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ARTICLE

Body Mass Index and Risk of Lung Cancer Among Never, Former, and Current Smokers

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Background Although obesity has been directly linked to the development of many cancers, many epidemiological studies have found that body mass index (BMI)—a surrogate marker of obesity—is inversely associated with the risk of lung cancer. These studies are difficult to interpret because of potential confounding by cigarette smoking, a major risk factor for lung cancer that is associated with lower BMI.

Methods We prospectively examined the association between BMI and the risk of lung cancer among 448 732 men and women aged 50–71 years who were recruited during 1995–1996 for the National Institutes of Health–AARP Diet and Health Study. BMI was calculated based on the participant's self-reported height and weight on the baseline questionnaire. We identified 9437 incident lung carcinomas (including 415 in never smokers) during a mean follow-up of 9.7 years through 2006. Multivariable Cox proportional hazards regression models were used to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) with adjustment for lung cancer risk factors, including smoking status. To address potential bias due to preexisting undiagnosed disease, we excluded potentially unhealthy participants in sensitivity analyses. All statistical tests were two-sided.

Results The crude incidence rate of lung cancer over the study follow-up period was 233 per 100 000 person-years among men and 192 per 100 000 person-years among women. BMI was inversely associated with the risk of lung cancer among both men and women (BMI ≥35 vs 22.5–24.99 kg/m^2: HR = 0.81, 95% CI = 0.70 to 0.94 and HR = 0.73, 95% CI = 0.61 to 0.87, respectively). The inverse association was restricted to current and former smokers and was stronger after adjustment for smoking. Among smokers, the inverse association persisted even after finely stratifying on smoking status, time since quitting smoking, and number of cigarettes smoked per day. Sensitivity analyses did not support the possibility that the inverse association was due to prevalent undiagnosed disease.

Conclusions Our results suggest that a higher BMI is associated with a reduced risk of lung cancer in current and former smokers. Our inability to attribute the inverse association between BMI and the risk of lung cancer to residual confounding by smoking or to bias suggests the need for considering other explanations.

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Epidemiological studies have consistently shown that obesity is associated with an increased risk of many cancers, including thyroid, colon, renal, and endometrial cancers (1–3). Conversely, body mass index (BMI)—a surrogate indicator of obesity—has been inversely associated with the risk of incident and fatal lung cancers in many prospective investigations (4–17). Because numerous cohort studies have found that this inverse association is observed only among ever or current smokers (4,7–9,12,14,16,17), the finding has been attributed to potential residual confounding by cigarette smoking. However, BMI has also been found to be unrelated with the risk of lung cancer irrespective of smoking status (18) or to be positively associated with risk among nonsmokers (8) or ever smokers (19).

Previous cohort studies have been limited in their ability to explore the relationship between BMI and lung cancer for a number of reasons. Some have only examined associations with lung cancer mortality (5,6,11,15,16,18). Others have not stratified the analyses by sex (17) or smoking status (15), potentially oversimplifying the relationship. Some studies have had small numbers of female current smokers (17,19), which precluded their ability to analyze associations within this important group. Furthermore, only two epidemiological studies (12,13) have presented results stratified by histological subtype. The suggestion that different histological types of lung cancer may represent largely distinct diseases with divergent etiologies (20) supports the need to examine associations between BMI and individual histological subgroups.

We attempted to clarify the relationship between BMI and incident lung cancer in the large prospective National Institutes of Health (NIH)–AARP Diet and Health Study. The large size of this cohort enabled us to evaluate detailed associations by sex and smoking status and to assess potential differences in associations according to histology.

Methods

Study Population

The NIH–AARP Diet and Health Study was established in 1995–1996, when a questionnaire requesting information on demographic characteristics, dietary intake, and health-related behaviors was sent to 3.5 million members of AARP (formerly known as the American Association of Retired Persons). The study design has been described elsewhere in detail (21). Those initially contacted were AARP members 50–71 years old who resided in one of six US states (California, Florida, Louisiana, New Jersey, North Carolina, or Pennsylvania) or two metropolitan areas (Atlanta, Georgia or Detroit, Michigan). A total of 617 119 people (17.6%) returned the questionnaire. Excluded were individuals who had more than 10 recording errors or indicated that they had consumed fewer than 10 types of food items (n = 8127), skipped parts of the questionnaire (n = 27 552), indicated that they were not the intended respondent and did not complete the questionnaire (n = 13 442), did not indicate whether they were male or female (n = 6), were duplicate respondents (n = 179), or had died (n = 261) or moved (n = 321) before their questionnaire was scanned, or subsequently withdrew from the study (n = 830). After these exclusions, the baseline study population included 566 401 participants who were potentially eligible for this analysis. Address changes were tracked annually through the National Change of Address database (US Postal Service), the processing of undeliverable mail, and directly from information provided by participants. Vital status was determined using the Social Security Administration Death Master File, the National Death Index, cancer registry linkages, and mailing responses. The NIH–AARP Diet and Health Study was approved by the Special Studies Institutional Review Board of the US National Cancer Institute, and all participants gave informed consent by virtue of completing and returning the questionnaire.

Cancer Incidence

Incident cases of lung cancer were identified by probabilistic linkage to cancer registries in the eight states of the cohort, as well as two states to which subjects tended to move (Texas and Arizona). The states selected for inclusion in the NIH–AARP Study were chosen in part because their registries had been shown to validly identify at least 90%–95% of cancer cases (22). Dates of diagnosis and tumor characteristics were obtained from the registries. Histology was defined using the *International Classification of Diseases for Oncology*, third edition (23) codes, and all primary incident carcinomas of the bronchus and lung were considered for this analysis. Lung cancers included small cell carcinomas (*International Classification of Diseases for Oncology* [*ICD-O*] codes 8002, 8041, 8042, 8043, 8044, 8045), adenocarcinomas (*ICD-O* codes 8140, 8200, 8250, 8251, 8252, 8253, 8254, 8255, 8260, 8310, 8323, 8430, 8480, 8481, 8490, 8550, 8574), squamous cell carcinomas (*ICD-O* codes 8050, 8052, 8070, 8071, 8072, 8073, 8074, 8075, 8083, 8084), undifferentiated or large cell carcinomas (*ICD-O* codes 8012, 8020, 8021, 8022, 8031, 8032), non–small cell carcinomas not otherwise specified (NOS) (*ICD-O* code 8046), and other carcinomas NOS (*ICD-O* codes 8010, 8011, 8030, 8033, 8123, 8560, 8562, 8575). Summary stage at the initial diagnosis or treatment of the reportable carcinoma was classified as localized, regional, or distant according to the US National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) Program guidelines.

Exposure Assessment

Study participants reported their current height and body weight at the time of the baseline questionnaire; we used this information to calculate the participant's BMI using the formula weight in kilograms divided by height in meters squared (kg/m^2). Categories for BMI were defined as less than 18.5, 18.5–22.49, 22.5–24.99, 25–29.99, 30–34.99, and 35 kg/m^2 or higher according to World

CONTEXT AND CAVEATS

Prior knowledge

Many prospective investigations have reported that body mass index (BMI)—a surrogate indicator of obesity—is inversely associated with the risk of lung cancer. However, cigarette smoking is associated with lower BMI, thus confounding interpretation of the data.

Study design

A prospective cohort study examined the association between BMI and the risk of lung cancer among men and women aged 50–71 years who were recruited during 1995–1996 for the National Institutes of Health–AARP Diet and Health Study. BMI was calculated from the participant's self-reported height and weight on a baseline questionnaire. The questionnaire also captured information on lung cancer risk factors, including smoking status, time since quitting smoking, and number of cigarettes smoked per day.

Contribution

BMI was inversely associated with the risk of lung cancer among both men and women. The inverse association was restricted to current and former smokers and persisted even after finely stratifying on smoking status, time since quitting smoking, and number of cigarettes smoked per day. Sensitivity analyses did not support the possibility that the inverse association was due to prevalent undiagnosed disease.

Implications

Inverse associations between BMI and the risk of lung cancer among current and former smokers cannot be fully explained by residual confounding by smoking or reverse causality. This finding suggests the need to consider alternative explanations for the inverse association between BMI and risk of lung cancer among smokers.

Limitations

Data on smoking habits, BMI, and health conditions were based on a single questionnaire. Smoking duration was not collected at baseline. Results may not be generalizable to the general US population.

From the Editors

Health Organization classifications (24) as a guide because of their presumed clinical relevance. A BMI less than 18.5 kg/m² was considered underweight, 18.5–24.99 kg/m² was considered normal weight, 25–29.99 kg/m² was considered overweight, and 30 kg/m² or higher was considered obese. In analyses stratified by detailed smoking information, we excluded underweight individuals and combined subjects in the two highest categories of BMI due to small case numbers within these strata.

Study participants were also asked to provide information on demographic characteristics (eg, race or ethnicity and level of education), dietary characteristics (eg, usual alcohol intake over the previous 12 months), and medical history (eg, history of heart disease and emphysema). Participants were also asked how often they participated in a period of vigorous physical activity at work or home, defined as one of at least 20 minutes in the past 12 months that caused an increase in breathing or heart rate, or worked up a sweat. On the questionnaire, participants were asked if they had ever smoked 100 cigarettes during their lifetime. If so, they were asked whether they currently smoked, and, if not, when they stopped. Smokers (current and former) were also asked how many cigarettes per day they usually smoked. In addition, all participants were asked if they had ever smoked pipes, cigars, or both.

Analytic Population

For this analysis, we excluded 15 760 participants whose questionnaire was completed by proxy. In addition, we excluded 27 923 men and 24 311 women who self-reported or were diagnosed with any cancer other than non-melanoma skin cancer before baseline; 10 men and 11 women who died or were diagnosed with lung cancer on the first day of follow-up; 16 453 men and 15 347 women who were missing information on tobacco smoking (either cigarette or pipe and cigar smoking); 2219 men and 1540 women who had extreme values for caloric intake (defined as more than two interquartile ranges above the 75th percentile or below the 25th percentile of log-transformed intake); 4927 men and 5558 women who were missing information on BMI; and 2404 men and 1206 women who had extreme values for BMI (ie, more than two interquartile ranges above the 75th percentile or below the 25th percentile). The final analytic population, therefore, included 271 238 men and 177 494 women. Study entry and follow-up began on the date that the baseline questionnaire was scanned and continued until December 31, 2006, or the date on which the participant was diagnosed with lung cancer, moved out of the registry area, or died of any cause, whichever occurred first. During follow-up, 6093 men and 3344 women were diagnosed with lung carcinoma.

Statistical Analysis

We used Cox proportional hazards regression as implemented in SAS 9.1.3 software (SAS Institute Inc, Cary, NC), with age as the time scale and ties handled by complete enumeration (25), to estimate the hazard ratios (HRs) and 95% confidence intervals (CIs) of developing lung cancer. We originally tested for confounding by using myriad possible risk factors but eventually chose a parsimonious combination of factors that were associated with BMI and lung cancer and contributed statistically significantly to the multivariable model. We first examined risk estimates adjusted for age at study entry (continuous). Our multivariable models then controlled for detailed smoking information using response categories provided on the baseline questionnaire, including smoking status (never, former, or current smoker), time since smoking cessation among former smokers (1–4, 5–9, or ≥10 years), number of cigarettes smoked per day among former and current smokers (1–10, 11–20, 21–30, 31–40, 41–60, or ≥61 cigarettes per day), and pipe or cigar smoking (no, yes). Our final multivariable models also included race or ethnicity (initially categorized as white, black, Hispanic, Asian or Pacific Islander or American Indian or native Alaskan, or unknown; these categories were collapsed to white, nonwhite, or unknown for analyses stratified by smoking status), education level (college graduate: no, yes, or unknown), history of emphysema (no, yes), vigorous physical activity (<3 times per week, ≥3 times per week, or unknown), and usual alcohol intake during the previous 12 months (nondrinker, ≤5, >5–10, >10–20, >20–35, or >35 g/d). The cut points for alcohol intake were based on the distribution of consumption in the cohort, and the cut point for physical activity was based on American College of Sports Medicine's physical activity guidelines (26), which recommend at least 20 minutes of continuous vigorous exercise three times per week as a means of improving cardiorespiratory fitness. In analyses stratified by smoking status, never smokers were defined as participants who reported that they had never smoked any tobacco products; men and women who had never smoked cigarettes but had smoked pipes or cigars were excluded. Participants who reported on the baseline questionnaire that they had quit smoking within the last year were classified as current smokers. Adjustment for additional potential confounding factors, such as marital status; frequency of physical activity as a teenager; history of heart, colon, kidney, or gallbladder disease; fruit, vegetable, meat, and total caloric intakes; and, among women, type of and age at menopause and use of menopausal hormone therapy had minimal effects on the results, and, thus, those results are not presented. Models were stratified by sex, smoking status, time since quitting smoking (using the cut points described above), and number of cigarettes smoked per day using cut points selected to maintain adequate numbers in each stratum (≤20 cigarettes per day, >20 cigarettes per day—ie, ≤1 pack of cigarettes per day, >1 pack per day).

To address potential bias due to prevalent undiagnosed disease, we conducted a series of analyses in which we progressively restricted the analytic population by first excluding men and women who reported having poor or fair health or emphysema on the baseline questionnaire, followed by exclusion of participants who were diagnosed with lung cancer within 7 years of entry into the cohort. The 7-year cutoff was a more conservative cut point (ie, ensuring to the best of our ability that we excluded anyone with prevalent disease at baseline) while still having a sufficient number of lung cancer cases within each BMI stratum. In addition, we examined whether the association between BMI and lung cancer incidence differed by histological subtype (ie, small cell carcinoma, adenocarcinoma, or squamous cell carcinoma), follow-up time (ie, excluding the first 4 years and first 7 years of follow-up), and stage at diagnosis. To test the proportional hazards assumption, we generated time-dependent covariates by including an interaction term for BMI and the natural log of age (the time metric); P values were greater than .05, consistent with the assumption of proportional hazards. Tests for linear trend across categories of BMI were estimated from the Wald test. Probability values less than .05 were considered statistically significant. All tests of statistical significance were two-tailed.

Results

The analytic sample consisted of 271 238 men, who contributed 2 610 585 person-years during an average follow-up of 9.6 years (average follow-up was 5.6 years among case subjects and 9.7 years among non–case subjects) and 177 494 women who contributed 1 745 327 person-years over an average follow-up of 9.8 years (average follow-up was 5.7 years among case subjects and 9.9 years among non–case subjects). The median age at baseline was 62.7 years (range = 50.3–71.5 years) for men and 62.2 years (range = 50.3–71.5 years) for women.

Among the men, the median BMI was 26.6 kg/m^2 (range = 16.9–42.6 kg/m^2). Nearly half of the men (49.7%) had a BMI that placed them in the overweight category, and another one-fifth were considered obese (16.6% had a BMI of 30–34.99 kg/m^2; 4.2% had a BMI ≥35 kg/m^2). Approximately 30% of the men (29.1%) had a BMI that corresponded to normal weight, and 0.4% of the men were categorized as underweight. Among the women, the median BMI was 25.8 kg/m^2 (range = 13.7–49.3 kg/m^2). Most of the women (43.1%) were considered to be of normal weight, nearly one-third (32.7%) were overweight but not obese. Slightly more than one-fifth of the women were obese (14.7% had a BMI of 30–34.99 kg/m^2; 8.1% had a BMI ≥35 kg/m^2), and very few (1.3%) were classified as underweight.

Obese individuals tended, on average, to be younger compared with those with a BMI of 22.5–24.99 kg/m^2 (Table 1). They were also more likely to be black, less likely to be a college graduate, less physically active, less likely to drink more than 5 g of alcohol per day, and less likely to currently smoke cigarettes but more likely to smoke cigars or pipes. In general, underweight individuals exhibited distributions of baseline characteristics similar to those of normal weight individuals, with a few notable exceptions: underweight individuals were more likely to have a history of emphysema and were less physically active compared with those with a BMI of 22.5–24.99 kg/m^2.

Seventy percent of men and 56% of women reported having ever smoked. Among both men and women, former smokers were the heaviest group (the mean BMI was 27.5 kg/m^2 among men and 27.1 kg/m^2 among women), followed by never smokers (the mean BMI was 26.7 kg/m^2 among men and 26.9 kg/m^2 among women); current smokers were the leanest (the mean BMI was 26.5 kg/m^2 among men and 25.5 kg/m^2 among women). In addition, among former smokers, those who smoked more than 20 cigarettes per day were, on average, slightly heavier than nonsmokers (the mean BMI for former smokers of >20 cigarettes per day was 28.0 kg/m^2 among men and 27.8 kg/m^2 among women).

As of December 31, 2006, a total of 6093 men and 3344 women had been diagnosed with lung carcinoma, including 166 and 249 diagnoses, respectively, among never smokers. The crude incidence rate of lung cancer over the study follow-up period was 233 per 100 000 person-years among men and 192 per 100 000 person-years among women. Among the men who had been diagnosed, 37.8% of the carcinomas were adenocarcinomas, 22.3% were squamous cell, 14.0% were small cell, 11.8% were non–small cell NOS, 8.6% were other types of carcinomas NOS, and 5.5% were large cell carcinomas. Among the women who had been diagnosed, 43.2% of carcinomas were adenocarcinomas, 16.5% were small cell, 14.4% were squamous cell, 11.9% were non–small cell NOS, 8.9% were other types NOS, and 5.1% were large cell carcinomas. Among the men, 11.9% of the lung carcinomas were local stage at diagnosis, 17.1% were regional stage, 30.0% were distant stage, and 42.0% were missing stage at diagnosis. Among the women, 14.1% of the lung carcinomas were local stage at diagnosis, 17.6% were regional stage, 26.4% were distant stage, and 41.9% were missing stage information.

As shown in Table 2, cigarette smoking was a critical adjustment factor when assessing the association between BMI and the risk of lung cancer, such that inverse associations became stronger after adjustment for smoking, whereas additional adjustment for other lung cancer risk factors had minimal effects on the hazard ratios. Among men, BMI was statistically significantly and inversely associated with the risk of lung cancer in the fully adjusted multivariable model (HR for BMI ≥35 vs 22.5–24.99 kg/m^2 = 0.81, 95% CI = 0.70 to 0.94). Among women, the inverse association was somewhat stronger (HR for BMI ≥35 vs 22.5–24.99 kg/m^2 = 0.73, 95% CI = 0.61 to 0.87).

We also examined the association between BMI and the risk of lung cancer among groups stratified by smoking status. Among current smokers, compared with individuals with a BMI of 22.5–24.99 kg/m^2, those with a BMI of 35 kg/m^2 or higher had a reduced risk of lung cancer in the fully adjusted model (men: HR = 0.76, 95% CI = 0.58 to 0.98; women: HR = 0.63, 95% CI = 0.48 to 0.84). Among former smokers, the inverse association between BMI and the risk of lung cancer was slightly attenuated (BMI ≥35 vs 22.5–24.99 kg/m^2, men: HR = 0.84, 95% CI = 0.70 to 1.01; women: HR = 0.78, 95% CI = 0.62 to 0.99). For both former and current smokers, the inverse trend between BMI and risk of lung cancer was observed regardless of whether the multivariable model was adjusted for smoking related covariates only or for all covariates. However, among never smokers, we observed no association between BMI and the risk of lung cancer in either age-adjusted or multivariable-adjusted models. For never smokers, the multivariable hazard ratios for men and women who had a BMI of 35 kg/m^2 or higher compared with those with a BMI of 22.5–24.99 kg/m^2 were 1.04 (95% CI = 0.41 to 2.67) and 1.00 (95% CI = 0.58 to 1.74), respectively, and the *P* values for trend were .44 and .85, respectively.

To test for any potential residual confounding effects of smoking, we examined the association between BMI and the risk of lung cancer in models stratified by smoking status, the amount of time since quitting smoking (for former smokers), and the number of cigarettes smoked per day (Table 3). Among smokers, higher BMI tended to be associated with reduced risk of lung cancer within all smoking strata, with the exception of men who quit smoking 20 cigarettes or fewer per day 10 or more years ago, and women who quit smoking more than 20 cigarettes per day 5–9 years ago.

The inverse association between BMI and the risk of lung cancer was apparent even after we excluded potentially unhealthy

Table 1. Distribution of select baseline characteristics across categories of body mass index (BMI) among 271 238 men and 177 494 women, NIH–AARP Diet and Health Study*

	Men						Women					
	BMI category (kg/m²)						BMI category (kg/m²)					
Characteristic	**<18.5**	**18.5–22.49**	**22.5–24.99**	**25–29.99**	**30–34.99**	**≥35**	**<18.5**	**18.5–22.49**	**22.5–24.99**	**25–29.99**	**30–34.99**	**≥35**
No. of subjects	1051	21 510	57 436	134 850	45 030	11 361	2392	36 214	40 212	58 128	26 129	14 419
Mean age at study entry, y	62.9	62.6	62.2	62.2	61.5	60.9	62.3	61.6	61.9	62.0	61.7	60.9
Race/ethnicity, %												
White	89.3	91.7	92.8	93.2	93.0	92.8	92.8	93.2	91.8	89.2	87.4	85.5
Black	2.5	2.3	1.9	2.6	3.5	3.7	2.9	2.0	3.5	6.1	8.3	10.3
Hispanic	2.1	1.5	1.7	2.0	1.9	1.7	1.0	1.5	1.9	2.1	2.0	1.8
Asian, Pacific Islander, American Indian, or Native Alaskan	4.1	3.7	2.6	1.4	0.7	0.7	2.0	2.4	1.8	1.3	0.9	0.7
College graduate, %	46.0	51.8	51.2	44.3	38.4	35.3	36.3	36.9	32.0	28.0	25.5	24.2
History of emphysema, %	11.0	5.5	2.9	2.3	2.6	3.6	6.7	2.6	2.1	2.1	2.2	2.5
Vigorous physical activity three or more times/wk in the last year, %	46.2	55.3	57.4	50.3	39.7	29.9	44.2	51.0	47.7	40.0	30.9	22.4
Alcohol intake in g/d, %												
None	26.5	22.9	19.5	19.7	22.1	26.3	30.9	23.6	24.1	29.0	35.7	42.7
≤5	30.6	31.6	32.1	33.8	37.1	40.9	38.3	43.6	46.8	48.7	49.6	47.8
5.01–10	8.5	9.9	11.1	11.0	10.2	8.6	7.2	9.1	8.8	7.2	5.3	3.6
10.01–20	12.7	14.5	15.6	14.0	11.3	8.4	12.3	13.6	11.6	8.3	4.9	2.9
20.01–35	7.9	8.0	9.0	8.5	7.2	5.6	5.9	6.1	4.9	3.7	2.4	1.3
>35	13.9	13.1	12.8	13.0	12.1	10.2	5.4	4.1	3.8	3.2	2.2	1.7
Smoking status and dose combined†, %												
Never smoker of tobacco	25.1	30.1	28.4	23.7	20.5	19.8	37.7	42.4	43.5	44.4	46.0	45.7
Former smoker, ≤20 cigarettes/d	26.5	27.4	30.6	31.0	27.5	25.3	22.7	26.6	27.1	28.5	27.8	27.6
Former smoker, >20 cigarettes/d	22.9	18.0	21.9	30.0	37.1	40.8	7.8	9.1	11.3	13.4	15.2	17.7
Current smoker, ≤20 cigarettes/d	13.8	11.6	8.3	5.7	4.9	3.8	23.0	16.4	13.4	9.8	7.7	6.1
Current smoker, >20 cigarettes/d	7.5	8.2	5.6	4.2	4.1	4.2	8.7	5.5	4.7	3.9	3.2	2.8
Ever smoker of pipes or cigars, %	22.3	25.1	26.6	29.2	31.6	33.0	0.3	0.4	0.4	0.4	0.4	0.6

* Missing values were included in the denominator for column percentage calculations. NIH = National Institutes of Health.

† Percentages for smoking status and dose may not sum to 100 because 14 844 men and 62 women who never smoked cigarettes but smoked pipes or cigars are not shown.

Table 2. Association between body mass index (BMI) and risk of lung cancer among 271 238 men and 177 494 women, NIH–AARP Diet and Health Study*

All participants	**Men (n = 271 238)**					**Women (n = 177 494)**				
BMI, kg/m²	**Person-years**	**No. of cancers**	**HR† (95% CI)**	**HR‡ (95% CI)**	**HR§ (95% CI)**	**Person-years**	**No. of cancers**	**HR† (95% CI)**	**HR‡ (95% CI)**	**HR§ (95% CI)**
<18.5	9530	38	1.66 (1.21 to 2.30)	1.25 (0.91 to 1.73)	1.15 (0.83 to 1.59)	22 646	81	1.82 (1.45 to 2.29)	1.28 (1.02 to 1.61)	1.23 (0.97 to 1.54)
18.5–22.49	203 617	650	1.34 (1.22 to 1.47)	1.17 (1.06 to 1.28)	1.12 (1.02 to 1.23)	355 901	852	1.25 (1.13 to 1.38)	1.15 (1.04 to 1.27)	1.15 (1.04 to 1.26)
22.5–24.99	554 888	1327	1.00 (referent)	1.00 (referent)	1.00 (referent)	397 914	775	1.00 (referent)	1.00 (referent)	1.00 (referent)
25–29.99	1 304 578	2905	0.96 (0.90 to 1.02)	0.92 (0.87 to 0.99)	0.92 (0.86 to 0.98)	573 067	1082	0.96 (0.88 to 1.06)	1.00 (0.91 to 1.10)	0.99 (0.90 to 1.08)
30–34.99	431 475	953	0.99 (0.92 to 1.08)	0.90 (0.82 to 0.98)	0.87 (0.80 to 0.95)	256 073	388	0.79 (0.70 to 0.89)	0.88 (0.78 to 0.99)	0.85 (0.75 to 0.96)
≥35	106 497	220	0.99 (0.86 to 1.14)	0.86 (0.75 to 1.00)	0.81 (0.70 to 0.94)	139 726	166	0.65 (0.55 to 0.77)	0.76 (0.65 to 0.90)	0.73 (0.61 to 0.87)
P_{trend}‖			<.001	<.001	<.001			<.001	<.001	<.001
Never smokers	**Men (n = 66 480)**					**Women (n = 78 190)**				
BMI, kg/m²	**Person-years**	**No. of cancers**	**HR† (95% CI)**	**HR¶ (95% CI)**		**Person-years**	**No. of cancers**	**HR† (95% CI)**	**HR¶ (95% CI)**	
<18.5	2593	0	NA	NA		9057	5	1.79 (0.72 to 4.48)	1.81 (0.72 to 4.52)	
18.5–22.49	64 038	16	1.03 (0.58 to 1.84)	1.04 (0.58 to 1.86)		154 566	54	1.17 (0.81 to 1.71)	1.17 (0.80 to 1.70)	
22.5–24.99	162 002	39	1.00 (referent)	1.00 (referent)		176 267	54	1.00 (referent)	1.00 (referent)	
25–29.99	317 786	77	1.02 (0.70 to 1.51)	1.01 (0.68 to 1.48)		259 005	78	0.98 (0.69 to 1.38)	1.00 (0.71 to 1.42)	
30–34.99	90 598	29	1.40 (0.87 to 2.27)	1.38 (0.85 to 2.24)		119 841	41	1.14 (0.76 to 1.71)	1.19 (0.79 to 1.80)	
≥35	21 690	5	1.06 (0.42 to 2.69)	1.04 (0.41 to 2.67)		65 230	17	0.93 (0.54 to 1.60)	1.00 (0.58 to 1.74)	
P_{trend}‖			.36	.44				.57	.85	
Former smokers	**Men (n = 155 896)**					**Women (n = 69 202)**				
BMI, kg/m²	**Person-years**	**No. of cancers**	**HR† (95% CI)**	**HR‡ (95% CI)**	**HR§ (95% CI)**	**Person-years**	**No. of cancers**	**HR† (95% CI)**	**HR‡ (95% CI)**	**HR§ (95% CI)**
<18.5	4482	14	1.45 (0.86 to 2.47)	1.30 (0.77 to 2.21)	1.22 (0.72 to 2.07)	6215	10	0.83 (0.44 to 1.57)	0.90 (0.48 to 1.68)	0.85 (0.45 to 1.60)
18.5–22.49	92 113	245	1.20 (1.04 to 1.39)	1.21 (1.05 to 1.40)	1.16 (1.00 to 1.35)	126 860	261	1.14 (0.96 to 1.34)	1.21 (1.02 to 1.43)	1.21 (1.02 to 1.43)
22.5–24.99	291 322	641	1.00 (referent)	1.00 (referent)	1.00 (referent)	152 507	281	1.00 (referent)	1.00 (referent)	1.00 (referent)
25–29.99	771 767	1750	1.08 (0.98 to 1.18)	0.96 (0.88 to 1.05)	0.96 (0.87 to 1.05)	227 426	463	1.09 (0.94 to 1.26)	1.01 (0.87 to 1.17)	1.00 (0.86 to 1.17)
30–34.99	270 973	626	1.17 (1.04 to 1.30)	0.93 (0.83 to 1.04)	0.90 (0.81 to 1.01)	104 988	184	0.96 (0.80 to 1.16)	0.86 (0.71 to 1.03)	0.83 (0.68 to 1.00)
≥35	67 965	147	1.17 (0.98 to 1.41)	0.89 (0.74 to 1.07)	0.84 (0.70 to 1.01)	60 369	95	0.94 (0.74 to 1.19)	0.82 (0.65 to 1.04)	0.78 (0.62 to 0.99)
P_{trend}‖			.16	.0012	<.001			.12	<.001	<.001
Current smokers	**Men (n = 34 018)**					**Women (n = 30 040)**				
BMI, kg/m²	**Person-years**	**No. of cancers**	**HR† (95% CI)**	**HR‡ (95% CI)**	**HR§ (95% CI)**	**Person-years**	**No. of cancers**	**HR† (95% CI)**	**HR‡ (95% CI)**	**HR§ (95% CI)**
<18.5	2042	22	1.18 (0.77 to 1.80)	1.17 (0.76 to 1.79)	1.07 (0.70 to 1.64)	7374	66	1.36 (1.05 to 1.76)	1.34 (1.03 to 1.73)	1.27 (0.98 to 1.65)
18.5–22.49	37 444	386	1.16 (1.02 to 1.32)	1.14 (1.00 to 1.29)	1.10 (0.97 to 1.25)	74 391	537	1.12 (0.99 to 1.28)	1.12 (0.99 to 1.27)	1.11 (0.98 to 1.26)
22.5–24.99	71 960	633	1.00 (referent)	1.00 (referent)	1.00 (referent)	68 997	440	1.00 (referent)	1.00 (referent)	1.00 (referent)
25–29.99	142 547	1045	0.88 (0.79 to 0.97)	0.87 (0.79 to 0.96)	0.87 (0.79 to 0.96)	86 420	540	1.00 (0.88 to 1.14)	0.99 (0.87 to 1.12)	0.98 (0.86 to 1.11)
30–34.99	43 822	290	0.85 (0.74 to 0.97)	0.83 (0.72 to 0.95)	0.81 (0.71 to 0.93)	31 170	163	0.87 (0.73 to 1.04)	0.85 (0.71 to 1.02)	0.83 (0.69 to 0.99)
≥35	10 165	64	0.86 (0.67 to 1.11)	0.81 (0.63 to 1.05)	0.76 (0.58 to 0.98)	14 054	54	0.68 (0.51 to 0.90)	0.66 (0.50 to 0.87)	0.63 (0.48 to 0.84)
P_{trend}‖			<.001	<.001	<.001			<.001	<.001	<.001

* CI = confidence interval; HR = hazard ratio; NIH = National Institutes of Health; NA = not applicable.

† HRs and 95% CIs adjusted for age at study entry.

‡ HRs and 95% CIs adjusted for age at study entry, detailed smoking status and dose, and cigar or pipe smoking.

§ HRs and 95% CIs adjusted for age at study entry, detailed smoking status and dose, cigar/pipe smoking, race/ethnicity, education level, history of emphysema, physical activity, and alcohol intake.

‖ *P* values for trend (two-sided) from the Wald test exclude participants with BMI < 18.5 kg/m².

¶ HRs and 95% CIs adjusted for age at study entry, race/ethnicity, education level, physical activity, and alcohol intake.

Table 3. Association between body mass index (BMI) and risk of lung cancer by smoking status, time since quitting smoking, and number of cigarettes smoked per day, NIH–AARP Diet and Health Study*

	Men						Women					
	BMI (kg/m²), continuous†, n = 271 238		BMI (kg/m²) category				BMI (kg/m²), continuous†, n = 177 494		BMI (kg/m²) category			
			18.5–24.99, n = 78 946	25–29.99, n = 134 850	≥30, n = 56 391				18.5–24.99, n = 76 426	25–29.99, n = 58 128	≥30, n = 40 548	
Smoking status	No. of cancers	HR (95% CI)	HR	HR (95% CI)	HR (95% CI)	P_{trend}	No. of cancers	HR (95% CI)	HR	HR (95% CI)	HR (95% CI)	P_{trend}
Never smoker‡	166	1.08 (0.88 to 1.33)	1.00 (referent)	1.01 (0.71 to 1.43)	1.32 (0.85 to 2.04)	.31	249	0.97 (0.86 to 1.10)	1.00 (referent)	0.91 (0.68 to 1.22)	1.03 (0.75 to 1.43)	.85
Former smoker	3423	0.91 (0.87 to 0.96)	1.00 (referent)	0.92 (0.85 to 0.99)	0.86 (0.78 to 0.94)	.002	1294	0.91 (0.86 to 0.96)	1.00 (referent)	0.93 (0.82 to 1.05)	0.75 (0.65 to 0.87)	<.001
Quit ≥10 y ago	2021	0.96 (0.90 to 1.01)	1.00 (referent)	0.93 (0.84 to 1.04)	0.96 (0.84 to 1.09)	.47	597	0.90 (0.83 to 0.98)	1.00 (referent)	0.89 (0.74 to 1.07)	0.72 (0.58 to 0.91)	.005
≤20 cigarettes/d	638	0.95 (0.85 to 1.06)	1.00 (referent)	1.03 (0.86 to 1.23)	1.06 (0.84 to 1.34)	.61	286	0.81 (0.71 to 0.92)	1.00 (referent)	0.85 (0.66 to 1.10)	0.51 (0.35 to 0.73)	<.001
>20 cigarettes/d	1383	0.96 (0.89 to 1.03)	1.00 (referent)	0.88 (0.77 to 1.01)	0.91 (0.78 to 1.06)	.20	311	0.97 (0.87 to 1.08)	1.00 (referent)	0.95 (0.73 to 1.24)	0.94 (0.70 to 1.26)	.67
Quit 5–9 y ago	803	0.85 (0.78 to 0.93)	1.00 (referent)	0.91 (0.77 to 1.08)	0.66 (0.53 to 0.81)	<.001	390	0.97 (0.88 to 1.07)	1.00 (referent)	1.01 (0.80 to 1.28)	0.97 (0.74 to 1.26)	.90
≤20 cigarettes/d	198	0.74 (0.60 to 0.90)	1.00 (referent)	0.87 (0.63 to 1.19)	0.51 (0.32 to 0.80)	.01	157	0.84 (0.71 to 1.00)	1.00 (referent)	0.85 (0.60 to 1.21)	0.66 (0.42 to 1.03)	.08
>20 cigarettes/d	605	0.88 (0.80 to 0.98)	1.00 (referent)	0.93 (0.76 to 1.13)	0.70 (0.55 to 0.89)	.002	233	1.04 (0.92 to 1.17)	1.00 (referent)	1.16 (0.84 to 1.58)	1.23 (0.88 to 1.72)	.20
Quit 1–4 y ago	599	0.86 (0.77 to 0.96)	1.00 (referent)	0.85 (0.70 to 1.03)	0.83 (0.66 to 1.05)	.14	307	0.86 (0.76 to 0.97)	1.00 (referent)	0.90 (0.70 to 1.16)	0.58 (0.42 to 0.81)	.001
≤20 cigarettes/d	176	0.89 (0.72 to 1.11)	1.00 (referent)	0.95 (0.67 to 1.33)	0.99 (0.64 to 1.54)	.88	150	0.82 (0.69 to 0.98)	1.00 (referent)	0.83 (0.58 to 1.18)	0.46 (0.28 to 0.76)	.002
>20 cigarettes/d	423	0.85 (0.75 to 0.96)	1.00 (referent)	0.81 (0.64 to 1.03)	0.78 (0.59 to 1.02)	.10	157	0.89 (0.76 to 1.04)	1.00 (referent)	0.99 (0.69 to 1.42)	0.71 (0.46 to 1.10)	.11
Current smoker	2440	0.89 (0.84 to 0.94)	1.00 (referent)	0.84 (0.77 to 0.92)	0.77 (0.68 to 0.87)	<.001	1800	0.87 (0.83 to 0.92)	1.00 (referent)	0.91 (0.82 to 1.02)	0.72 (0.62 to 0.84)	<.001
≤20 cigarettes/d	1171	0.87 (0.80 to 0.94)	1.00 (referent)	0.88 (0.78 to 0.99)	0.73 (0.60 to 0.88)	<.001	1132	0.84 (0.78 to 0.90)	1.00 (referent)	0.88 (0.77 to 1.00)	0.67 (0.55 to 0.82)	<.001
>20 cigarettes/d	1269	0.91 (0.85 to 0.98)	1.00 (referent)	0.81 (0.72 to 0.92)	0.81 (0.69 to 0.95)	.002	668	0.92 (0.85 to 1.00)	1.00 (referent)	0.97 (0.82 to 1.16)	0.79 (0.63 to 1.00)	.08

* HRs and 95% CIs adjusted for age at study entry, detailed smoking status and dose, cigar or pipe smoking, race/ethnicity, education level, history of emphysema, physical activity, and alcohol intake. CI = confidence interval; HR = hazard ratio; NIH = National Institutes of Health.

† Risk estimates are per five units of BMI.

‡ Models for never smokers did not adjust for emphysema or smoking information.

participants from the analysis (Table 4). Among healthy men who were not diagnosed with lung cancer during the first 7 years of follow-up, compared with those who had a BMI of 22.5–24.99 kg/m^2, those with a BMI of 30–34.99 kg/m^2 had a 9% reduced risk of developing lung cancer (HR = 0.91, 95% CI = 0.78 to 1.07); among all men, there was a 13% reduced risk (HR = 0.87, 95% CI = 0.80 to 0.95). Among healthy women who were not diagnosed with lung cancer during the first 7 years of follow-up, compared with those who had a BMI of 22.5–24.99 kg/m^2, those with a BMI of 30–34.99 kg/m^2 had a 16% reduced risk of developing lung cancer (HR = 0.84, 95% CI = 0.67 to 1.05); among all women, there was a 15% reduced risk (HR = 0.85, 95% CI = 0.75 to 0.96). Null findings among never smokers and inverse trends among former and current smokers after these exclusions were similar to those observed among all participants.

When we stratified the analysis by histological subtype, the reduction in risk was restricted to adenocarcinomas in men (HR for BMI ≥35 vs 22.5–24.99 kg/m^2 = 0.73, 95% CI = 0.58 to 0.93; P_{trend} < .001) and women (HR for BMI ≥35 vs 22.5–24.99 kg/m^2 = 0.66, 95% CI = 0.50 to 0.86; P_{trend} < .001) and squamous cell carcinomas in women (HR for BMI ≥35 vs 22.5–24.99 kg/m^2 = 0.68, 95% CI = 0.43 to 1.06; P_{trend} = .005) (Table 5). Results for adenocarcinomas stratified by smoking status resembled those for all carcinomas: there was no association between BMI and the risk of lung cancer in never smokers, but an inverse association among former and current smokers (Supplementary Table 1, available online).

A higher BMI was associated with a reduced risk of lung cancer throughout all periods of follow-up (Supplementary Table 2, available online) and for all stages of disease (Supplementary Table 3, available online). Hazard ratios did not differ substantially in analyses stratified by follow-up time, or according to whether the tumors were at local, regional, or distant stage at diagnosis (Supplementary Tables 2 and 3, available online).

Discussion

In the largest prospective investigation to comprehensively examine the association between BMI and the risk of lung cancer, we found strong inverse associations among both men and women. Because of the large numbers of lung cancers and never smokers, we were able to stratify the analysis by smoking status and found that the inverse association was restricted to former and current smokers, with no association seen among never smokers. Given that smokers were, on average, leaner than nonsmokers, we initially hypothesized that the inverse association observed in this study was due to residual confounding by smoking. However, our analyses that attempted to assess the role of confounding by smoking showed that heavier people were at reduced risk of lung cancer, even in models that were finely stratified by smoking status, time since quitting smoking, and number of cigarettes smoked per day. This finding suggests the need to consider alternative explanations for the inverse association between BMI and risk of lung cancer.

Our findings of an overall inverse trend for BMI and lung cancer risk are consistent with results from eight (4,7,9,10,12–14,17) of 10 (4,7–10,12–14,17,19) previous cohort studies (summarized in Supplementary Tables 4 and 5, available online). Similarly, three previous cohorts of women (7,8,13) and two of men (9,10) have observed an inverse association between BMI and risk of lung cancer in smokers. In previous studies, it has been difficult to assess differences by sex because only three cohorts have included both men and women (4,17,19). Our results show slightly stronger inverse associations between BMI and risk of lung cancer for women compared with men, particularly among current smokers (HRs for BMI ≥35 vs 22.5–24.99 kg/m^2, 0.63 vs 0.76, respectively). By contrast, in the Agricultural Health Study (4), which included both men and women, BMI was statistically significantly inversely associated with the risk of lung cancer only among male smokers. In a study from Singapore (17), BMI was inversely associated with the risk of lung cancer only among current smokers, and the analyses were not stratified by sex. In the third study that included men and women (19), a positive association between BMI and the risk of lung cancer was apparent among male smokers; in this Korean cohort, only 6% of women had ever smoked (compared with 56% in our study population), and the association between BMI and the risk of lung cancer among female smokers was not reported. Other potential reasons for the varying results for BMI associations by smoking and sex across studies include the small numbers of cases, incomplete adjustment for smoking, inaccurate reporting of BMI and covariates, and population differences, including variations in the predisposition to develop different histological types of lung cancer or in the prevalence of obesity. For example, in the two Asian studies (17,19), less than 3% of participants would have been considered obese as defined in this study.

In this study, the inverse association between BMI and the risk of lung cancer was restricted to smokers; we observed no association among never smokers (in whom 415 cases of lung carcinoma developed). Similar results have been seen in five previous cohort studies that included from 51 to 287 never smokers who developed lung cancer (4,7,12,14,17). By contrast, two studies (10,13) reported an inverse association between BMI and the risk of lung cancer among never smokers. Among never smokers in the Iowa Women's Health Study (13), in whom 76 cases of lung cancer developed, those in the upper quintile of BMI had a 56% lower risk of developing lung cancer compared with those in the lowest quintile (relative risk = 0.44, 95% CI = 0.21 to 0.95). In a cohort of Finnish men in which 10 lung cancers developed among the never smokers, the inverse association was most obvious among never smokers, although the very small numbers of cancers make such stratifications difficult to interpret (10).

The vast majority of lung cancers occur among smokers, and the inverse associations we observed between BMI and the risk of lung cancer among both current and former smokers were relatively strong. In fact, in multivariable analyses, we observed that the risk estimates for the inverse association were stronger after adjustment for smoking. Furthermore, the inverse associations persisted across all but two strata defined by smoking status, time since smoking cessation and number of cigarettes smoked per day. Although we were unable to adjust for age at initiation of smoking because this information was not collected on the baseline questionnaire, it seems unlikely that this variable would explain the inverse association between BMI and risk of lung cancer among smokers, given the consistent results across all other smoking

Table 4. Association between body mass index (BMI) and risk of lung cancer among progressively restricted populations of men and women, NIH–AARP Diet and Health Study*

	All men		Healthy men		Healthy men, excluding those diagnosed during the first 7 y of follow-up		Healthy men, by smoking status and excluding those diagnosed during the first 7 y of follow-up: Never smoker		Former smoker		Current smoker	
	n = 271 238		n = 236 091†		n = 233 267‡		n = 61 448‡		n = 132 650‡		n = 25 659‡	
BMI, kg/m²	No. of cancers	HR§ (95% CI)	No. of cases	HR‖ (95% CI)	No. of cancers	HR‖ (95% CI)	No. of cancers	HR¶ (95% CI)	No. of cancers	HR# (95% CI)	No. of cancers	HR** (95% CI)
<18.5	38	1.15 (0.83 to 1.59)	23	1.21 (0.80 to 1.83)	8	1.14 (0.57 to 2.30)	0	NA	3	1.06 (0.34 to 3.31)	3	0.78 (0.25 to 2.46)
18.5–22.49	650	1.12 (1.02 to 1.23)	461	1.14 (1.02 to 1.28)	170	1.10 (0.92 to 1.31)	4	0.69 (0.23 to 2.09)	64	1.06 (0.80 to 1.40)	100	1.16 (0.90 to 1.48)
22.5–24.99	1327	1.00 (referent)	1030	1.00 (referent)	405	1.00 (referent)	15	1.00 (referent)	209	1.00 (referent)	176	1.00 (referent)
25–29.99	2905	0.92 (0.86 to 0.98)	2314	0.94 (0.88 to 1.02)	903	0.93 (0.83 to 1.05)	34	1.15 (0.63 to 2.12)	559	0.94 (0.80 to 1.10)	292	0.87 (0.72 to 1.05)
30–34.99	953	0.87 (0.80 to 0.95)	692	0.88 (0.80 to 0.98)	280	0.91 (0.78 to 1.07)	9	1.18 (0.51 to 2.72)	193	0.95 (0.78 to 1.16)	76	0.84 (0.64 to 1.10)
≥35	220	0.81 (0.70 to 0.94)	136	0.84 (0.70 to 1.01)	66	1.06 (0.82 to 1.38)	1	0.62 (0.08 to 4.78)	47	1.11 (0.80 to 1.53)	18	1.10 (0.67 to 1.79)
P_{trend}††		<.001		<.001		.13		.52		.75		.03

	All women		Healthy women		Healthy women, excluding those diagnosed during the first 7 y of follow-up		Healthy women, by smoking status and excluding those diagnosed during the first 7 y of follow-up: Never smoker		Former smoker		Current smoker	
	n = 177 494		n = 153 752†		n = 152 177‡		n = 69 767‡		n = 58 713‡		n = 23 644‡	
BMI, kg/m²	No. of cancers	HR§ (95% CI)	No. of cancers	HR‖ (95% CI)	No. of cancers	HR‖ (95% CI)	No. of cancers	HR¶ (95% CI)	No. of cancers	HR# (95% CI)	No. of cancers	HR** (95% CI)
<18.5	81	1.23 (0.97 to 1.54)	57	1.22 (0.93 to 1.60)	22	1.18 (0.76 to 1.83)	3	2.40 (0.72 to 7.97)	3	0.95 (0.30 to 2.99)	16	1.15 (0.69 to 1.94)
18.5–22.49	852	1.15 (1.04 to 1.26)	686	1.13 (1.02 to 1.26)	276	1.12 (0.95 to 1.33)	24	1.11 (0.63 to 1.94)	70	0.98 (0.72 to 1.34)	182	1.21 (0.97 to 1.51)
22.5–24.99	775	1.00 (referent)	636	1.00 (referent)	260	1.00 (referent)	25	1.00 (referent)	94	1.00 (referent)	141	1.00 (referent)
25–29.99	1082	0.99 (0.90 to 1.08)	838	0.98 (0.88 to 1.09)	308	0.89 (0.75 to 1.05)	23	0.66 (0.37 to 1.16)	130	0.88 (0.68 to 1.15)	154	0.93 (0.74 to 1.17)
30–34.99	388	0.85 (0.75 to 0.96)	270	0.85 (0.73 to 0.98)	107	0.84 (0.67 to 1.05)	14	0.97 (0.50 to 1.88)	44	0.71 (0.49 to 1.02)	49	0.93 (0.67 to 1.29)
≥35	166	0.73 (0.61 to 0.87)	88	0.65 (0.52 to 0.82)	27	0.50 (0.34 to 0.75)	4	0.63 (0.22 to 1.82)	15	0.53 (0.31 to 0.93)	8	0.41 (0.20 to 0.84)
P_{trend}††		<.001		<.001		<.001		.21		.012		<.001

* CI = confidence interval; HR = hazard ratio; NIH = National Institutes of Health; NA = not applicable.

† Excludes participants with a history of emphysema and self-reported poor or fair health.

‡ Numbers across categories of smoking status do not sum to the total number for healthy participants excluding cases diagnosed within 7 years of baseline because those who never smoked cigarettes but smoked pipes or cigars are not shown.

§ HRs and 95% CIs adjusted for age at study entry, detailed smoking status and dose, cigar or pipe smoking, race/ethnicity, education level, history of emphysema, physical activity, and alcohol intake.

‖ HRs and 95% CIs adjusted for age at study entry, detailed smoking status and dose, cigar or pipe smoking, race/ethnicity, education level, physical activity, and alcohol intake.

¶ HRs and 95% CIs adjusted for age at study entry, race/ethnicity, education level, physical activity, and alcohol intake.

HRs and 95% CIs adjusted for age at study entry, smoking cessation and dose, cigar or pipe smoking, race/ethnicity, education level, physical activity, and alcohol intake.

** HRs and 95% CIs adjusted for age at study entry, smoking dose, cigar or pipe smoking, race/ethnicity, education level, physical activity, and alcohol intake.

†† P values for trend (two-sided) from the Wald test exclude participants with BMI < 18.5 kg/m².

Table 5. Association between body mass index (BMI) and risk of lung cancer by histological subtype, NIH–AARP Diet and Health Study*

	Men					
	Small cell carcinoma		Adenocarcinoma		Squamous cell carcinoma	
BMI, kg/m²	No. of cancers	HR (95% CI)	No. of cancers	HR (95% CI)	No. of cancers	HR (95% CI)
<18.5	7	1.38 (0.65 to 2.94)	12	1.06 (0.60 to 1.89)	7	0.89 (0.42 to 1.88)
18.5–22.49	79	0.88 (0.68 to 1.15)	242	1.19 (1.02 to 1.39)	143	1.08 (0.88 to 1.32)
22.5–24.99	191	1.00 (referent)	495	1.00 (referent)	285	1.00 (referent)
25–29.99	406	0.94 (0.79 to 1.11)	1132	0.92 (0.83 to 1.03)	634	0.95 (0.83 to 1.09)
30–34.99	136	0.93 (0.74 to 1.16)	341	0.79 (0.68 to 0.91)	234	1.01 (0.85 to 1.21)
≥35	35	0.98 (0.68 to 1.41)	79	0.73 (0.58 to 0.93)	56	0.97 (0.73 to 1.30)
P_{trend}†		.98		<.001		.49
	Women					
	Small cell carcinoma		Adenocarcinoma		Squamous cell carcinoma	
BMI, kg/m²	No. of cancers	HR (95% CI)	No. of cancers	HR (95% CI)	No. of cancers	HR (95% CI)
<18.5	7	0.61 (0.28 to 1.30)	40	1.57 (1.13 to 2.19)	10	0.99 (0.52 to 1.89)
18.5–22.49	122	1.04 (0.80 to 1.34)	375	1.22 (1.05 to 1.41)	124	1.13 (0.88 to 1.46)
22.5–24.99	117	1.00 (referent)	327	1.00 (referent)	114	1.00 (referent)
25–29.99	196	1.22 (0.97 to 1.54)	471	1.02 (0.88 to 1.17)	155	0.94 (0.73 to 1.19)
30–34.99	78	1.22 (0.91 to 1.64)	166	0.85 (0.70 to 1.03)	55	0.77 (0.56 to 1.07)
≥35	32	1.05 (0.71 to 1.57)	65	0.66 (0.50 to 0.86)	24	0.68 (0.43 to 1.06)
P_{trend}†		.21		<.001		.005

* HRs and 95% CIs adjusted for age at study entry, detailed smoking status and dose, cigar or pipe smoking, race/ethnicity, education level, history of emphysema, physical activity, and alcohol intake. CI = confidence interval; HR = hazard ratio; NIH = National Institutes of Health.

† *P* values for trend (two-sided) from the Wald test exclude participants with BMI < 18.5 kg/m².

strata. We were thus prompted to consider explanations other than confounding for the inverse association between BMI and the risk of lung cancer among smokers. We thought that an examination of risks related to histology might bring some clarity to the inverse association between BMI and risk of lung cancer because some histological types are thought to be more strongly influenced by smoking; however, we continued to observe an inverse association between BMI and the risk of adenocarcinoma, the largest subgroup in this analysis and the histological type thought to be least influenced by smoking (27). Inverse associations for adenocarcinomas were also observed in two previous studies (12,13). We also observed a statistically significant inverse trend for BMI and the risk of squamous cell carcinoma among women, as did the Iowa Women's Health Study (13).

Another explanation for the observed inverse association between BMI and the risk of lung cancer is that undiagnosed lung carcinoma at study entry may have caused subjects to lose weight. Although we did not collect information on recent weight changes, we did attempt to assess this potential bias in several ways. We sequentially restricted the population to include only the healthiest participants at baseline by excluding men and women with emphysema, those who reported poor or fair health at baseline, and those with less than 7 years of follow-up. These exclusions did not substantially change our findings among smokers, consistent with results of another study that used similar approaches (6). We also assessed the association between BMI and the risk of lung cancer with respect to disease stages at diagnosis and failed to observe distinctive relationships.

Our analyses were limited by the single baseline measures of BMI and smoking; it is possible that changes in weight and smoking status over the course of the follow-up period may have influenced our findings. We therefore stratified our results by follow-up time to examine whether the inverse trend would be present after the first few years of follow-up. Results in men were not materially changed, whereas the inverse association among women was somewhat strengthened, signifying that the apparent relationship was not due to effects of weight loss related to undiagnosed disease or other potential changes in exposure status, a finding consistent with a number of other studies (7–10,13,14,17,19).

Thus, although we considered extensive alternative explanations for the inverse association between BMI and risk of lung cancer among smokers, we could not definitively determine an explanation, including the idea that the association reflected residual confounding by cigarette smoking. Given previous studies that have shown differences in lung cancer risk factors between never and ever smokers (28), it is possible that there could be a beneficial interaction with BMI among smokers. Studies that have shown increased risks of lung cancer associated with either an early age at natural menopause or bilateral oophorectomy (29–33) and reduced risks of lung cancer associated with use of menopausal hormones (34–36) have led to speculations that estrogens may exert beneficial effects. Given that obesity is well recognized as being strongly correlated with increases in endogenous levels of estrogens (37,38), it is not entirely inconceivable that estrogens could be involved in the inverse association between BMI and the risk of lung cancer among smokers. This biological mechanism would also be consistent with our finding that BMI appears to be more strongly associated with reductions in lung cancer risk among women compared with men. It has also been hypothesized that estrogens may have a higher affinity than carcinogenic aromatic hydrocarbons in cigarette smoke to bind to estrogen receptors (35), which have been shown to be abundant in normal and cancerous lung tissue (39). Furthermore, several studies have observed inverse associations between BMI and circulating levels of DNA adducts (40–42), a mechanism by which smoking is believed to initiate lung cancer (43).

Limitations of this study include the lack of follow-up data on smoking habits and health conditions. Smoking information at baseline did not include depth of inhalation, cigarette content, or age at initiation of smoking, which prevented us from calculating smoking duration and number of pack-years of smoking. Future cohort studies would be strengthened by updating smoking status and BMI exposure data over time. In addition, BMI reflects lean muscle and fat mass, and our study could not distinguish between the two. BMI was also calculated using self-reported height and weight. Previous studies have noted that although self-reported weight tends to be underestimated and self-reported height tends to be overestimated, the measures are highly correlated to the true value (44,45). Baseline BMI among our cohort participants was comparable to national averages (21); however, cohort participants were predominantly non-Hispanic white, more educated, and less likely to currently smoke compared with the general US population (21), potentially limiting the generalizability of these findings to other subpopulations. Finally, the limited sample size of never smokers may have produced unstable estimates in sensitivity analyses that excluded or restricted large numbers of individuals.

This study had a number of strengths, most notably its size, with nearly half a million participants and 10000 cases of lung cancer. In addition, to our knowledge, this study included more lung cancers, in both men and women, than any other study that assessed the association between BMI and lung cancer incidence in a Western population, allowing us to comprehensively examine possible confounding and other biases. In this study, we were also able to examine whether associations differed by histological subtype.

In summary, we found an inverse association between BMI and the risk of lung cancer, which was restricted to smokers. Although we attempted to explain this association on the basis of residual confounding by cigarette smoking, we were unable to expressly demonstrate such confounding. We were also unable to identify any sources of bias that could explain the association. Although it is still possible that the association between BMI and the risk of lung cancer is an artifact, the possibility of a distinct relationship between BMI and lung cancer among smokers should be considered. Future efforts to determine correlates of obesity that are associated with the risk of lung cancer could therefore be informative.

References

1. Calle EE, Kaaks R. Overweight, obesity and cancer: epidemiological evidence and proposed mechanisms. *Nat Rev Cancer.* 2004;4(8):579–591.
2. Renehan AG, Soerjomataram I, Leitzmann MF. Interpreting the epidemiological evidence linking obesity and cancer: a framework for population-attributable risk estimations in Europe. *Eur J Cancer.* 2010;46(14): 2581–2592.
3. Renehan AG, Tyson M, Egger M, et al. Body-mass index and incidence of cancer: a systematic review and meta-analysis of prospective observational studies. *Lancet.* 2008;371(9612):569–578.
4. Andreotti G, Hou L, Beane Freeman LE, et al. Body mass index, agricultural pesticide use, and cancer incidence in the Agricultural Health Study cohort. *Cancer Causes Control.* 2010;21(11):1759–1775.
5. Calle EE, Rodriguez C, Walker-Thurmond K, et al. Overweight, obesity, and mortality from cancer in a prospectively studied cohort of U.S. adults. *N Engl J Med.* 2003;348(17):1625–1638.
6. Henley SJ, Flanders WD, Manatunga A, et al. Leanness and lung cancer risk: fact or artifact? *Epidemiology.* 2002;13(3):268–276.
7. Kabat GC, Kim M, Hunt JR, et al. Body mass index and waist circumference in relation to lung cancer risk in the Women's Health Initiative. *Am J Epidemiol.* 2008;168(2):158–169.
8. Kabat GC, Miller AB, Rohan TE. Body mass index and lung cancer risk in women. *Epidemiology.* 2007;18(5):607–612.
9. Kark JD, Yaari S, Rasooly I, et al. Are lean smokers at increased risk of lung cancer? The Israel Civil Servant Cancer Study. *Arch Intern Med.* 1995;155(22):2409–2416.
10. Knekt P, Heliovaara M, Rissanen A, et al. Leanness and lung-cancer risk. *Int J Cancer.* 1991;49(2):208–213.
11. Leung CC, Lam TH, Yew WW, et al. Lower lung cancer mortality in obesity. *Int J Epidemiol.* 2011;40(1):174–182.
12. Oh SW, Yoon YS, Shin SA. Effects of excess weight on cancer incidences depending on cancer sites and histologic findings among men: Korea National Health Insurance Corporation Study. *J Clin Oncol.* 2005;23(21): 4742–4754.
13. Olson JE, Yang P, Schmitz K, et al. Differential association of body mass index and fat distribution with three major histologic types of lung cancer: evidence from a cohort of older women. *Am J Epidemiol.* 2002;156(7): 606–615.
14. Samanic C, Chow WH, Gridley G, et al. Relation of body mass index to cancer risk in 362,552 Swedish men. *Cancer Causes Control.* 2006;17(7): 901–909.
15. Tsai SP, Donnelly RP, Wendt JK. Obesity and mortality in a prospective study of a middle-aged industrial population. *J Occup Environ Med.* 2006; 48(1):22–27.
16. Yang L, Yang G, Zhou M, et al. Body mass index and mortality from lung cancer in smokers and nonsmokers: a nationally representative prospective study of 220,000 men in China. *Int J Cancer.* 2009; 125(9):2136–2143.
17. Koh WP, Yuan JM, Wang R, et al. Body mass index and smoking-related lung cancer risk in the Singapore Chinese Health Study. *Br J Cancer.* 2010;102(3):610–614.
18. Eichholzer M, Bernasconi F, Jordan P, et al. Body mass index and the risk of male cancer mortality of various sites: 17-year follow-up of the Basel cohort study. *Swiss Med Wkly.* 2005;135(1–2):27–33.
19. Jee SH, Yun JE, Park EJ, et al. Body mass index and cancer risk in Korean men and women. *Int J Cancer.* 2008;123(8):1892–1896.
20. Egleston BL, Meireles SI, Flieder DB, et al. Population-based trends in lung cancer incidence in women. *Semin Oncol.* 2009;36(6):506–515.
21. Schatzkin A, Subar AF, Thompson FE, et al. Design and serendipity in establishing a large cohort with wide dietary intake distributions: the National Institutes of Health-American Association of Retired Persons Diet and Health Study. *Am J Epidemiol.* 2001;154(12):1119–1125.
22. Michaud DS, Midthune D, Hermansen S, et al. Comparison of cancer registry case ascertainment with SEER estimates and self-reporting in a subset of the NIH-AARP Diet and Health Study. *J Regist Manag.* 2005;32(2):70–75.
23. SEER. ICD-O-3 Coding Materials. http://seer.cancer.gov/icd-o-3/. Accessed March 13, 2012.
24. Obesity: preventing and managing the global epidemic. Report of a WHO consultation. *World Health Organ Tech Rep Ser.* 2000;894:i–xii; 1–253.
25. Gail MH. Evaluating serial cancer marker studies in patients at risk of recurrent disease. *Biometrics.* 1981;37(1):67–78.
26. American College of Sports Medicine position stand. The recommended quantity and quality of exercise for developing and maintaining cardiorespiratory and muscular fitness in healthy adults. *Med Sci Sports Exerc* 1990;22:265–74.
27. Freedman ND, Leitzmann MF, Hollenbeck AR, et al. Cigarette smoking and subsequent risk of lung cancer in men and women: analysis of a prospective cohort study. *Lancet Oncol.* 2008;9(7):649–656.
28. Samet JM, Avila-Tang E, Boffetta P, et al. Lung cancer in never smokers: clinical epidemiology and environmental risk factors. *Clin Cancer Res.* 2009;15(18):5626–5645.
29. Baik CS, Strauss GM, Speizer FE, et al. Reproductive factors, hormone use, and risk for lung cancer in postmenopausal women, the Nurses'

Health Study. *Cancer Epidemiol Biomarkers Prev.* 2010;19(10): 2525–2533.
30. Brinton LA, Gierach GL, Andaya A, et al. Reproductive and hormonal factors and lung cancer risk in the NIH-AARP Diet and Health Study cohort. *Cancer Epidemiol Biomarkers Prev.* 2011;20(5): 900–911.
31. Koushik A, Parent ME, Siemiatycki J. Characteristics of menstruation and pregnancy and the risk of lung cancer in women. *Int J Cancer.* 2009;125(10): 2428–2433.
32. Parker WH, Broder MS, Chang E, et al. Ovarian conservation at the time of hysterectomy and long-term health outcomes in the nurses' health study. *Obstet Gynecol.* 2009;113(5):1027–1037.
33. Weiss JM, Lacey JV Jr, Shu X-O, et al. Menstrual and reproductive factors in association with lung cancer in female lifetime nonsmokers. *Am. J. Epidemiol.* 2008;168(11):1319–1325.
34. Ramnath N, Menezes RJ, Loewen G, et al. Hormone replacement therapy as a risk factor for non-small cell lung cancer: results of a case-control study. *Oncology.* 2007;73(5–6):305–310.
35. Schabath MB, Wu X, Vassilopoulou-Sellin R, et al. Hormone replacement therapy and lung cancer risk: a case-control analysis. *Clin Cancer Res.* 2004;10(1, pt 1):113–123.
36. Schwartz AG, Wenzlaff AS, Prysak GM, et al. Reproductive factors, hormone use, estrogen receptor expression and risk of non small-cell lung cancer in women. *J Clin Oncol.* 2007;25(36):5785–5792.
37. Key TJ, Appleby PN, Reeves GK, et al. Body mass index, serum sex hormones, and breast cancer risk in postmenopausal women. *J Natl Cancer Inst.* 2003;95(16):1218–1226.
38. Key TJ, Appleby PN, Reeves GK, et al. Circulating sex hormones and breast cancer risk factors in postmenopausal women: reanalysis of 13 studies. *Br J Cancer.* 2011;105(5):709–722.
39. Siegfried JM, Hershberger PA, Stabile LP. Estrogen receptor signaling in lung cancer. *Semin Oncol.* 2009;36(6):524–531.
40. Godschalk RW, Feldker DE, Borm PJ, et al. Body mass index modulates aromatic DNA adduct levels and their persistence in smokers. *Cancer Epidemiol Biomarkers Prev.* 2002;11(8):790–793.
41. Palli D, Vineis P, Russo A, et al. Diet, metabolic polymorphisms and DNA adducts: the EPIC-Italy cross-sectional study. *Int J Cancer.* 2000;87(3): 444–451.
42. Rundle A, Madsen A, Orjuela M, et al. The association between benzo[a] pyrene-DNA adducts and body mass index, calorie intake and physical activity. *Biomarkers.* 2007;12(2):123–132.
43. Vineis P, Perera F. DNA adducts as markers of exposure to carcinogens and risk of cancer. *Int J Cancer.* 2000;88(3):325–328.
44. Palta M, Prineas RJ, Berman R, et al. Comparison of self-reported and measured height and weight. *Am J Epidemiol.* 1982;115(2):223–230.
45. Stewart AW, Jackson RT, Ford MA, et al. Underestimation of relative weight by use of self-reported height and weight. *Am J Epidemiol.* 1987;125(1): 122–126.

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