.76 (0.51, 1.13)	114/256	0.57 (0.41, 0.80)	0.61 (0.41, 0.90)
15 to <25%	113/214	0.65 (0.46, 0.91)	0.72 (0.47, 1.09)	105/214	0.63 (0.45, 0.89)	0.69 (0.46, 1.04
25 to <35%	67/153	0.53 (0.36, 0.78)	0.53 (0.33, 0.84)	51/153	0.43 (0.28, 0.64)	0.44 (0.27, 0.71)
≥35%	122/222	0.67 (0.48, 0.94)	0.53 (0.35, 0.80)	85/222	0.49 (0.34, 0.70)	0.51 (0.34, 0.78)
p_{trend}*		0.040	0.001		<0.001	0.002

[1]Adjusted for age, gender, ethnicity, tobacco smoking status, pack-years, education and calories. [2]Adjusted for age, gender, ethnicity, education, tobacco smoking status, pack-years, drinking status, drinking years and calories. *Negative BMI change (weight loss) excluded.
Abbreviations: BMI: body mass index; SCC: squamous cell carcinoma.

Epidemiology

and there was no detectable heterogeneity across strata of quit time for BMI gain and lung ($p_{heterogeneity} = 0.931$) and UADT ($p_{heterogeneity} = 0.637$) cancers. Our findings suggest that the potential for residual confounding by tobacco smoking in the observed associations between adult BMI changes and lung and UADT cancers might be minimal.

Experimental studies have suggested that tobacco smoking may act as a modifier of the BMI change and cancer association by influencing anabolism and metabolism. Anabolism and metabolism are complex pathways necessary for proper utilization of nutrients and that help determine body size and ability to increase body mass over time. Smokers who are able to gain weight during adulthood might represent a subpopulation with anabolic or metabolic advantages. One mechanism that might confer biological advantage in smokers is neurologic resistance to the anorexigenic effect of nicotine. Exposure to nicotine is expected to activate the melanocortin axis in the brain, thereby suppressing the appetite and reducing food intake; however, mice that are genetically immune to activation of this neural pathway did not experience appetite suppression or change in food intake after exposure to nicotine, in comparison to normal mice.[33] Tobacco smoking may also be related to sex steroids. Some lung tumors have been shown to express estrogen receptors,[42] which suggest that estrogen may be associated with lung cancer. However, there remains no in-depth study to support this hypothesis. As the conversion of androgens to estrogens is most frequently observed in overweight and obese individuals, it may be one of the mechanisms linking obesity with the development of cancer.[43] Cigarette smoke exposure is a risk factor for lung cancer but, as it is also an inhibitor of estrogen bioavailability,[44,45] smoke exposure might modify the risk of lung cancer in those with large BMI gains. This effect modification might also occur with UADT cancers that express estrogen receptors. However, there is no direct evidence to support this hypothesis.

Information bias might be present in our study because our study relied on self-report of anthropometric measures, smoking behaviors and alcohol drinking behaviors. There is a possibility that these measures may be subject to recall bias because of the case–control study design. However, as body weight and height are not recognized as risk factors for lung or UADT cancers, recall bias of anthropometric measures is expected to be nondifferential between cases and controls.

Table 3. Association between BMI change and lung cancer, stratified by risk factors

	<−5% (weight loss)	−5 to <+5%	5 to <25%	≥25%	p_{trend}*
BMI at age 21[1] (kg/m^2)					
Tertile 1					
Case/controls	5/1	39/36	90/137	102/169	
Adj OR (95% CI)[2]	2.22 (0.21, 22.88)	1.00	0.63 (0.33, 1.22)	0.41 (0.21, 0.80)	0.005
Tertile 2					
Case/controls	21/8	32/51	81/174	53/113	
Adj OR (95% CI)[2]	2.64 (0.89, 7.78)	1.00	0.87 (0.46, 1.64)	0.63 (0.32, 1.25)	0.161
Tertile 3					
Case/controls	25/30	42/52	74/159	34/93	
Adj OR (95% CI)[2]	0.60 (0.24, 1.45)	1.00	0.64 (0.33, 1.23)	0.47 (0.22, 1.00)	0.042
Tobacco smoking status					
Never					
Case/controls	4/12	10/70	54/224	37/176	
Adj OR (95% CI)[3]	1.59 (0.36, 7.02)	1.00	1.45 (0.66, 3.19)	1.11 (0.49, 2.54)	0.787
Former					
Case/controls	30/15	63/42	142/168	120/132	
Adj OR (95% CI)[3]	1.60 (0.72, 3.54)	1.00	0.67 (0.41, 1.08)	0.54 (0.33, 0.90)	0.017
Current					
Case/controls	17/12	40/27	49/78	32/67	
Adj OR (95% CI)[3]	0.81 (0.31, 2.10)	1.00	0.40 (0.21, 0.78)	0.28 (0.13, 0.57)	0.001
Alcohol drinking status					
Never					
Case/controls	11/14	25/33	66/100	61/109	
Adj OR (95% CI)[4]	0.77 (0.24, 2.47)	1.00	1.12 (0.53, 2.38)	0.68 (0.31, 1.49)	0.173
Former					
Case/controls	21/10	51/26	104/83	70/78	
Adj OR (95% CI)[4]	0.76 (0.25, 2.24)	1.00	0.69 (0.35, 1.36)	0.43 (0.21, 0.89)	0.017
Current					
Case/controls	19/15	37/79	74/286	58/187	
Adj OR (95% CI)[4]	1.63 (0.62, 4.29)	1.00	0.62 (0.35, 1.09)	0.48 (0.26, 0.88)	0.021
Tobacco smoking pack-years					
<20					
Case/controls	10/15	10/48	44/163	33/120	
Adj OR (95% CI)[3]	2.07 (0.65, 6.63)	1.00	1.24 (0.54, 2.84)	0.78 (0.32, 1.90)	0.328
≥20					
Case/controls	37/12	93/21	147/83	119/79	
Adj OR (95% CI)[3]	0.74 (0.31, 1.73)	1.00	0.37 (0.21, 0.67)	0.25 (0.13, 0.45)	<0.001
Time since quitting tobacco smoking					
≤3 years					
Case/controls	23/7	50/8	93/24	71/17	
Adj OR (95% CI)[3]	0.53 (0.13, 2.16)	1.00	1.16 (0.41, 3.27)	0.65 (0.22, 1.91)	0.300
>3 years					
case/controls	7/8	13/34	49/144	49/115	
Adj OR (95% CI)[3]	1.34 (0.35, 5.10)	1.00	0.89 (0.40, 1.96)	0.78 (0.35, 1.75)	0.478

[1]Tertile 1 <20.96, Tertile 2 from 20.96 to <23.56 and Tertile 3 ≥23.56. [2]Adjusted for age, gender, ethnicity, tobacco smoking status, pack-years, education and calories. [3]Adjusted for age, gender, ethnicity, education and calories. [4]Adjusted for age, gender, ethnicity, tobacco smoking status, pack-years, education and calories. *Negative BMI change (weight loss) excluded.
Abbreviations: Adj: adjusted; BMI: body mass index; SCC: squamous cell carcinoma.

Table 4. Association between BMI change and SCC UADT cancer, stratified by risk factors

	<−5% (weight loss)	−5 to <+5%	5 to <25%	≥25%	p_{trend}**
BMI at 21 (kg/m^2)					
Tertile 1 (<20.9)					
Case/controls	8/1	29/36	59/137	64/169	
Adj OR (95% CI)[1]	9.36 (0.92, 95.0)	1.00	0.71 (0.34, 1.48)	0.52 (0.24, 1.11)	0.084
Tertile 2 (20.96 to <23.56)					
Case/controls	12/8	37/51	72/174	42/113	
Adj OR (95% CI)[1]	1.50 (0.46, 4.91)	1.00	0.48 (0.26, 0.88)	0.42 (0.22, 0.81)	0.017
Tertile 3 (≥23.56)					
Case/controls	31/30	41/52	88/159	30/93	
Adj OR (95% CI)[1]	0.96 (0.44, 2.07)	1.00	0.72 (0.41, 1.26)	0.44 (0.22, 0.87)	0.014
Tobacco smoking status					
Never					
Case/controls	14/12	26/70	78/224	40/176	
Adj OR (95% CI)[2]	2.37 (0.88, 6.39)	1.00	0.99 (0.57, 1.74)	0.69 (0.37, 1.27)	0.146
Former					
Case/controls	30/15	51/42	107/168	77/132	
Adj OR (95% CI)[2]	1.59 (0.67, 3.80)	1.00	0.53 (0.30, 0.93)	0.41 (0.23, 0.76)	0.006
Current					
Case/controls	7/12	30/27	34/78	19/67	
Adj OR (95% CI)[2]	0.39 (0.11, 1.38)	1.00	0.39 (0.17, 0.85)	0.23 (0.09, 0.58)	0.004
Alcohol drinking status					
Never					
Case/controls	6/14	18/33	43/100	32/109	
Adj OR (95% CI)[3]	0.51 (0.14, 1.85)	1.00	0.67 (0.32, 1.41)	0.59 (0.27, 1.28)	0.187
Former drinker					
Case/controls	28/10	50/26	113/83	75/78	
Adj OR (95% CI)[3]	1.35 (0.53, 3.42)	1.00	0.86 (0.47, 1.58)	0.62 (0.33, 1.17)	0.136
Current					
Case/controls	16/15	39/79	63/286	28/187	
Adj OR (95% CI)[3]	1.98 (0.83, 4.72)	1.00	0.44 (0.26, 0.74)	0.26 (0.14, 0.49)	<0.001
Tobacco smoking pack-years					
<20					
Case/controls	12/15	19/48	51/163	39/120	
Adj OR (95% CI)[2]	1.52 (0.52, 4.42)	1.00	0.62 (0.31, 1.23)	0.53 (0.25, 1.12)	0.157
≥20					
Case/controls	25/12	62/21	90/83	57/79	
Adj OR (95% CI)[2]	0.57 (0.22, 1.48)	1.00	0.36 (0.18, 0.71)	0.22 (0.10, 0.45)	<0.001
Time since quitting tobacco smoking					
≤3 years					
Case/controls	24/7	40/8	63/24	39/17	
Adj OR (95% CI)[2]	0.66 (0.18, 2.47)	1.00	0.56 (0.19, 1.59)	0.39 (0.12, 1.23)	0.133
>3 years					
Case/controls	6/8	11/34	44/144	38/115	
Adj OR (95% CI)[2]	2.60 (0.56, 12.0)	1.00	0.86 (0.36, 2.03)	0.74 (0.30, 1.79)	0.394

[1]Adjusted for age, gender, ethnicity, tobacco smoking status, pack-years, drinking status, drinking years, education and calories. [2]Adjusted for age, gender, ethnicity, drinking status, drinking years, education and calories. [3]Adjusted for age, gender, ethnicity, tobacco smoking status, pack-years, education and calories.

**Negative BMI change (weight loss) excluded.

Abbreviations: Adj: adjusted; BMI: body mass index; SCC: squamous cell carcinoma.

Table 5. Joint association of BMI change and pack-years in lung and UADT cancers

		Lung cancer		SCC UADT cancer	
BMI change	Pack-years	Ca/Co	Adjusted OR[1] (95% CI)	Ca/Co	Adjusted OR[2] (95% CI)
(a) All subjects					
≥25%	0	37/176	1.00	40/176	1.00
<25%[3]	0	64/294	1.17 (0.73, 1.89)	104/294	1.49 (0.97, 2.31)
≥25%	>0 to <20	33/120	4.60 (2.35, 8.98)	39/120	2.61 (1.28, 5.30)
<25%[3]	>0 to <20	54/211	5.59 (2.98, 10.5)	70/211	3.03 (1.56, 5.86)
≥25%	≥20	119/79	42.9 (21.3, 86.6)	57/79	6.16 (2.86, 13.2)
25%[3]	≥20	240/104	85.2 (41.8, 173)	152/104	12.2 (5.70, 26.1)
ROR			1.66 (0.98, 2.80)		1.47 (0.81, 2.67)
(b) Among smokers					
≥25%	>0 to <20	33/120	1.00	39/120	1.00
<25%[3]	>0 to <20	54/211	1.22 (0.71, 2.08)	70/211	1.29 (0.77, 2.17)
≥25%	≥20	119/79	8.12 (4.65, 14.1)	57/79	2.06 (1.14, 3.72)
<25%[3]	≥20	240/104	16.4 (0.49, 28.4)	152/104	4.26 (2.47, 7.35)
ROR			1.65 (0.85, 3.20)		1.59 (0.77, 3.28)

[1]Adjusted for age, ethnicity, gender, education, tobacco smoking status and calories. [2]Adjusted for age, ethnicity, gender, education, tobacco smoking status, drinking status, drinking years and calories. [3]Negative BMI change category (weight loss) excluded.Abbreviations: BMI: body mass index; ROR: ratio of odds ratios; SCC: squamous cell carcinoma.

Measures of body fat distribution, such as waist circumference or waist to hip ratio, were not measured in our study, and we could not evaluate the independent associations between distribution of body fat and both cancers. In addition, body fat distribution might confound our observed associations between BMI change and lung or UADT cancers. However, in two prospective cohort studies by Kabat *et al.*[21] and Olson *et al.*,[12] the inverse associations observed for BMI and lung cancer persisted after adjusting for waist circumference and lung cancer.[12,21]

With regard to smoking and alcohol drinking history, recall bias may exist. However, the associations between smoking, alcohol and lung and UADT cancers observed in our study are consistent with published associations from prospective cohort studies. Therefore, it is unlikely that recall bias distorted the associations. Potential selection bias might be present in our study, given the case–control study design. For lung and UADT cancer cases, 30 and 14%, respectively, did not participate because they were deceased or ill.[23] Consequently, cases with advanced cancers might not be represented in the case groups. However, as our study confirmed the established associations between smoking and lung and UADT cancers and between alcohol drinking and UADT cancer, the possibility of selection bias of the observed associations may be largely reduced. Lastly, reverse causality might be of concern if a positive association was noted between BMI loss and lung and UADT cancers, given the possibility for subclinical weight loss before cancer diagnosis. However, there is no clear association in our study for adult weight loss and increased risk of lung or UADT cancers.

This is the first study in the United States, in both men and women, to examine the potential association between BMI change and both lung and UADT cancers. In our study, we found that a gain in adulthood BMI is inversely associated with the risk of lung and UADT cancers in both men and women. However, given that the inverse association between BMI gain and lung and UADT cancers persists in smokers, future studies should focus on understanding the potential interaction between BMI gain and smoking. It would be advantageous to explore the potential biological pathways in relation to BMI change to understand the underlying mechanisms for the relationship between adulthood BMI gain and lung and UADT cancers.

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