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Original Contribution

Body Mass Index and Waist Circumference in Relation to Lung Cancer Risk in the Women's Health Initiative

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Investigators in several epidemiologic studies have observed an inverse association between body mass index (BMI) and lung cancer risk, while others have not. The authors used data from the Women's Health Initiative to study the association of anthropometric factors with lung cancer risk. Over 8 years of follow-up (1998–2006), 1,365 incident lung cancer cases were ascertained among 161,809 women. Cox proportional hazards models were used to estimate hazard ratios adjusted for covariates. Baseline BMI was inversely associated with lung cancer in current smokers (highest quintile vs. lowest: hazard ratio (HR) = 0.62, 95% confidence interval (CI): 0.42, 0.92). When BMI and waist circumference were mutually adjusted, BMI was inversely associated with lung cancer risk in both current smokers and former smokers (HR = 0.40 (95% CI: 0.22, 0.72) and HR = 0.61 (95% CI: 0.40, 0.94), respectively), and waist circumference was positively associated with risk (HR = 1.56 (95% CI: 0.91, 2.69) and HR = 1.50 (95% CI: 0.98, 2.31), respectively). In never smokers, height showed a borderline positive association with lung cancer. These findings suggest that in smokers, BMI is inversely associated with lung cancer risk and that waist circumference is positively associated with risk.

adiposity; body mass index; body weight changes; health status; lung neoplasms; smoking; waist-hip ratio

Abbreviations: BMI, body mass index; CI, confidence interval; HR, hazard ratio; WHI, Women's Health Initiative.

Obesity is associated with increased total mortality as well as with mortality from coronary heart disease, diabetes, and certain cancers; however, the health consequences of different degrees of body mass index (BMI) are currently being vigorously debated (1, 2). Lung cancer is one outcome for which the role of BMI requires clarification. Investigators in a number of epidemiologic studies, but not all, have observed an inverse association between BMI and lung cancer risk (3–21). Some of these researchers have presented data only on all subjects combined, whereas others have presented results stratified by smoking status. Among those who presented results stratified by smoking status, investigators in three studies reported inverse associations in current smokers, former smokers, and never smokers (8, 14, 18), whereas in two other studies the associations differed by smoking status (7, 19). Evidence for an inverse association is more consistent in ever smokers than in never smokers (15, 19, 20).

Assessment of an association of BMI with lung cancer is difficult due to complex interrelations between smoking habits and body weight over time. There is justified concern that such an association may due to uncontrolled confounding by smoking, unmeasured effects of smoking on BMI, or preclinical weight loss among persons who later develop lung cancer. Few investigators have had information on measures of central adiposity or weight at multiple time points throughout adulthood, which might help to clarify the significance of the association.

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In order to assess the association between BMI and lung cancer risk in a more comprehensive fashion, we used data from the Women's Health Initiative (WHI). In the WHI, weight, height, and waist and hip circumferences were measured at baseline, and information was collected on (self-reported) weight during different periods of life, as well as on weight loss, smoking habits, and other potentially confounding variables. Thus, the WHI provided us with an unusual opportunity to examine a variety of anthropometric variables in relation to lung cancer risk.

MATERIALS AND METHODS

The WHI is a large, multifaceted study designed to advance understanding of the determinants of major chronic diseases in women. It is composed of a clinical trial component and an observational study component (22). The WHI Clinical Trial included several randomized controlled clinical trials designed to test the effects of a low-fat dietary pattern, calcium plus vitamin D supplementation, and administration of postmenopausal estrogen alone or estrogen plus progestin on the risks of coronary heart disease, breast cancer, colorectal cancer, and fractures. The WHI Observational Study was designed to obtain detailed information on a full range of lifestyle factors and medical history from a sample of postmenopausal women for comparison with the Clinical Trial results. Between 1993 and 1998, women between the ages of 50 and 79 years representing major racial/ethnic groups were recruited from the general population at 40 clinical centers throughout the United States. Details on the study design and the reliability of the baseline measures have been published previously (23, 24).

Data collection

At baseline, information was collected on demographic factors, medical, reproductive, and family histories, and dietary and lifestyle factors. Clinical outcomes (including cancer diagnosis) were updated annually (in the Observational Study) or semiannually (in the Clinical Trial) by mailed or telephone-administered questionnaires. Self-reported lung cancers were verified by local review of pathology reports (25). Since lung cancer was not a primary or secondary outcome in the WHI Clinical Trial, stage and lung cancer histology were not recorded. As of December 18, 2006, a total of 1,365 incident lung cancer cases had been diagnosed among 161,809 women enrolled in the Clinical Trial or the Observational Study after an average follow-up period of 7.8 years.

All study participants had their weight, height, and waist and hip circumferences measured at baseline. In addition, Observational Study participants provided information on weight and height during earlier periods of life (at ages 18, 35, and 50 years), maximum and minimum weight, and weight loss during different periods of life. BMI was computed as measured weight (kg) divided by the square of measured height $(cm)^2$. Information on smoking habits collected at baseline included whether the subject had ever smoked (at least 100 cigarettes) and, for those who had ever smoked, age at starting to smoke regularly (nine categories), current smoking (yes/no), age at quitting (former smokers—11 categories), whether the smoker had quit for health reasons, number of cigarettes smoked per day (both current and former smokers—seven categories), and number of years of smoking (seven categories).

TABLE 1. Pearson correlations between anthropometric variables in the Women's Health Initiative, 1998–2006*

	Body mass index†	Waist:hip ratio
Waist:hip ratio	0.34	
Waist circumference	0.83	0.67
Height	−0.08	−0.05
Weight	0.93	0.31
Weight at age 18 years‡	0.29	0.07
Weight at age 35 years‡	0.53	0.19
Weight at age 50 years‡	0.71	0.26

* All correlations were significant at the $p < 0.0001$ level.

† Measured weight (kg) divided by the square of measured height $(cm)^2$.

‡ Self-reported information on weight at these ages was available only in the Observational Study; other variables were based on measurements taken at baseline in the total population.

After exclusion of participants for whom measured weight or height at baseline was missing ($n = 1{,}428$) or who were missing information on lung cancer as an outcome ($n = 722$), a total of 159,659 women enrolled in either the Clinical Trial or the Observational Study were available for analysis (1,353 cases and 158,306 noncases).

Statistical analysis

Pack-years of cigarette smoking were computed by multiplying the midpoint of the smoking frequency interval by the midpoint of the duration interval and dividing the product by 20. Quintiles of anthropometric measures were based on the population of noncases.

Correlations among different anthropometric variables were assessed using Pearson correlation coefficients (table 1). Because of the strong correlation between BMI and waist circumference, two approaches were used to obtain estimates of the effect of each variable adjusted for the other. First, both variables were included in the models. Second, we used the residuals method (26) to obtain BMI adjusted for waist circumference and waist circumference adjusted for BMI. The results derived using both approaches were similar, and we present results of the first approach.

Cox proportional hazards models were used to estimate hazard ratios and 95 percent confidence intervals for associations between the variables of interest and risk of lung cancer, both in the total population and separately among current smokers, former smokers, and never smokers. Due to differences in variables available in the Observational Study and the Clinical Trial, some analyses were performed

on the combined data, and further analyses were performed using variables limited to the Observational Study. Weight change was computed as the difference between weight measured at baseline and self-reported weight at age 18 years (available for Observational Study participants only). The resulting continuous variable was categorized as follows: lost 10 pounds or more ($-\geq$4.5 kg); gained or lost less than 10 pounds ($\pm<$4.5 kg; reference group); gained 10–<20 pounds (+4.5–9 kg); gained 20–<30 pounds (+9.1–13.5 kg); and gained 30 pounds or more ($+\geq$13.6 kg).

The following variables were included as covariates in the regression models, either because they were significantly associated with lung cancer or because their inclusion in the multivariate model changed the parameter estimate for BMI by more than 10 percent: age (years) at enrollment; education (less than high school graduation, high school graduation, some college, college graduation, or postcollege); ethnicity (White, Black, or other); pack-years of smoking (none, >0–<20, 20–<40, 40–<60, or $\geq$60); age (years) at quitting smoking (six levels); quitting smoking because of health problems (yes/no); physical activity (metabolic equivalents per week—continuous); ever use of hormone replacement therapy (yes/no); and intakes of total fat (g/day), fruits (servings/day), vegetables (servings/day), alcohol (drinks/week), and total calories (kcal/day) (all continuous). In analyses of the Observational Study and the Clinical Trial combined, we included an indicator variable for study (Observational Study/Clinical Trial). Tests for trend were performed by assigning the median value to each category and modeling this variable as a continuous variable (27). In order to rule out an effect of general ill health or of weight loss due to preclinical disease, we repeated the main analyses after excluding women who assessed their health status at baseline as ''poor'' and, alternatively, excluding those whose lung cancer was diagnosed within 3 years of baseline. All p values presented are two-sided.

RESULTS

Baseline BMI showed a modest positive correlation with baseline waist:hip ratio ($r = 0.34$) and a strong correlation with waist circumference ($r = 0.83$) (table 1). In addition, baseline BMI showed increasingly strong correlations with self-reported weight at ages 18, 35, and 50 years ($r = 0.29$, $r = 0.53$, and $r = 0.71$, respectively). All correlations shown in table 1 were significant at the $p < 0.0001$ level. Correlations seen in the total WHI population were similar to those for current, former, and never smokers (data not shown).

Table 2 presents age-adjusted and multivariable-adjusted hazard ratios for lung cancer risk in association with selected demographic and lifestyle variables. Smoking status and pack-years of smoking were both strongly associated with lung cancer risk. Age-adjusted alcohol intake showed a significant association with lung cancer which totally disappeared after adjustment for pack-years of smoking and other covariates. Age-adjusted associations with education, fruit intake, and physical activity were all attenuated when adjusted for pack-years of smoking and other covariates. In contrast, inverse associations of BMI with lung cancer were similar in the age-adjusted and multivariable-adjusted models.

Associations of anthropometric variables with lung cancer risk are presented in table 3. Body mass index, weight, and BMI adjusted for waist circumference were inversely associated with lung cancer in current smokers: hazard ratios for the highest quintile versus the lowest were 0.62 (95 percent confidence interval (CI): 0.42, 0.92; p-trend = 0.002), 0.60 (95 percent CI: 0.41, 0.87; p-trend = 0.004), and 0.40 (95 percent CI: 0.22, 0.72; p-trend = 0.001), respectively. Waist circumference alone showed a borderline inverse association with lung cancer risk in current smokers; however, after adjustment for BMI, waist circumference showed a borderline positive association with lung cancer risk in current smokers (hazard ratio (HR) = 1.56, 95 percent CI: 0.91, 2.69; p-trend = 0.12). In former smokers, BMI adjusted for waist circumference was inversely associated with risk (HR = 0.61, 95 percent CI: 0.40, 0.94; p-trend = 0.02), and waist circumference adjusted for BMI was positively associated with risk (HR = 1.50, 95 percent CI: 0.98, 2.31; p-trend = 0.004). In never smokers, height showed a borderline positive association with lung cancer (HR = 1.44, 95 percent 0.91, 2.27; p-trend = 0.05), whereas the other variables were not associated with altered risk. Weights at ages 18, 35, and 50 years were not associated with risk in any of the smoking-status strata. The associations shown in table 3 were not altered by exclusion of women who reported that they were in poor health at baseline or of cases diagnosed within 3 years following enrollment (data not shown).

Table 4 provides hazard ratios for BMI and for BMI and waist circumference adjusted for each other, by strata of cigarettes smoked per day among current and former smokers. Among current smokers, the inverse associations of BMI and waist circumference-adjusted BMI with lung cancer were largely consistent across strata of amount smoked. Adjusted waist circumference showed evidence of a positive association in three of four strata among current smokers, but the association was most pronounced among women who smoked 35 or more cigarettes per day. Among former smokers, a decreasing trend in risk with increasing levels of adjusted BMI was evident, particularly among smokers of 15–24 and $\geq$35 cigarettes per day. Adjusted waist circumference was fairly consistently associated with increased risk in former smokers.

Among current smokers in the Observational Study, there was a suggestion that women who gained more weight between age 18 years and baseline were at reduced risk of lung cancer (table 5). Relative to women who had gained or lost less than 10 pounds (<4.5 kg), women who had gained 30 or more pounds ($\geq$13.6 kg) had a 37 percent reduction in risk (HR = 0.63, 95 percent CI: 0.43, 0.93; p-trend = 0.009). A similar trend was seen in former smokers, but the hazard ratio and test for trend were not significant. No association was seen with degree of weight change in never smokers. When cases diagnosed in the first 3 years of follow-up were excluded, the hazard ratio for weight gain of 30 or more pounds was attenuated in current smokers (HR = 0.71, 95 percent CI: 0.45, 1.12; p-trend = 0.10) but became significant in former smokers (HR = 0.66, 95 percent CI: 0.45, 0.98; p-trend = 0.03).

TABLE 2. Age- and multivariable-adjusted hazard ratios for the association of demographic and lifestyle characteristics with lung cancer in the Women's Health Initiative, 1998–2006

Characteristic	No. of cases	Person-years of follow-up	Age-adjusted		Multivariable-adjusted*	
			HR†	95% CI†	HR	95% CI
Education						
Less than high school graduation	90	131,924	1.00	Reference	1.00	Reference
High school graduation	268	439,624	0.93	0.73, 1.17	0.93	0.72, 1.21
Some college	549	897,501	0.89	0.71, 1.11	0.87	0.68, 1.11
College graduation	143	251,118	0.82	0.63, 1.07	0.92	0.69, 1.23
Postcollege education	292	440,569	0.65	0.51, 0.83	0.76	0.58, 0.99
Smoking status						
Never smoker	197	317,923	1.00	Reference	1.00	Reference
Former smoker	736	1,171,423	4.53	3.89, 5.28	4.34	3.69, 5.11
Current smoker	404	660,882	18.25	15.43, 21.57	17.10	14.26, 20.50
Pack-years of smoking						
None	197	317,923	1.00	Reference	1.00	Reference
>0–<20	231	360,418	2.23	1.85, 2.70	2.08	1.69, 2.55
20–<40	317	529,577	8.07	6.75, 9.64	7.96	6.59, 9.62
40–<60	292	475,458	17.29	14.43, 20.71	16.35	13.47, 19.86
≥60	278	428,263	22.95	19.12, 27.55	22.71	18.68, 27.60
Alcohol consumption						
Nondrinker	69	117,265	1.00	Reference	1.00	Reference
Former drinker	292	449,656	2.61	2.01, 3.40	1.08	0.82, 1.41
Current drinker						
<1 drink/month	146	223,141	2.03	1.52, 2.70	0.91	0.68, 1.22
<1 drink/week	272	464,296	2.22	1.71, 2.90	1.11	0.85, 1.46
1–<7 drinks/week	336	539,768	2.21	1.71, 2.87	1.02	0.78, 1.34
≥7 drinks/week	227	364,462	3.20	2.44, 4.19	1.00	0.76, 1.33
Fruit intake (servings/day)						
<0.82	362	603,590	1.00	Reference	1.00	Reference
0.82–<1.32	295	461,345	0.75	0.64, 0.88	1.05	0.89, 1.24
1.32–<2.02	244	409,381	0.59	0.50, 0.69	0.89	0.74, 1.06
2.02–<3.00	197	314,840	0.52	0.43, 0.62	0.87	0.71, 1.07
≥3.00	206	311,420	0.46	0.38, 0.54	0.85	0.68, 1.05
p for trend				<0.0001		0.04
Physical activity (metabolic equivalents/week)						
<1.38	310	478,363	1.00	Reference	1.00	Reference
1.38–<5.52	261	425,184	0.83	0.70, 0.98	0.99	0.83, 1.17
5.52–<11.69	261	405,951	0.80	0.68, 0.95	1.02	0.86, 1.22
11.69–<21.02	208	335,581	0.64	0.54, 0.76	0.89	0.74, 1.07
≥21.02	231	359,244	0.72	0.61, 0.86	1.06	0.88, 1.28
p for trend				<0.0001		0.22
Body mass index‡						
<23.1	314	498,884	1.00	Reference	1.00	Reference
23.1–<25.6	311	516,999	0.98	0.84, 1.15	1.04	0.88, 1.23
25.6–<28.3	236	370,208	0.74	0.63, 0.88	0.77	0.64, 9.93
28.3–<32.2	265	411,730	0.85	0.72, 1.00	0.81	0.68, 0.98
≥32.2	227	377,170	0.79	0.67, 0.94	0.79	0.65, 0.96
p for trend				0.001		0.001

* Adjusted for age (years—continuous), smoking status (never, former, or current smoker), pack-years of smoking (none, >0–<20, 20–<40, 40–<60, or ≥60), education (less than high school graduation, high school graduation, some college, college graduation, or postcollege), ethnicity (White, Black, or other), use of hormone replacement therapy (never/ever), intakes of total fat (g/day), fruits (servings/day), vegetables (servings/day), alcohol (drinks/week), and total calories (kcal/day) (all continuous), physical activity (metabolic equivalents per week—continuous), and study (Observational Study/Clinical Trial).

† HR, hazard ratio; CI, confidence interval.

‡ Measured weight (kg) divided by the square of measured height $(cm)^2$.

TABLE 3. Multivariable-adjusted hazard ratios* for the association of anthropometric variables with lung cancer, by smoking status, in the Women's Health Initiative, 1998–2006

Variable	Never smokers (197 cases)		Former smokers (736 cases)				Current smokers (404 cases)			
	HR†	95% CI†	HR‡	95% CI	HR§	95% CI	HR‡	95% CI	HR¶	95% CI
BMI†,#										
<23.1	1.00	Reference	1.00	Reference	1.00	Reference	1.00	Reference	1.00	Reference
23.1–<25.6	1.24	0.80, 1.89	1.05	0.82, 1.34	0.98	0.76, 1.27	1.06	0.81, 1.39	1.06	0.81, 1.39
25.6–<28.3	0.94	0.60, 1.50	0.88	0.68, 1.13	0.73	0.56, 0.96	0.67	0.49, 0.92	0.71	0.52, 0.98
28.3–<32.2	0.73	0.45, 1.21	1.07	0.83, 1.37	0.85	0.65, 1.10	0.74	0.53, 1.02	0.73	0.53, 1.01
≥32.2	0.83	0.50, 1.38	1.13	0.87, 1.47	0.85	0.65, 1.12	0.59	0.40, 0.87	0.62	0.42, 0.92
p for trend		0.15		0.28		0.21		0.0008		0.002
Waist:hip ratio										
<0.75	1.00	Reference	1.00	Reference	1.00	Reference	1.00	Reference	1.00	Reference
0.75–<0.79	1.02	0.65, 1.60	1.17	0.88, 1.55	0.94	0.69, 1.27	1.06	0.73, 1.54	0.96	0.66, 1.40
0.79–<0.82	0.94	0.59, 1.50	1.25	0.94, 1.65	1.02	0.76, 1.36	0.82	0.56, 1.21	0.72	0.49, 1.06
0.82–<0.87	0.91	0.57, 1.47	1.40	1.07, 1.84	1.01	0.76, 1.34	1.09	0.76, 1.57	0.90	0.63, 1.30
≥0.87	1.01	0.64, 1.66	1.63	1.25, 2.13	1.02	0.77, 1.35	1.10	0.77, 1.57	0.89	0.62, 1.27
p for trend		0.96		<0.0001		0.71		0.42		0.67
Waist circumference (cm)										
<74.6	1.00	Reference	1.00	Reference	1.00	Reference	1.00	Reference	1.00	Reference
74.6–<81.1	1.02	0.66, 1.59	0.94	0.72, 1.23	0.86	0.64, 1.14	0.80	0.59, 1.09	0.81	0.59, 1.10
81.1–<88.1	1.19	0.77, 1.83	1.18	0.91, 1.52	0.94	0.71, 1.23	0.77	0.56, 1.05	0.74	0.54, 1.02
88.1–<97.6	0.70	0.42, 1.17	1.10	0.84, 1.43	0.78	0.59, 1.04	0.78	0.57, 1.08	0.71	0.52, 0.98
≥97.6	0.85	0.51, 1.42	1.48	1.14, 1.92	0.97	0.74, 1.29	0.82	0.59, 1.14	0.76	0.54, 1.06
p for trend		0.28		0.0005		0.82		0.28		0.09
BMI adjusted for waist circumference**										
<23.1	1.00	Reference	1.00	Reference	1.00	Reference	1.00	Reference	1.00	Reference
23.1–<25.6	1.16	0.72, 1.87	0.91	0.69, 1.20	0.91	0.68, 1.22	0.99	0.72, 1.35	1.06	0.78, 1.46
25.6–<28.3	0.88	0.49, 1.55	0.64	0.47, 0.89	0.68	0.48, 0.95	0.54	0.36, 0.81	0.66	0.43, 1.00
28.3–<32.2	0.75	0.38, 1.47	0.66	0.46, 0.95	0.71	0.49, 1.03	0.47	0.29, 0.75	0.57	0.35, 0.92
≥32.2	0.91	0.41, 2.05	0.56	0.37, 0.84	0.61	0.40, 0.94	0.30	0.16, 0.53	0.40	0.22, 0.72
p for trend		0.47		0.003		0.02		<0.0001		0.0014
Waist circumference adjusted for BMI**										
<74.6	1.00	Reference	1.00	Reference	1.00	Reference	1.00	Reference	1.00	Reference
74.6–<81.1	1.03	0.63, 1.67	1.05	0.78, 1.41	0.94	0.70, 1.29	0.87	0.63, 1.21	0.83	0.60, 1.15
81.1–<88.1	1.34	0.78, 2.32	1.51	1.10, 2.08	1.19	0.85, 1.67	1.05	0.71, 1.53	0.89	0.61, 1.31
88.1–<97.6	0.88	0.44, 1.74	1.58	1.10, 2.28	1.15	0.78, 1.68	1.40	0.90, 2.16	1.08	0.69, 1.69
≥97.6	1.01	0.45, 2.28	2.37	1.58, 3.57	1.50	0.98, 2.31	2.10	1.24, 3.56	1.56	0.91, 2.69
p for trend		0.97		<0.0001		0.004		0.01		0.12
Height (cm)										
<156.5	1.00	Reference	1.00	Reference	1.00	Reference	1.00	Reference	1.00	Reference
156.5–<160.2	0.85	0.53, 1.36	1.08	0.85, 1.38	1.08	0.83, 1.39	1.26	0.89, 1.80	1.25	0.88, 1.78
160.2–<163.5	0.85	0.52, 1.37	1.00	0.78, 1.29	0.95	0.72, 1.24	1.17	0.82, 1.67	1.14	0.80, 1.62
163.5–<167.1	1.23	0.79, 1.94	1.12	0.87, 1.43	1.11	0.85, 1.44	1.44	1.02, 2.05	1.37	0.96, 1.94
≥167.1	1.44	0.91, 2.27	1.12	0.86, 1.44	1.17	0.89, 1.53	1.22	0.85, 1.75	1.19	0.83, 1.70
p for trend		0.05		0.39		0.26		0.25		0.35

Table continues

TABLE 3. Continued

Variable	Never smokers (197 cases)		Former smokers (736 cases)				Current smokers (404 cases)			
	HR	95% CI	HR‡	95% CI	HR§	95% CI	HR‡	95% CI	HR¶	95% CI
Weight (pounds)††										
<132.5	1.00	Reference	1.00	Reference	1.00	Reference	1.00	Reference	1.00	Reference
132.5–<147.7	1.04	0.68, 1.60	1.00	0.78, 1.27	0.90	0.69, 1.16	0.83	0.62, 1.10	0.87	0.65, 1.15
147.7–<164.0	0.78	0.49, 1.24	0.87	0.68, 1.12	0.72	0.55, 0.94	0.73	0.54, 0.99	0.75	0.55, 1.01
164.0–<187.4	0.95	0.61, 1.50	1.04	0.81, 1.33	0.82	0.62, 1.06	0.74	0.54, 1.01	0.75	0.54, 1.03
≥187.4	0.78	0.47, 1.30	1.09	0.84, 1.41	0.79	0.60, 1.05	0.57	0.39, 0.83	0.60	0.41, 0.87
p for trend		0.31		0.40		0.14		0.002		0.004
Weight (pounds) at age 18 years										
<109.5	1.00	Reference	1.00	Reference	1.00	Reference	1.00	Reference	1.00	Reference
109.5–<117.5	1.16	0.66, 2.06	1.01	0.72, 1.40	0.94	0.65, 1.35	0.81	0.50, 1.30	0.83	0.52, 1.34
117.5–<124.5	1.14	0.65, 2.01	0.99	0.72, 1.37	1.04	0.74, 1.47	0.76	0.48, 1.23	0.78	0.48, 1.25
124.5–<134.5	0.97	0.52, 1.79	1.06	0.77, 1.46	1.12	0.79, 1.57	0.91	0.57, 1.43	0.98	0.62, 1.54
≥134.5	0.98	0.52, 1.85	1.13	0.82, 1.55	1.04	0.74, 1.47	1.09	0.71, 1.67	1.07	0.70, 1.64
p for trend		0.84		0.39		0.57		0.49		0.52
Weight (pounds) at age 35 years										
<117.5	1.00	Reference	1.00	Reference	1.00	Reference	1.00	Reference	1.00	Reference
117.5–<125.5	0.87	0.49, 1.56	0.87	0.65, 1.17	0.87	0.63, 1.19	1.01	0.66, 1.53	1.05	0.69, 1.60
125.5–<134.5	1.39	0.80, 2.40	1.03	0.77, 1.40	1.11	0.81, 1.53	0.82	0.50, 1.34	0.80	0.49, 1.31
134.5–<140.5	0.63	0.33, 1.22	0.81	0.60, 1.10	0.95	0.69, 1.31	1.00	0.65, 1.55	1.08	0.70, 1.67
≥140.5	0.79	0.42, 1.50	0.75	0.54, 1.05	0.76	0.53, 1.08	0.90	0.56, 1.43	0.89	0.56, 1.42
p for trend		0.40		0.09		0.19		0.63		0.63
Weight (pounds) at age 50 years										
<124.5	1.00	Reference	1.00	Reference	1.00	Reference	1.00	Reference	1.00	Reference
124.5–<134.5	1.11	0.64, 1.94	1.14	0.84, 1.55	1.24	0.90, 1.72	0.96	0.63, 1.46	1.02	0.67, 1.55
134.5–<145.5	0.80	0.46, 1.39	0.95	0.71, 1.27	0.94	0.68, 1.28	0.82	0.55, 1.22	0.91	0.61, 1.37
145.5–<160.5	0.73	0.39, 1.37	0.91	0.66, 1.26	0.93	0.64, 1.31	0.60	0.37, 0.98	0.59	0.36, 0.97
≥160.5	0.80	0.41, 1.55	0.87	0.60, 1.25	0.85	0.58, 1.26	0.89	0.55, 1.45	0.86	0.53, 1.40
p for trend		0.31		0.25		0.20		0.34		0.26

* In never smokers, covariates included age (years—continuous), education (less than high school graduation, high school graduation, some college, college graduation, or postcollege), ethnicity (White, Black, or other), use of hormone replacement therapy (never/ever), intakes of total fat (g/day), fruits (servings/day), vegetables (servings/day), alcohol (drinks/week), and total calories (kcal/day) (all continuous), physical activity (metabolic equivalents per week—continuous), height (cm), and study (Observational Study/Clinical Trial). Models for former smokers included the additional variables pack-years of smoking (>0–<20, 20–<40, 40–<60, or ≥60), age at quitting smoking (<35, 35–44, 45–49, 50–54, 55–59, or ≥60 years), and whether the participant had quit smoking because of a health problem (yes/no). Models for current smokers included pack-years of smoking in addition to the variables listed above for never smokers.

† HR, hazard ratio; CI, confidence interval; BMI, body mass index.

‡ Unadjusted for smoking variables but adjusted for all other variables.

§ Adjusted for pack-years and age at quitting smoking in addition to all of the other covariates listed above.

¶ Adjusted for pack-years of smoking in addition to all of the other covariates listed above.

Measured weight (kg) divided by the square of measured height $(cm)^2$.

** From the model including quintiles of BMI and waist circumference.

†† 1 pound = 0.45 kg.

Unintentional weight loss of 15 pounds or more (≥6.8 kg) within the past 6 months (6 months of baseline), intentional loss of 10 pounds or more (≥4.5 kg) in the last 20 years, number of times weight went up or down by 10 or more pounds (≥4.5 kg), maximum adult weight, and minimum adult weight were not associated with risk of lung cancer (data not shown).

TABLE 4. Multivariable-adjusted hazard ratios* for the association of body mass index†, body mass index adjusted for waist circumference, and waist circumference adjusted for body mass index with lung cancer among current and former smokers, by level of smoking, in the Women's Health Initiative, 1998–2006

No. of cigarettes smoked per day and quintile of BMI‡ or WC‡	No. of cases		BMI				WC-adjusted BMI				BMI-adjusted WC			
	Current smokers	Former smokers	Current smokers		Former smokers		Current smokers		Former smokers		Current smokers		Former smokers	
			HR‡	95% CI‡	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI
5–14	85	138												
1			1.00	Reference	1.00	Reference	1.00	Reference	1.00	Reference	1.00	Reference	1.00	Reference
2			0.83	0.45, 1.53	1.45	0.82, 2.57	0.81	0.40, 1.63	1.45	0.74, 2.82	0.64	0.30, 1.35	0.68	0.33, 1.39
3			0.77	0.40, 1.50	0.93	0.49, 1.75	0.68	0.29, 1.62	0.86	0.38, 1.92	1.15	0.51, 2.56	1.23	0.59, 2.25
4			0.66	0.32, 1.37	0.72	0.36, 1.44	0.59	0.22, 1.63	0.63	0.24, 1.62	1.12	0.43, 2.96	0.93	0.39, 2.25
5			0.68	0.28, 1.62	1.70	0.91, 3.18	0.55	0.31, 1.44	1.31	0.47, 3.65	1.14	0.35, 3.73	1.31	0.48, 3.58
p for trend				0.25		0.31		0.28		0.79		0.67		0.47
15–24	178	248												
1			1.00	Reference	1.00	Reference	1.00	Reference	1.00	Reference	1.00	Reference	1.00	Reference
2			1.34	0.89, 2.01	0.78	0.50, 1.21	1.46	0.92, 2.32	0.77	0.46, 1.27	0.74	0.46, 1.20	1.03	0.61, 1.74
3			0.72	0.44, 1.17	0.78	0.50, 1.21	0.74	0.39, 1.41	0.77	0.44, 1.35	0.70	0.39, 1.26	1.07	0.60, 1.92
4			0.69	0.41, 1.15	0.97	0.64, 1.48	0.62	0.29, 1.32	0.88	0.48, 1.63	0.98	0.50, 1.90	0.87	0.45, 1.69
5			0.65	0.35, 1.21	0.74	0.46, 1.18	0.51	0.20, 1.32	0.52	0.25, 1.07	1.14	0.48, 2.67	1.61	0.79, 3.27
p for trend				0.02		0.48		0.10		0.18		0.94		0.27
25–34	71	113												
1			1.00	Reference	1.00	Reference	1.00	Reference	1.00	Reference	1.00	Reference	1.00	Reference
2			1.12	0.60, 2.08	0.69	0.33, 1.46	1.43	0.68, 2.99	0.56	0.25, 1.28	0.89	0.40, 1.95	1.16	0.47, 2.86
3			0.80	0.38, 1.70	0.85	0.43, 1.70	1.09	0.40, 2.98	0.61	0.26, 1.45	0.65	0.26, 1.64	1.78	0.70, 4.51
4			0.89	0.42, 1.88	1.24	0.64, 2.39	1.19	0.38, 3.73	0.86	0.33, 2.20	0.50	0.17, 1.48	1.64	0.58, 4.59
5			0.44	0.14, 1.32	1.08	0.54, 2.16	0.39	0.09, 1.80	0.76	0.26, 2.22	1.00	0.29, 3.48	1.60	0.51, 5.02
p for trend				0.13		0.34		0.45		0.99		0.57		0.41
≥35	50	162												
1			1.00	Reference	1.00	Reference	1.00	Reference	1.00	Reference	1.00	Reference	1.00	Reference
2			0.58	0.23, 1.46	1.09	0.66, 1.78	0.42	0.14, 1.21	1.07	0.62, 1.86	1.33	0.45, 3.96	0.98	0.53, 1.80
3			0.70	0.28, 1.77	0.58	0.34, 1.01	0.22	0.06, 0.85	0.49	0.25, 0.96	0.89	0.22, 3.56	0.88	0.44, 1.77
4			1.10	0.47, 2.57	0.52	0.30, 0.92	0.19	0.05, 0.81	0.35	0.16, 0.75	4.69	1.20, 18.26	1.58	0.75, 3.31
5			0.60	0.22, 1.64	0.51	0.29, 0.90	0.09	0.02, 0.47	0.30	0.13, 0.71	8.85	1.75, 44.70	1.77	0.74, 4.21
p for trend				0.62		0.002		0.007		0.001		0.01		0.14

* Adjusted for age (years—continuous), education (less than high school graduation, high school graduation, some college, college graduation, or postcollege), ethnicity (White, Black, or other), hormone replacement therapy (never/ever), intakes of total fat (g/day), fruits (servings/day), vegetables (servings/day), alcohol (drinks/week), and total calories (kcal/day) (all continuous), physical activity (metabolic equivalents per week—continuous), study (Observational Study/Clinical Trial), and years of smoking (seven levels). In models for former smokers, age at quitting smoking (11 levels) was included.

† Measured weight (kg) divided by the square of measured height $(cm)^2$.

‡ BMI, body mass index; WC, waist circumference; HR, hazard ratio; CI, confidence interval.

DISCUSSION

In this large cohort of postmenopausal women, baseline BMI, weight, and waist circumference were inversely associated with subsequent risk of lung cancer in current smokers but not in never smokers or former smokers. However, after mutual adjustment, BMI was inversely associated with risk and waist circumference was positively associated with risk in both current and former smokers. These associations were unchanged following exclusion of women who reported at baseline that their health was ''poor'' or of cases diagnosed within 3 years of enrollment. Self-reported weight at ages 18, 35, and 50 years showed no association with lung cancer risk; however, weight gain between age 18 and baseline was inversely associated with risk in current smokers.

Because smoking is a strong risk factor for lung cancer and because smoking habits affect both body weight and body

TABLE 5. Multivariate-adjusted hazard ratios* for the relation between change in weight from age 18 years to baseline and risk of lung cancer, by smoking status, in the Women's Health Initiative (Observational Study only), 1998–2006

Weight change from age 18 years to baseline	No. of cases†	Person-years of follow-up	Hazard ratio	95% confidence interval
Current smokers ($n = 202$)				
Weight loss of ≥10 pounds (≥4.5 kg)	19	34,486	1.03	0.59, 1.80
Weight change of <10 pounds (±<4.5 kg)	53	78,514	1.00	Reference
Weight gain				
10–<20 pounds (4.5–9 kg)	33	59,945	0.84	0.54, 1.33
20–<30 pounds (9.1–13.5 kg)	29	40,478	0.69	0.43, 1.10
≥30 pounds (≥13.6 kg)	64	112,615	0.63	0.43, 0.93
p for trend				0.009
Former smokers ($n = 431$)				
Weight loss of ≥10 pounds (≥4.5 kg)	18	24,069	0.97	0.55, 1.71
Weight change of <10 pounds (±<4.5 kg)	63	94,449	1.00	Reference
Weight gain				
10–<20 pounds (4.5–9 kg)	58	96,641	0.82	0.56, 1.21
20–<30 pounds (9.1–13.5 kg)	76	115,988	1.05	0.76, 1.50
≥30 pounds (≥13.6 kg)	216	336,250	0.76	0.56, 1.03
p for trend				0.09
Never smokers ($n = 120$)				
Weight loss of ≥10 pounds (≥4.5 kg)	6	9,695	1.53	0.62, 3.80
Weight change of <10 pounds (±<4.5 kg)	23	32,929	1.00	Reference
Weight gain				
10–<20 pounds (4.5–9 kg)	18	29,821	0.86	0.45, 1.64
20–<30 pounds (9.1–13.5 kg)	19	28,923	0.99	0.53, 1.84
≥30 pounds (≥13.6 kg)	54	85,725	0.76	0.45, 1.30
p for trend				0.24

* All models included age (years—continuous), education (less than high school graduation, high school graduation, some college, college graduation, or postcollege), ethnicity (White, Black, or other), use of hormone replacement therapy (never/ever), intakes of total fat (g/day), fruits (servings/day), vegetables (servings/day), alcohol (drinks/week), and total calories (kcal/day) (all continuous), and physical activity (metabolic equivalents per week—continuous). Models for former smokers included the additional variables pack-years of smoking (>0–<20, 20–<40, 40–<60, or ≥60), age at quitting smoking (<35, 35–44, 45–49, 50–54, 55–59, or ≥60 years), and whether the participant had quit smoking because of a health problem (yes/no). Models for current smokers included pack-years of smoking in addition to the variables listed above for never smokers.

† Numbers of cases were reduced because participants were asked about weight at age 18 years in the Observational Study only.

composition, observed associations with anthropometric variables could be confounded by the effects of smoking. Reported smoking habits showed a strong association with lung cancer risk (for ≥60 pack-years of smoking vs. never smoking, HR = 22.7), and adjustment for smoking totally eliminated an apparent association with alcohol consumption and attenuated other associations. Adjustment for pack-years of smoking had a modest effect on the estimates for BMI and BMI adjusted for waist circumference but had a stronger effect on the estimates for waist circumference adjusted for BMI, reducing them toward the null value (table 3).

Studies that have assessed the validity of self-reports of number of cigarettes smoked per day among current smokers, particularly those that have compared self-reports with numbers of cigarette butts collected daily, have indicated that amount smoked is reported with a high degree of accuracy (28–31). Nevertheless, it is likely that there is some measurement error in reporting of amount smoked, and we cannot discount the possibility that the observed inverse associations of BMI and BMI adjusted for waist circumference with lung cancer are due, at least in part, to residual confounding. Stram et al. (32) have shown that the residual

confounding which results from high measurement error in the smoking variable and a modest correlation (e.g., −0.25) between a covariate and the true amount smoked can induce a spurious association between the covariate and lung cancer risk, generating risk ratios in the range of 1.3–2.3. In our data, however, the correlations of both BMI and BMI adjusted for waist circumference with cigarettes smoked per day among current smokers were considerably weaker: $r = -0.03$ and $r = -0.12$, respectively. Furthermore, the hazard ratio for the association between BMI adjusted for waist circumference (highest quintile vs. lowest) and lung cancer in current smokers was 0.40 (or 2.5, comparing the lowest quintile with the highest). This suggests that residual confounding by amount smoked may not totally account for the observed inverse association with BMI.

A second concern is that an association of BMI with lung cancer risk may be due to preclinical weight loss among women who later develop lung cancer. However, exclusion of women whose health was reported as ''poor'' and of cases diagnosed within the first 3 years of follow-up did not affect the association.

A number of studies have provided some evidence of an inverse association of BMI with lung cancer risk, particularly in ever smokers (7, 8, 10, 12, 14, 18, 19, 21), in whom the vast majority of lung cancer cases occur. Most investigators have reported that the inverse association persisted after adjustment for smoking habits (7, 8, 10, 12, 14, 19), and some, but not all, cohort studies indicated that the inverse association persisted after exclusion of cases diagnosed early in the follow-up period (7, 9, 11, 12, 19). However, few studies have included measurements of adiposity other than BMI and weight.

Both BMI and waist circumference provide simple yet sensitive indicators of total and central adiposity in adult women (33), and both measures have been shown to contribute independently to the prediction of nonabdominal, abdominal, and visceral fat (34). However, the interrelations between these variables and smoking are complex and are subject to change over time. Smokers who quit smoking tend to gain weight, and former smokers tend to have higher BMIs than never smokers and current smokers (35, 36). Current smokers tend to have lower BMIs than never smokers (37–39) but appear to have increased central adiposity (36, 40–44), a phenomenon which has been referred to as the low-BMI–high-waist-circumference paradox (41). In addition to the divergence of BMI and waist circumference in current smokers, BMI may also have serious limitations as a valid measure of adiposity in current smokers, because weight loss associated with smoking may be due to a reduction in lean mass rather than fat mass, a distinction which BMI may not fully capture (44).

Our results suggest that, in both current and former smokers, the inverse association of BMI with lung cancer was strengthened after adjustment for waist circumference. Furthermore, waist circumference was positively associated with lung cancer risk in both current and former smokers after controlling for BMI. These results are similar to those of Olson et al. (14), who found an inverse association for BMI and a positive association for waist circumference (each controlled for the other). The finding that BMI and waist circumference must be considered jointly may explain some of the inconsistency in the results of previous epidemiologic studies that considered only BMI.

Lipophilic carcinogens present in tobacco smoke, such as polycyclic aromatic hydrocarbons, are believed to initiate cancer by forming DNA adducts (45), and DNA adduct levels may provide a measure of biologically effective dose (46). In addition, lipophilic aromatic compounds derived from tobacco smoke may accumulate in adipose tissue (47). Three studies that measured DNA adduct levels in peripheral blood found an inverse association between BMI and levels of DNA adducts (48–50). In conjunction with the results of epidemiologic studies, these findings suggest that both body habitus and body composition may affect lung cancer risk in smokers, possibly through their effect on storage, mobilization, and metabolism of tobacco smoke carcinogens.

In view of the interrelations between smoking, anthropometric measures, and cancer risk, it is of interest that, similar to the literature on BMI and lung cancer, an inverse association of BMI with other smoking-related cancers has also been reported (51–53).

Our finding of a positive association of height with lung cancer risk, which was limited to never smokers, is difficult to interpret. Few investigators have examined this association (10, 11), and none that we know of presented results stratified by smoking status. In a case-control study, Goodman and Wilkens (10) reported a borderline positive association of height with lung cancer in women but not in men. In view of the large number of comparisons made in our analysis, this finding should be interpreted cautiously.

Strengths of the present study include the relatively large number of cases, the detailed information collected on a wide range of potential risk factors (including measurement of height, weight, and hip and waist circumferences at baseline in the entire WHI cohort), and the completeness of follow-up. Although several previous studies have had data on self-reported weight at age 18 or 20 years (6, 10, 11, 14, 19) as well as on weight at baseline (cohort studies) or weight prior to diagnosis (case-control studies), the present study is the first to have included data on weight at multiple points in time throughout adulthood. More importantly, few researchers have presented data on indices of adiposity other than weight and BMI (11, 13, 14).

The WHI questionnaire required ever smokers to select one of seven levels of frequency of cigarette smoking and one of seven levels of duration of smoking and required former smokers to select one of 11 levels of age at quitting. These categorizations assessed a wide range of exposure to cigarette smoke, enhancing the ability to detect associations.

This study had a number of limitations. The WHI questionnaire did not elicit information on certain aspects of smoking behavior that have been shown to improve the prediction of tobacco smoke exposure (i.e., measures of habituation and type of cigarette smoked) (28). In addition, data on certain variables were available only for the WHI Observational Study (e.g., weight earlier in life, questions about weight loss), and therefore numbers of cases, particularly in never smokers, were somewhat limited for some analyses. Furthermore, information on weight earlier in life was

obtained by self-report, and recall of weight in the distant past may be inaccurate; however, it is unlikely to have been recalled with different degrees of accuracy by women who subsequently became cases and those who did not. Finally, another important limitation was the lack of information on the histologic types of lung cancer diagnosed in WHI participants.

In conclusion, in a large prospective cohort study of postmenopausal women, baseline BMI, BMI adjusted for waist circumference, weight, and weight gain from age 18 years to baseline showed inverse associations with lung cancer risk in current smokers, whereas waist circumference showed a positive association, after results were controlled for BMI. In former smokers, only BMI adjusted for waist circumference showed an inverse association with lung cancer, and waist circumference adjusted for BMI was positively associated with risk. In never smokers, only height showed a borderline positive association with lung cancer. Our findings suggest that both body habitus and body composition may affect lung cancer risk in smokers, possibly through their effect on storage, mobilization, and metabolism of tobacco smoke carcinogens.

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