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Body mass index and lung cancer risk in never smokers

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Background. *A relationship between body mass index (BMI) and lung cancer risk in never smokers has not been reported precisely. To evaluate the risk of lung cancer associated with BMI in never smokers, we conducted a case-control study.*

Methods. *The relationship between BMI and the risk of lung cancer in never smokers was investigated in a study of 204 lung cancer cases and 398 controls admitted between 1987 and 2005. Controls were selected from hospitalized age-matched never-smoking patients with non-malignant respiratory disease.*

Results. *When compared with BMI of the leanest group (BMI<20.8) in men, no inverse association between BMI and lung cancer was observed after the adjustment for age (the second BMI group: BMI≥ 20.8 to < 22.9; p=0.683, the third BMI group: BMI≥ 22.9 to < 24.9; p=0.745, and the highest BMI group: BMI≥ 25.0; p=0.327). Similarly, no association in women was found between BMI and lung cancer in these three BMI groups (the second group, p=0.639; the third group, p=0.667; the highest group, p=0.978) when compared with that of the leanest BMI group.*

Conclusions. *Our present study indicated that the association between leanness and the risk of lung cancer might be influenced by other factors such as smoking.*

Key words: lung neoplasms – epidemiology; risk factors; adenocarcinoma; body mass index; smoking

Introduction

An elevated risk of lung cancer associated with lower levels of body mass index (BMI) has been reported in previous studies.[1-9] However, the interpretation of the association between low BMI and lung cancer is complicated by the fact that weight loss may be a sign of smoking. In general, smokers tend to be lighter than non-smokers,[1, 10-15] and it is believed that nicotine is responsible for the effect of smoking on body weight because nicotine appears to increase the metabolic rate.

We have recently performed a case-control study of subjects participating in a mass-screening program and found an increased risk of lung cancer for lower BMI in male patients.[16] Most of them were current smokers.[16] However, the inverse

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association between the risk of lung cancer and BMI was not found in female patients. This was inconsistent with the results of previous studies.[1-9] The difference between the findings of previous studies and our own was most probably due to difference in study population. The subjects in previous studies were symptomatic, but all the subjects in our recent study were asymptomatic preclinical patients.[16] In addition, there were higher proportions of never-smoking women and lung adenocarcinoma in our study, and the different results might also be influenced by them.

Whereas, it remains an unsettled question whether there is an inverse association between the risk of lung cancer and BMI among never smokers, especially in those with lung adenocarcinoma. In order to evaluate the association between BMI and the risk of lung cancer in patients who never smoked, we conducted a hospital-based case-control study. In this study, we also estimated the association between BMI and the risk of lung adenocarcinoma in never-smokers.

Methods

Study Design

A hospital-based case-control study was conducted from January 1987 to September 2005 in Respiratory Division of Tsukuba University Hospital, to explore the risk of lung cancer associated with lower levels of BMI at the time of initial diagnosis.

Patients

All cases and controls were recruited at Tsukuba University Hospital and were identified from the medical record. All patients who were histopatologically confirmed to have lung cancer were included in this analysis. Pathological diagnoses were based on the 1999 WHO classification of lung neoplasms. Only lung cancer patients as well as control subjects, who had never smoked and without occupational or domestic exposure to other recognized carcinogens, were included in this study. The hospital-based controls matched by age (±5 yr), gender, and time of hospitalization were recruited from our division, including inpatients with non-malignant respiratory diseases. Patients with other cancer at any site were excluded. This study was approved by the institutional ethics committee of University of Tsukuba.

Statistical analysis

BMI was calculated from body height and weight, which were measured and reported by nurses at the time of admission, using the formula for Quetelet's index (expressed in kg/m^2). BMI was categorized into four levels on the basis of the distribution in the total study population ($BMI < 20.8$, leanest; $20.8 \leq BMI < 22.9$, second; $22.9 \leq BMI < 25.0$, third; $25.0 \leq BMI$, highest), which was the same category as our previous study based on the results of community mass screening.[16] We used the leanest category ($BMI < 20.8$) as the reference group for analyses.

Logistic regression was used to examine the effect of BMI on lung cancer risk. Results with a p value less than 0.05 were regarded as significant. The software package SSPE (SSPE Inc., Chicago, IL, USA) and Microsoft Excel (Microsoft, Redmond, WA, USA) were used to perform the analyses stated above.

Results

During the study period, 919 patients with primary lung cancer were diagnosed in our division. Among them, a total of 204

(22.2 %) documented never-smokers with primary lung cancer were registered.

Table 1 shows the characteristics of 204 lung cancer cases. Three-fourths of all cases were women. Although the age range for this study was between 22 and 85 years, median age of the male and female patients was 64 and 67 years, respectively. Twenty-four (64.9 %) of 37 male patients, and 151 (90.4 %) of 167 female patients had lung adenocarcinoma. There was no patient with small cell lung cancer in both genders (Table 1). Among the 204 patients, 81 had stage IA-IIIA, 35 had stage IIIB, and 88 had stage IV disease.

Table 1. Characteristics of 204 lung cancer patients

Characteristics	Men	Women
Number of patients	37	167
Age (median, range), Yr	64, 22 – 80	67, 35 – 85
Histologic types		
Adenocarcinoma	24	151
Squamous cell carcinoma	10	9
Large cell carcinoma	1	4
Others	2	3
Stage		
IA – IIIA	11	70
IIIB	11	24
IV	15	73

Table 2 shows odd ratios and 95 percent confidence intervals for the association between the risk of lung cancer and lower levels of BMI at the time of diagnosis with lung cancer. When compared with BMI of the leanest group (BMI<20.8) in men, no inverse association between BMI and lung cancer was observed after the adjustment for age (the second BMI group: BMI≥ 20.8 to < 22.9; p = 0.683, the third BMI group: BMI≥ 22.9 to < 24.9; p = 0.745, and the highest BMI group: BMI≥ 25.0; p = 0.327). In women, no association was found between BMI and lung cancer in these three BMI group (the second BMI group, p = 0.639; the third BMI group, p = 0.667; the highest BMI group, p = 0.978) when compared with that of the leanest BMI group. In male adenocarcinoma, the second BMI group (p=0.967), the third BMI group (p=0.310), and the highest BMI group (p = 0.378) did not exhibit higher odd ratio than that of the leanest BMI group after the adjustment for age.

As above mentioned, 175 of 204 patients were adenocarcinomas. There were too-few

Table 2. Association of BMI with lung cancer

BMI	Case Patients, No.	Control Subjects No.	OR	95% CI	p-value
Men					
< 20.8	13	32	1.0		
20.8 – 22.8	10	20	0.8	0.3 – 2.2	0.683
22.9 – 24.9	5	10	0.8	0.2 – 2.8	0.745
≥ 25.0	9	13	0.6	0.2 – 1.7	0.327
Women					
< 20.8	67	131	1.0		
20.8 – 22.8	43	75	0.9	0.6 – 1.4	0.639
22.9 – 24.9	23	51	1.1	0.6 – 2.0	0.667
≥ 25.0	34	66	1.0	0.6 – 1.7	0.978

OR: odd ratio; CI: confidence interval

Table 3. Association of BMI with lung adenocarcinoma

BMI	Case Patients, No.	Control Subjects No.	OR	95%CI	p-value
Men					
< 20.8	8	26	1.0		
20.8 – 22.8	6	19	1.0	0.3 – 3.5	0.967
22.9 – 24.9	4	6	2.2	0.5 – 9.6	0.310
≥ 25.0	6	11	1.7	0.5 – 6.3	0.378
Women					
< 20.8	61	120	1.0		
20.8 – 22.8	36	67	1.1	0.6 – 1.8	0.831
22.9 – 24.9	22	46	0.9	0.5 – 1.7	0.841
≥ 25.0	32	58	1.1	0.6 – 1.8	0.762

OR: odd ratio; CI: confidence interval

patients to stratify the histologic subtypes in both men and women, therefore, we examined the association only in adenocacinoma cases (Table 3). In men, the second BMI group (p = 0.967), the third BMI group (p = 0.310), and the highest BMI group (p = 0.378) did not exhibit higher odd ratio than that of the leanest BMI group after the adjustment for age. In women, no association was found between BMI and lung cancer in these three BMI groups (the second BMI group, p = 0.831; the third BMI group, p = 0.841; the highest BMI group, p = 0.762) when compared with that of leanest BMI group. For adenocarcinoma, therefore, the inverse association was not observed in both genders.

Discussion

An inverse gradient between BMI and the incidence of lung cancer has been reported in several case control and cohort studies.[1-9] However, the interpretation of the association between low BMI and lung cancer is complicated by the fact that low BMI may be influenced by other factors such as smoking. It is possible that smokers tend to have lighter body weight, possibly a consequence of the metabolic effects of nicotine.

In order to investigate the association between lower levels of BMI and the risk of lung cancer in never-smoking patients, we, therefore, conducted a hospital-based case-control study.

The results of the present study indicate two important points. The first point of importance is that we found the absence of an inverse gradient between BMI and the risk of lung cancer in never-smoking female patients, which was consistent with our recent study of subjects participating in a mass screening program.[16] Interestingly, Rauscher *et al* reported an elevated risk of lung cancer associated with not "low" but "high" levels of BMI in non-smoking female patients.[17] The difference between the findings of Rauscher and our own was probably due to different study populations. All patients and controls in our study were never-smokers. On the other hand, however, not all subjects in the study by Rauscher *et al* were never-smokers.[17] They included 188 patients who haven't smoked more

than 100 cigarettes in their lifetime and 224 patients who haven't smoked more than 100 cigarettes during the last 10 years.[17] Therefore, there was a possibility that the results were influenced by the residual effects of smoking.

The majority of published results investigating the association between lower BMI and lung cancer risk were based on studies conducted in Western countries where the prevalence of obesity is high.[2,8,17] The difference in categorized BMI levels might also influence the difference between the findings of previous authors and our own. The second important point is that both thin male and female never smokers did not have an increased risk of lung adenocarcinoma. The results of the present study indicate that lower BMI is not significantly associated with the risk of lung adenocarcinoma. Some lung adenocarcinomas in never smokers can arise without the growth promoting effects of the carcinogens present in cigarette smoke,[18] one can postulate that the mechanism of carcinogenesis of adenocarcinomas arising in smokers and never-smokers may be different, and these distinct tumorigenic mechanisms can imply differences in tumor biology, demographic characteristics as Brownson and colleague suggested.[19]

Although we showed the above-mentioned two findings of importance, we must acknowledge the limitation of this study. First, it was a hospital-based case-control study. As with any hospital-based case-control study, it has been suggested that such case-control studies may reflect the presence of disease other than lung cancer in control subjects.[2] The second limitation of the present study is that it included only small number of patients and controls in a single institute. The third, 123 (60.3%) of 204 patients had locally advanced or metastatic lung cancer and stage of the disease would be important in that more advanced disease might itself be associated with weight loss. It is interesting to know the association between BMI and the risk of lung cancer among patients with early disease, but we could not evaluate the association because of small number of study population. The last, we could not examine the impact of environmental tobacco smoke (ETS) exposure on this association. An accurate assessment of the amount of ETS exposure in never smokers is necessary for determining the lung cancer risks associated with ETS exposure.

It is well known that smokers tend to be leaner than non-smokers.[1,10-15] Several previous studies have reported an association between leanness and risk of lung cancer, mainly among smokers,[12,14] and among men with smoking-related disease.[14] Inconsistence with previous studies,[1-9] our results indicated the possibility that the previously reported association between leanness and the risk of lung cancer might be influenced by other factors such as smoking. A large cohort study will be needed to confirm the current results.

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