Association of Body Mass Index with Risk of Lung Cancer: Evidence from a Middle-Aged male Cohort in Shanghai, China

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OBJECTIVE To investigate the relationship between body mass index (BMI) and lung cancer risk among men in urban Shanghai, China.

METHODS Between January 1,1986 and September 30,1989, a total of 18,244 male residents of urban Shanghai were recruited in the prospective cohort study. The eligible study subjects were those aged 45 to 64 years and without history of cancer. Through July 10th, 2003 (17 years follow-up), 467 new cases of lung cancer were identified in the cohort. Cox regression models were used to estimate the adjusted relative risks (RRs) and 95% confidence intervals (CIs).

RESULTS The risk of lung cancer decreased with increasing in BMI. After adjustment for some potential confounding factors, a relative risk of 0.6 (highest versus lowest quintile of BMI) was observed (P-trend =0.01). Stratified by smoking status, an inverse association of body mass index with lung cancer risk still existed among current smokers. There were too few cases of lung cancer to draw a valid result among men who never smoked. The results also showed that the association of BMI with the risk of lung adenocarcinoma was more apparent than with other histological subtypes.

CONCLUSION An inverse association of BMI with lung cancer risk may exist among men in Shanghai.

Key words: prospective cohort study, lung cancer, body mass index, male.

Body Mass Index(BMI), defined as a person's weight in kilograms divided by the square of height in meters, is often used in epidemiologic studys as an approximate measure of general body fat. BMI has been shown to be positively associated with risk of a variety of cancers, including endometrial, colon and prostate cancer, lung cancer, however, is an exception, for which an inverse association between BMI and lung cancer risk has often been observed [1-6]. The precise relationship between body mass index and the risk of lung cancer remains controversial [7,8], and information on the relationship among adults in China is minimal [9-11]. The goal of this study was to prospectively examine the relationship between the BMI and risk of lung cancer in a large cohort of middle-aged men in Shanghai, China.

MATERIALS AND METHODS

Between January 1, 1986 and September 30, 1989, men ageD 45-64 years living in four small geographically defined areas of urban Shanghai were invited to participate in a prospective study of diet and

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cancer. At recruitment, each subject was interviewed in person using a structured questionnaire that included information on level of education, occupation, adult height and usual adult weight, history of tobacco and alcohol use, current diet (45 food items), and medical history. During the 3-year recruitment period, 18,224 men (about 80% of eligible subjects) enrolled in the study.

All surviving members of the cohort were contacted annually. Retired nurses employed by Shanghai Cancer Institute visited the last known address of each living cohort member and recorded details of the interim health history. Another supplementary method for identifying new cancer cases among cohort members was through linkage with the population-based Shanghai Cancer Registry. Medical abstracts were collected from hospitals to confirm the diagnosis for every new cancer case. For those subjects who died, copies of their death certificates were collected from the Shanghai vital statistics unit. By July 10th 2003, the 18,244 original participants in the cohort contributed 247,644 person-years of follow-up. Follow-up was lost for only 405 subjects (2.2%).

The BMI was calculated using self-reported usual adult weight in kilograms divided by the square of self-reported height in meters (kg/m^2). We classified cohort members into five categories of BMI according to the quintile cut-off points. Relative risks (RRs) were used to measure the association between lung cancer risk and BMI. Using the lowest quintile of BMI as reference, we calculated the relative risks of lung cancer for other categories of BMI after adjustment for age, educational level, cigarette smoking and history of emphysema. Cox proportional hazards regression was used to estimate RRs and their corresponding 95% confidence intervals. To test for a linear trend across BMI categories, an equally-spaced ordinal variable for five BMI categories was included in the regression model. All P-values are two-sided. The histologic subtypes were grouped as follows: squamous carcinoma of the lung, adenocarcinoma of the lung, and all others/unkown subtypes.

RESULTS

At recruitment, 50% of the cohort members were current smokers, 7% were former smokers, and the remaining 43% had never smoked. Of the study subjects, 43% drank alcoholic beverages regularly and the other 57% were non-drinkers. By July 10^{th}, 2003, 467 incidence lung cancers in the cohort were identified.

As shown in Table 1, the risk of lung cancer was negatively associated with the level of education. Compared with subjects without higher than primary school education, those with middle or high school education had a 20% reduced risk of lung cancer, and those with college education had a 30% reduced risk of lung cancer (RR = 0.7, 95%CI: 0.5 ~1.0, P for trend= 0.03). Compared with those who never smoked, former smokers had a 3-fold increased risk of lung cancer (RR = 3.1, 95%CI: 1.9 ~ 4.8), current smokers had a statistically significant 6-fold increased risk of lung cancer after adjustment for age (RR=6.4, 95%CI: 4.8~8.5). Similarly, smoking in pack-years was also associated with increased lung cancer risk(*P* for trend< 0.01). No association was found between consumption of alcohol and risk of lung cancer. Compared with those without a history of emphysema, those with a history of emphysema had a 2-fold increased risk of lung cancer after adjustment for age and pack-years of smoking (RR = 1.8, 95% CI: 1.3 ~2.5). Pulmonary tuberculosis and asthma might slightly increase the risk to develop lung cancer(RR=1.1, 95%CI: 0.9~1.4; RR=1.2, 95%CI: 0.8~1.8, respectively).

Firstly, we examined the association of body mass index with lung cancer risk of all histologic subtypes combined. Table 2 shows that increasing BMI was associated with decreasing risk of lung cancer. After adjustment for age, educational level, pack-years of smoking, men in the highest quintile of BMI were at a 40% lower risk of developing lung cancer than were men in the lowest quintile (RR= 0.6, 95%CI: 0.5~0.9). After stratification by smoking status, the inverse association between BMI and risk of lung cancer was still observed among current smokers, the relative risks across the quintiles were 1.0, 0.8, 0.8, 0.8 and 0.7, respectively (*P*-trend = 0.03). However, among non-smokers the lung cancer risk across increasing BMI quintiles displayed no clear pattern: compared with men in the lowest quintile, the relative risks were 0.7, 1.0, 1.2 and 0.7, respectively, for each succeeding quintile. To evaluate whether undiagnosed lung cancer cases during the baseline survey affected the body weight reported at recruitment, analyses were performed in two ways: 1) with all years of follow-up and lung cancer cases included and 2) with the first two years of follow-up as well as lung cancer cases identified during the first two years excluded. Risk estimates were altered only slightly when the first two years of follow-up as well as lung cancer cases diagnosed in the first two years were excluded. Thus,

Table 1. Age- and smoking-adjusted associatioin of educational level, lifestyle and medical historty with lung cancer risk in the Shanghai middle-aged men cohort study, 1986-2003

Varibale	Lung cancer cases	Person-years	Age-adjusted RR(95%CI)*	Smoking-adjusted** RR(95%CI)
Educational level				
≤primary school	212	68.249	1.0	1.0
middle school	127	72.568	0.6(0.5-0.8)	0.8(0.6-0.9)
high school	83	58.919	0.6(0.4-0.8)	0.8(0.6-1.1)
≥college	45	47.908	0.4(0.3-0.6)	0.7(0.5-1.0)
			P trend<0.01	*P* trend=0.03
Smoking status at baseline				
never	53	107.939	1.0	
former	29	16.041	3.1(1.9-4.8)	
current	385	123.664	6.4(4.8-8.5)	
Pack-years of smoking				
none	53	107.939	1.0	
1-19	78	63.517	2.7(1.9-3.8)	
20-39	191	55.699	6.9(5.1-9.3)	-
40+	145	20.489	11.6(8.5-16.0)	
			P trend<0.01	
Alcohol consumption(gram per day)				
never	224	142.038	1.0	1.0
1-19	79	49.978	1.0(0.8-1.4)	0.8(0.6-1.1)
20+	164	55.628	1.7(1.4-2.1)	1.0(0.8-1.3)
			P trend<0.01	*P* trend=0.96
Pulmonary tuberculosis				
no	380	205.213	1.0	1.0
yes	87	42.431	1.0(0.8-1.3)	1.1(0.9-1.4)
Asthma				
no	438	239.176	1.0	1.0
yes	29	8.468	1.7(1.2-2.4)	1.2(0.8-1.8)
Emphysema				
no	421	238.431	1.0	1.0
yes	46	9.213	2.4(1.7-3.2)	1.8(1.3-2.5)

*RR: relative risk; CI: confidence interval. **Adjusted for age and pack-years of smoking

this paper presents only those analyses that included all years of follow-up.

Then, we investigated the associations between BMI and risk of specific histologic subtypes of lung cancer. Among the 467 lung cancer cases there were 149 cases of squamous cell carcinoma, 117 cases of adeno-carcinoma, and 47 cases of other types (including small-cell carcinoma, large-cell carcinoma, etc.), the 154 remaining cases were not specified. As shown in Table 3, after adjustment for age, educational level, pack-years of smoking and history of emphysema, men in the upper quintiles of BMI were found to be at decreased risks of both squamous cell carcinoma and adenocarinoma. Compared with men in the lowest quintile of BMI, men in the highest quintile of BMI had statistically significant reduced risks of both squamous cell carcinoma and adenocarcinoma (RR= 0.6, 95% CI: 0.3 ~1.0). Furthermore, the trend of decreasing risk of lung cancer across increasing BMI quintiles was more pronounced for adenocarcinoma than squamous cell carcinoma (*P*-trend =0.03 for adenocarcinoma and P-trend=0.09 for squamous cell

Table 2. The assoaciation of body mass index with lung cancer risk by smoking status in Shanghai middle-aged men cohort study, 1986–2003

Body Mass Index(kg/m²)	Lung cancer cases	Person-years	RR(95%CI)[a]	RR(95%CI)
ALL subjects				
<19.5	127	48.954	1.0	1.0[b]
19.5-21.1	97	49.341	0.8(0.6-1.0)	0.8(0.6-1.1)
21.2-22.7	95	51.818	0.7(0.5-0.9)	0.8(0.6-1.1)
22.8-24.5	81	47.630	0.7(0.5-0.9)	0.8(0.6-1.1)
24.6-	67	49.901	0.5(0.4-0.7)	0.6(0.5-0.9)
			P trend<0.01	*P* trend=0.01
Current smokers				
<19.5	111	27.370	1.0	1.0[b]
19.5-21.1	82	27.019	0.8(0.6-1.0)	0.8(0.6-1.1)
21.2-22.7	77	25.985	0.8(0.6-1.0)	0.8(0.6-1.1)
22.8-24.5	65	21.978	0.7(0.5-1.0)	0.8(0.6-1.1)
24.6-	50	21.313	0.6(0.4-0.8)	0.7(0.5-0.9)
			P trend<0.01	*P* trend=0.03
Never smokers				
<19.5	11	19.024	1.0	1.0[c]
19.5-21.1	7	19.656	0.6(0.2-1.6)	0.7(0.3-1.7)
21.2-22.7	12	22.762	0.9(0.4-2.0)	1.0(0.4-2.2)
22.8-24.5	14	22.275	1.1(0.5-2.4)	1.2(0.5-2.7)
24.6-	9	24.223	0.6(0.3-1.5)	0.7(0.3-1.6)
			P trend=0.67	*P* trend=0.82

a: Adjusted for age b: Adjusted for age, educational level, pack-years of smoking and history of emphysema

c: Adjusted for age, educational level and history of emphysema

The results for former smokers is not reliable due to too few lung cancer cases (data not shown)

carcinoma). For other subtypes and those not specified, no clear pattern was observed.

DISCUSSION

A reduced risk of lung cancer associated with higher levels of BMI has been reported in both case control and cohort studies conducted in western countries. However, in China, the relationship between BMI and the risk of lung cancer has not been fully explored[9-11]. This is the first prospective study to evaluate the relationship between BMI and lung cancer risk among Chinese men. A cohort study conducted in Finland, which involved 25,994 male participants, showed that there was a significant inverse gradient between body mass index and the incidence of lung cancer. After adjustment for age, smoking, social class, self-perceived general health, history of stress symptoms and chronic cough, the relative risks of lung cancer were 1.0, 1.4, 1.5 and 1.8 (*P* for trend less than 0.001), respectively, from the highest to the lowest quartiles of body mass index [5]. Also, the Iowa Women's Health Study in the U.S.A, a prospective cohort study of 41,836 Iowa women, reported that lung cancer risk was inversely associated with body mass index. Compared with women in the lowest quintile of BMI, women in the highest quintile had a statistically significant reduced risk of lung cancer (RR=0.4, 95% CI: 0.3~0.7, *P* for trend<0.001) after accounting for established risk factors. The association between BMI and lung cancer risk persisted among current smokers, former smokers, and even among those who never smoked after stratification by smoking status [6].

It is well known that smoking is an established risk factor for lung cancer. On the other hand, smokers tend to be leaner than non-smokers due to the higher metabolic rate among smokers [12-14]. The inverse association of body mass index with lung cancer might stem from incomplete adjustment for the effects of cigarette smoking. To account for the effects of smoking as completely as possible, we stratified the analysis by smoking status. The inverse association between BMI and lung cancer risk persisted among current smokers after adjustment for pack-years of smoking, however, among those who never smoked no association was found between BMI and lung cancer risk, and among former smokers there were too few lung cancer cases to permit such an analysis. More lung cancer cases are needed to draw valid conclusions among those who never smoked and former smokers.

Table 3. The association of body mass index and lung cancer, by cell type, Shanghai middle-aged men cohort study, 1986-2003

Body Mass Index(kg/m²)	cases	RR(95%CI)ᵃ	RR(95%CI)ᵇ
Squamous cell carcinoma			
<19.5	43	1.0	1.0
19.5-21.1	28	0.7(0.4-1.1)	0.7(0.4-1.1)
21.2-22.7	34	0.8(0.5-1.2)	0.9(0.6-1.4)
22.8-24.5	24	0.6(0.4-1.0)	0.7(0.4-1.2)
24.6-	20	0.4(0.3-0.8)	0.6(0.3-1.0)
		P trend<0.01	*P* trend=0.09
Adenocarcinoma			
<19.5	35	1.0	1.0
19.5-21.1	27	0.8(0.5-1.3)	0.8(0.5-1.3)
21.2-22.7	19	0.5(0.3-0.9)	0.6(0.3-1.0)
22.8-24.5	18	0.5(0.3-0.9)	0.6(0.3-1.1)
24.6-	18	0.5(0.3-0.9)	0.6(0.3-1.0)
		P trend<0.01	*P* trend=0.03
Others and unknown			
<19.5	49	1.0	1.0
19.5-21.1	42	0.9(0.6-1.3)	0.9(0.6-1.4)
21.2-22.7	42	0.8(0.5-1.2)	1.0(0.6-1.5)
22.8-24.5	39	0.8(0.5-1.3)	1.1(0.7-1.6)
24.6-	29	0.6(0.4-0.9)	0.8(0.5-1.2)
		P trend=0.02	*P* trend=0.48

a: Adjusted for age

b: Adjusted for age, educational level, pack-years of smoking and history of emphysema

Because weight loss is usually observed among lung cancer patients, undiagnosed lung cancer at the baseline of the survey might affect the body weight reported, leading to the inverse association between BMI and lung cancer. To exclude this possibility, the first two or three years of follow-up have often been excluded from analysis in prospective cohort studies. In this study, similar results were obtained when we restricted the analysis to lung cancer cases and person-years of follow-up that occurred at least two years after enrollment.

Our results showed the trend of decreasing risk of lung cancer across increasing BMI quintiles was more apparent for adenocarcinoma than squamous cell carcinoma. This is probably because smoking is the primary risk factor for squamous cell carcinoma, while for adenocarcinoma there may have other important causes. Earlier studies suggested that adenocarcinoma was least closely associated with smoking and would have the highest probability of being influenced by non-tobacco-related causes [15,16].

One explanation of the observed inverse association between BMI and lung cancer risk is that an increased metabolic rate associated with leanness could, in turn, be associated with excess lung cancer via accelerated cell turnover in the lung [1]. Some investigators hypothesized that major action of various risk factors for human cancer is to increase cell division [17]. Another possibility is that leanness may be associated with decreased levels of nutrients that may play a protective role against lung cancer. The National Health and Nutrition Examination Survey data indicate that lean men had lower levels of vitamin A and carotene than did obese men [18]. In addition, the hormonal level associated with the body fatness may also play role in the etiology of lung cancer [8]. Further studies are needed to determine whether the inverse association of BMI and lung cancer risk is due to the influence of factors associated with obesity or to a biologic effect of obesity itself.

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