Tohoku J. Exp. Med., 2020, **251**, 51-59

Association between Adult Height and Risk of Lung Cancer Incidence among Japanese Men: The Miyagi Cohort Study

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It is already known that adult height is a factor associated with an increased risk of colon cancer and postmenopausal breast cancer, pancreatic cancer, premenopausal breast cancer, and ovarian cancer. However, the association between adult height and lung cancer incidence remains unclear. The purpose of the present study was to examine the association between adult height and the risk of lung cancer incidence in the Japanese population. We analyzed data for 43,743 men and women who were 40-64 years old at the baseline in 1990. We divided the participants into quintiles based on height at the baseline. Cox proportional hazards analysis was used to estimate the multivariate hazard ratios (HRs) and 95% confidence intervals (CIs) for the incidence of lung cancer according to adult height, after adjustment for potential confounders. We identified 1,101 incident case of lung cancer during 24.5 years of follow-up. The multivariate HRs and 95% CIs for the highest category relative to the lowest were 1.48 (1.15-1.91) in men and 1.35 (0.91-1.99) in women. Furthermore, the association between adult height and the incidence of lung cancer was found the significant increased risk among ever smokers in men, but not never smokers. We also observed that adult height tend to be associated with an increased risk of small cell lung cancer and squamous cell carcinoma. This prospective cohort study has demonstrated a positive association between adult height and the risk of lung cancer incidence among men, especially those who have ever smoked.

Keywords: adult height; incidence; Japanese; lung cancer; prospective cohort study
Tohoku J. Exp. Med., 2020 May, **251** (1), 51-59.

Introduction

In Japan, an estimated 125,424 people (83,790 men, 41,634 women) were newly diagnosed with lung cancer in 2016 and 74,328 deaths (52,401 men, 21,927 women) were recorded in 2018, accounting for 12.6% of all cancer incidence and 19.9% of all-cancer death. Age-standardized incidence rates (standard population: world population) for males and females have been recorded as 45.1 and 19.2, respectively (Cancer Information Service, National Cancer Center, Japan 2019). Histological type is classified into three major types (adenocarcinoma, small cell carcinoma, squamous cell carcinoma) and others. According to the Osaka Cancer Registry, in lung cancer cases from 1999 to 2003, adenocarcinoma accounted for 43% of male lung cancers and 67% of female lung cancers, squamous cell carcinoma accounted for 35% of male lung cancers and 16% of female lung cancers, and small cell carcinoma accounted for 16% of male lung cancers and 12% of female lung cancers (Toyoda et al. 2008).

Adult height is influenced by nutritional status during the embryonic period and childhood, and also by the dynamics of insulin, insulin-like growth factor-1(IGF-1), and other physiologically relevant molecules (Ben-Shlomo et al. 2003; Perkins et al. 2016). Adult height is also considered an important predictor of life health events

Received January 15, 2020; revised and accepted April 30, 2020. Published online May 28, 2020; doi: 10.1620/tjem.251.51.
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(Renehan et al. 2004; Paajanen et al. 2010). Many epidemiological studies have shown that adult height is significantly associated with an increased risk of cancers such as colon, postmenopausal breast, pancreatic, and ovarian cancers (Aune et al. 2012; Boursi et al. 2014; Zhang et al. 2015; World Cancer Research Fund International 2018). However, the results of previous studies focusing on the association between adult height and lung cancer incidence have been conflicting (Hebert et al. 1997; Gunnell et al., 2003; Sung et al. 2009; Green et al. 2011; Tang et al. 2012; Kabat et al. 2013, 2014; Walter et al. 2013; Khankari et al. 2016).

Two prospective American studies have reported a weakly positive association between adult height and lung cancer incidence in men and women (Kabat et al. 2013, 2014), whereas others have reported no such association (Hebert et al. 1997; Gunnell et al. 2003; Green et al. 2011; Walter et al. 2013). Only two studies have reported an association between adult height and the risk of lung cancer incidence in the Asia region (Sung et al. 2009; Tang et al. 2012). Those studies, conducted in Korea and China, concluded that adult height was associated with a risk of lung cancer in men, but not in women (Sung et al. 2009; Tang et al. 2012). A meta-analysis including eleven prospective cohort studies has also demonstrated a significantly increased risk of lung cancer incidence among taller men (Khankari et al. 2016). However, no study has yet examined the association between adult height and the risk of lung cancer in the Japanese population, which is characterized by a generally shorter stature in comparison with Western populations.

Additionally, cigarette smoking is a well-known major risk factor for lung cancer (Centers for Disease Control and Prevention 2004; World Health Organization 2012), and the proportions of smokers differ among countries (Organisation for Economic Cooperation and Development 2019).

Variations are seen in age-standardized incidence rates, histological type of lung cancer, and percentage of smokers by country (Nakamura and Saji 2014; Cheng et al. 2016). Hence, the association between adult height and lung cancer risk could potentially vary given the differences in histological types and percentages of smokers between Japanese and their Western counterparts. Few previous studies have investigated whether the association between adult height and the risk of lung cancer differs according to smoking status.

The purpose of the present study was to investigate the association between adult height and lung cancer incidence among the Japanese population in the context of smoking status.

Materials and Methods

Study population

We used data from the Miyagi Cohort Study, the design of which has been described in detail elsewhere (Fukao et al. 1995; Kuriyama et al. 2004; Sugiyama et al. 2010). Briefly, between June and August 1990, we delivered a self-administered questionnaire to men and women aged 40-64 years who were living in 14 municipalities, randomly selected from among 62 municipalities, in Miyagi Prefecture, northeastern Japan. The questionnaire included items on demographic and lifestyle factors.

Among 51,921 eligible subjects, 47,605 responded to the questionnaire (response rate: 91.7%). We excluded one subject who had withdrawn from the study area before the start of follow-up, leaving 47,604 subjects (22,836 men and 24,768 women) as the study cohort. For the present analysis, we excluded participants who had a history of cancer (n = 1,191), those for whom data on height (n = 2,488) and weight (n = 220) at the baseline were missing, and those who reported extreme values of height (sex-specific cutoffs for highest 0.5% and lowest 0.5%; n = 32). This left a final total of 43,743 subjects (21,083 men and 22,660 women) for the present study.

Exposure data

We collected data at the baseline for each individual using a self-administered questionnaire inquiring about age, height, weight, medical history, family history of any cancer, job status, marital status, education, and health-related lifestyle factors such as smoking status, alcohol consumption, and time spent walking per day.

We divided the participants into quintiles based on height at the baseline for men and women, respectively (men; ≤ 159.9 cm, 160.0-162.9 cm, 163.0-165.0 cm, 165.1-169.9 cm, and ≥ 170.0 cm, women; ≤ 148.0 cm, 148.1-150.4 cm, 150.5-153.0 cm, 153.1-156.9 cm, and ≥ 157.0 cm). The mean body height (standard deviation) of the participants was 164.1 (± 6.2) cm for men and 152.3 (± 5.4) cm for women.

The validity of self-reported body height and body weight at study entry had been reported previously. Among the study subjects, 7,153 had their body height and weight measured during health examinations provided by the local government in 1990. The Pearson's correlation coefficient (r) for body height was 0.85, and that for body weight was 0.97 (Kuriyama et al. 2004).

Follow-up

We followed up the participants from June 1, 1990 to December 31, 2014. The end point of our analysis was the date of diagnosis of lung cancer, death, emigration, or the end of the follow-up period, whichever occurred first. In order to follow-up the subjects for migration and mortality, we established a Follow-up Committee that comprised the Miyagi Cancer Society, the Community Health Divisions of all 14 municipalities, the Department of Health and Welfare of the Miyagi Prefectural Government, and the Division of Epidemiology, Tohoku University Graduate School of Medicine. The Committee periodically reviewed the Residential Registration Records of all municipalities, which allowed us to identify subjects who had either died or emigrated during the observation period. We discontinued the follow-up of participants who had moved from the study municipalities, because the Committee was unable to review the Residential Records from outside the study area. We also ascertained incident cases of cancer via computer link with the Miyagi Prefectural Cancer Registry, which covers the study area. The Miyagi Prefectural Cancer Registry is one of oldest and most accurate population-based cancer registries in Japan (Bray et al. 2017). Cancer cases were registered from clinics and hospitals (inpatients and outpatients), radiology and pathology departments, autopsy records, mass screening records and death certificates. Cancer incidence data were coded according to the International Classification of Diseases for Oncology, 3nd version (ICD-O-3) as lung cancer (C33-C34). Lung cancer cases included the following diseases: Adenocarcinoma (ICD-O-3 codes 8140/3, 8550/3, 8260/3, 8250/3, 8252/3, 8253, 8254/3, 8230/3, 8255/3, 8333/31, 8480/3, 8470/3, 8490/3, 8310/3), Small cell lung cancer (ICD-O-3 codes 8041/3, 8045/3), Squamous cell carcinoma (ICD-O-3 codes 8070/3, 8070/2, 8052/3, 8084/3, 8073/3, 8083/3), and other cases. Further, other cases were included the following diseases: Large cell carcinoma (ICD-O-3 codes 8012/3, 8013/3, 8123/3, 8082/3, 8310/3, 8014/3), Adenosquamous carcinoma (ICD-O-3 codes 8560/3, 8033/3, 8022/3, 8032/3, 8031/3, 8980/3, 8972/3), Carcinoid tumor (ICD-O-3 codes 8240/3, 8249/3), Carcinomas of salivary-gland type (ICD-O-3 codes 8430/3, 8200/3). In this cancer registry, the proportions of individuals registered by death certificate only (DCO) for trachea, bronchus, and lung cancer (C33-C34) were 12.4% for men and 17.1% for women during the period 2008-2010 (Bray et al. 2017).

Ethical issues

We considered the return of a signed self-administered questionnaire to imply each subject's consent to participate. The study protocol was approved by the Institutional Review Board of Tohoku University Graduate School of Medicine (approved number: 2014-1-838).

Statistical analysis

We prospectively counted person-years of follow-up for each subject. Next, we used Cox proportional hazards regression analysis to estimate the multivariate-adjusted hazard ratio (HR) and 95% confidence interval (95% CI) for incidence of lung cancer in relation to the lowest category of adult height as the reference group in both men and women. Then, we calculated the HRs and 95% CI for lung cancer incidence per 10 cm increase. We also conducted analysis stratified by smoking status (never smoker, or ever smoker), because current smokers would have a markedly higher risk of developing lung cancer than those who had never smoked. Moreover, we examined the incidence of lung cancer classified according to histological type (adenocarcinoma, small cell carcinoma, squamous cell carcinoma or other)

We considered the following variables as potential confounders: age (continuous variable), weight at the baseline (quintiles), family history of any cancer (yes or no), level of education (junior high school or less, high school, or college/university or higher), smoking status (never smoker, ex-smoker, current smoker 1-19 cigarettes/day, or current smoker ≥ 20 cigarettes/day), drinking status (never drinker, ex-drinker, current drinker), time spent walking per day (≤ 0.5 h, 0.5-1.0 h, or ≥ 1 h), vegetable consumption (quartiles, g/day), and fruit consumption (quartiles, g/day). These items were chosen as covariates because previous studies had shown that they are factors related to the incidence of lung cancer.

The p values for the test of linear trend (p-trend) were calculated using the height category as a continuous variable. The significance of multiplicative interactions between adult height and all confounders was examined using cross-product terms in the regression model.

All p values were two-sided, and differences at $p < 0.05$ were considered statistically significant. All statistical analyses were performed using the SAS statistical software package, version 9.4 (SAS Institute Inc, Cary, NC, USA).

Results

Table 1 shows the sex-specific baseline characteristics of the study participants according to the adult height quintile categories. For both men and women, participants in the higher adult height category tended to be younger, had a higher education level, and were more likely to be current smokers and drinkers. Furthermore, they were also less likely to walk for more than 1 hour per day. There were no inter-group differences in mean body mass index (BMI) or family history of cancer.

A total of 941,173 person-years were accrued, and 1,101 incident cases of lung cancer (798 men and 303 women) were observed. Table 2 shows the HRs and 95% CIs for the risks of lung cancer incidence according to height quintiles. We observed a positive association between adult height and the risk of lung cancer in men. In men, the multivariate HRs (95% CIs) for men in the other quintile groups versus the lowest quintile group were 1.17 (0.94-1.45) for body height 160.0-162.9 cm, 1.06 (0.85-1.32) for body height 163.0-165.0 cm, 1.27 (1.00-1.63) for body height 165.1-169.9 cm, and 1.48 (1.15-1.91) for body height ≥ 170.0 cm, respectively (p-trend < 0.01). Also, our study demonstrated that a 26% increased risk of lung cancer was associated with every 10 cm increase in body height. Similarly, for women, there was a positive association between adult height and the risk of lung cancer, but this was not significant. In women, the multivariate HRs (95% CIs) for women in the other quintile groups versus the lowest quintile group were 1.19 (0.84-1.69) for body height 148.1-150.4 cm, 1.10 (0.77-1.58) for body height 150.5-153.0 cm, 1.39 (0.96-2.00) for body height 153.1-156.9 cm, and 1.35 (0.91-1.99) for body height ≥ 157.0 cm, respec-

Table 1. Baseline characteristics of the subjects according to adult height.

	Men					Women				
	Height (cm)					Height (cm)				
	≤ 159.9	160.0-162.9	163.0-165.0	165.1-169.9	≥ 170.0	≤ 148.0	148.1-150.4	150.5-153.0	153.1-156.9	≥ 157.0
Number	4,122	3,961	5,075	3,597	4,328	5,010	4,052	4,775	4,210	4,613
Age, year (mean ± SD)	55.4 ± 6.8	52.7 ± 7.3	51.5 ± 7.4	49.8 ± 7.4	48.5 ± 7.2	55.1 ± 6.8	53.3 ± 7.1	51.9 ± 7.3	50.8 ± 7.4	49.2 ± 7.1
BMI	23.6 ± 2.7	23.6 ± 2.7	23.6 ± 2.8	23.6 ± 2.8	23.4 ± 2.8	24.1 ± 3.3	23.9 ± 3.1	23.9 ± 3.1	23.6 ± 3.0	23.2 ± 3.1
Body weight (kg)	56.9 ± 6.8	61.1 ± 7.1	63.5 ± 7.5	66.1 ± 7.8	69.9 ± 8.6	51.0 ± 6.8	53.7 ± 7.0	55.3 ± 7.1	56.7 ± 7.2	59.2 ± 7.9
Education (%)										
College/university or higher	7.5	11.5	12.9	16.7	18.6	7.7	9.8	13.2	13.6	16.5
High school	33.4	40.7	44.1	47.1	48.8	36.6	43.7	45.9	48.9	50.2
Junior high school or less	51.9	42.2	38.0	31.6	27.6	49.0	40.0	35.9	32.6	27.8
Missing	7.3	5.7	5.0	4.6	4.9	6.7	6.6	5.1	5.0	5.5
Family history of cancer (%)										
No	74.5	73.5	75.3	74.4	74.4	73.3	72.5	72.3	71.9	71.2
Yes	25.5	26.5	24.8	25.6	25.6	26.7	27.5	27.7	28.1	28.9
Smoking (%)										
Never	20.6	19.1	17.8	16.7	16.4	61.7	64.8	68.1	69.8	68.9
Past	19.1	20.7	18.7	19.7	18.8	1.4	1.2	1.5	1.8	2.0
Current < 20/day	16.4	14.5	14.4	13.9	13.0	3.3	4.2	4.2	5.1	5.3
Current ≥ 20/day	35.6	39.5	43.2	45.5	46.7	1.4	1.6	1.8	1.8	2.7
Missing	8.3	6.2	5.9	4.3	5.0	32.2	28.3	24.4	21.6	21.1
Alcohol drinking (%)										
Never	17.1	15.8	15.6	13.8	13.3	56.8	57.6	58.4	56.9	55.2
Past	9.0	7.3	7.1	5.7	5.8	2.7	3.2	2.9	3.7	3.7
Current	70.8	74.8	75.8	79.3	79.4	16.7	18.5	21.1	23.5	26.1
Missing	3.1	2.1	1.6	1.2	1.5	23.7	20.7	17.7	16.0	15.1
Time spent walking (%)										
≥ 1 hour/day	46.0	44.6	41.4	39.6	38.0	43.7	40.7	41.6	39.7	39.9
0.5-1.0 hour/day	20.0	21.0	22.7	22.7	24.1	21.1	22.4	22.8	22.6	23.5
≤ 0.5 hour/day	23.6	27.0	29.4	32.2	32.5	23.2	26.0	26.7	29.7	29.8
Missing	10.5	7.4	6.5	5.5	5.4	12.0	10.9	9.0	8.0	6.7
Daily intake (median, g/d)										
Green and yellow vegetable	23.8	24.8	23.8	23.8	21.0	38.5	40.3	40.5	40.5	40.3
Fruits	66.5	81.2	81.2	81.2	81.2	113.1	119.2	141.7	141.7	141.7

SD, standard deviation.

tively (p-trend = 0.09).

Cigarette smoking is an established risk factor for lung cancer (Centers for Disease Control and Prevention 2004; World Cancer Research Fund International 2018). We further conducted analysis stratified by smoking status in order to assess whether the association between adult height and the risk of lung cancer differed between subjects who had never smoked and those who had ever smoked. Table 3 shows the multivariate-adjusted HR for lung cancer incidence according to smoking status in men. We consistently observed a positive association between adult height and the risk of lung cancer in ever smokers. For ever-smokers, the multivariate HRs (95% CIs) in the other quintile groups versus the lowest quintile group were 1.17 (0.94-1.47) for body height 160.0-162.9 cm, 1.05 (0.84-1.32) for body height 163.0-165.0 cm, 1.29 (1.00-1.67) for body height 165.1-169.9 cm, and 1.52 (1.17-1.98) for body height ≥ 170.0 cm, respectively (p-trend < 0.01). Also, our study demonstrated that a 29% increased risk of lung cancer was associated with every 10-cm increase in body height. For men who had never smoked, there was a tendency for those who were taller to have an associated risk of lung cancer (body height ≥ 170.0 cm; HR = 1.14, 95% CI: 0.39-3.35), although the association was not significant. However, no statistically significant effect modifications between adult height and smoking status were observed (p-value for interaction = 0.81). Table 4 shows the multivariate-adjusted HR for lung cancer incidence according to smoking status in women. However, we observed no association between adult height and the risk of lung cancer in both ever and never smokers.

Table 5 shows the multivariate-adjusted HR for lung cancer incidence according to histological types. We observed a positive association between adult height and

Table 2. Cox proportional hazard ratios (HRs) and 95% confidence intervals (CI) for Lung cancer incidence according to adult height.

	Men, Height (cm)						
	≤ 159.9	160.0-162.9	163.0-165.0	165.1-169.9	≥ 170.0	*p* for trend†	10-cm Increment
Number	4,122	3,961	5,075	3,597	4,328		
Person-years	83,343	82,334	105,827	76,405	90,926		
No. of cases (n = 798)	191	165	175	125	142		
Age-adjusted HR	1.0	1.10 (0.89-1.35)	1.00 (0.81-1.23)	1.15 (0.92-1.45)	1.28 (1.02-1.60)	< 0.05	1.14 (1.02-1.28)
Multivariate HR‡	1.0	1.17 (0.94-1.45)	1.06 (0.85-1.32)	1.27 (1.00-1.63)	1.48 (1.15-1.91)	< 0.01	1.26 (1.10-1.44)
	Women, Height (cm)						
	≤ 148.0	148.1-150.4	150.5-153.0	153.1-156.9	≥ 157.0	*p* for trend†	10-cm Increment
Number	5,010	4,052	4,775	4,210	4,613		
Person-years	109,850	89,702	106,300	94,225	102,261		
No. of cases (n = 303)	69	60	59	60	55		
Age-adjusted HR	1.0	1.18 (0.83-1.67)	1.06 (0.75-1.50)	1.31 (0.92-1.86)	1.24 (0.86-1.78)	0.19	1.17 (0.94-1.45)
Multivariate HR‡	1.0	1.19 (0.84-1.69)	1.10 (0.77-1.58)	1.39 (0.96-2.00)	1.35 (0.91-1.99)	0.09	1.24 (0.98-1.57)

†*p*-trend were calculated by treating each of the categories of adult height as continuous variable.
‡Multivariate HR has been adjusted for age (continuous variables), weight at the baseline (quintiles, kg), family history of cancer (yes or no), level of educational (junior high school or less, high school, or college/university or higher), smoking status (non-smoker, ex-smoker, current smoker 1-19 cigarettes/day, or current smoker ≥ 20 cigarettes/day), dinking status (never drinkers, ex-drinkers, current drinkers), time spent walking (≤ 0.5 hour/day, 0.5-1.0 hour/day, or ≥ 1 hour/day), vegetable consumption (quartiles, g/day), and fruit consumption (quartiles, g/day).

Table 3. Cox proportional hazard ratios (HRs) and 95% confidence intervals (CI) for Lung cancer incidence stratified by smoking status in men.

	Height (cm)							
	≤ 159.9	160.0-162.9	163.0-165.0	165.1-169.9	≥ 170.0	*p* for trend†	*p* for interaction	10-cm Increment
Never								
Number	850	756	904	601	710			
Person-years	18,422	16,514	19,736	13,303	15,612			
No. of cases (n = 44)	9	10	10	7	8			
Age-adjusted HR	1.0	1.41(0.57-3.49)	1.29(0.52-3.19)	1.52(0.56-4.16)	1.61(0.60-4.29)	0.36		1.15(0.70-1.89)
Multivariate HR‡	1.0	1.17(0.46-2.93)	0.97(0.38-2.48)	1.06(0.36-3.07)	1.14(0.39-3.35)	0.91		0.88(0.49-1.59)
							0.81	
Ever								
Number	3,122	3,107	4,057	2,932	3,533			
Person-years	61,791	63,752	83,611	61,724	73,520			
No. of cases (n = 740)	177	153	161	117	132			
Age-adjusted HR	1.0	1.07(0.86-1.33)	0.95(0.76-1.18)	1.08(0.85-1.37)	1.21(0.96-1.52)	0.19		1.11(0.98-1.25)
Multivariate HR‡	1.0	1.17(0.94-1.47)	1.05(0.84-1.32)	1.29(1.00-1.67)	1.52(1.17-1.98)	< 0.01		1.29(1.12-1.48)

†*p*-trend were calculated by treating each of the categories of adult height as continuous variable.
‡Multivariate HR has been adjusted for age (continuous variables), weight at the baseline (quintiles, kg), family history of cancer (yes or no), level of educational (junior high school or less, high school, or college/university or higher), dinking status (never drinkers, ex-drinkers, current drinkers), time spent walking (≤ 0.5 hour/day, 0.5-1.0 hour/day, or ≥ 1 hour/day),vegetable consumption (quartiles, g/day), fruit consumption (quartiles, g/day) and smoking status (ex-smoker, 1-19 cigarettes/day, or ≥ 20 cigarettes/day).

risks of small cell lung cancer and squamous cell carcinoma. For small cell lung cancer, multivariate HRs (95% CIs) were 0.86 (0.44-1.65) for body height 160.0-162.9 cm, 1.10 (0.60-2.02) for body height 163.0-165.0 cm, 1.67 (0.87-3.19) for body height 165.1-169.9 cm, and 1.73 (0.87-3.19) for body height ≥ 170.0 cm, (*p*-trend < 0.05). Further, our study demonstrated that every 10-cm increment in body height was associated with a 48% increase in the risk of small cell lung cancer. Similarly, for squamous cell carcinoma, multivariate HR (95% CI) was 1.24 (0.98-1.58) for every 10-cm increase in body height.

We also conducted analysis stratified by all of the

Table 4. Cox proportional hazard ratios (HRs) and 95% confidence intervals (CI) for Lung cancer incidence stratified by smoking status in women.

	Height (cm)							
	≤ 148.0	148.1-150.4	150.5-153.0	153.1-156.9	≥ 157.0	*p* for trend†	*p* for interaction	10-cm Increment
Never								
Number	3,092	2,624	3,252	2,938	3,180			
Person-years	68,300	58,239	72,933	66,026	71,127			
No. of cases (n = 189)	43	36	36	40	34			
Age-adjusted HR	1.0	1.09(0.70-1.69)	0.94(0.60-1.47)	1.24(0.80-1.93)	1.09(0.69-1.73)	0.55		1.08(0.75-1.43)
Multivariate HR[b]	1.0	1.09(0.70-1.71)	0.95(0.60-1.50)	1.28(0.81-2.02)	1.16(0.71-1.91)	0.41		1.13(0.83-1.54)
							0.55	
Ever								
Number	331	305	380	388	488			
Person-years	6,686	6,399	7,532	8,127	10,082			
No. of cases (n = 37)	9	7	5	6	10			
Age-adjusted HR	1.0	0.96(0.36-2.58)	0.63(0.21-1.90)	0.80(0.28-2.30)	1.18(0.47-2.99)	0.84		1.23(0.68-2.23)
Multivariate HR‡	1.0	0.84(0.30-2.35)	0.69(0.22-2.14)	0.93(0.31-2.79)	1.37(0.49-3.82)	0.53		1.49(0.77-2.85)

†*p*-trend were calculated by treating each of the categories of adult height as continuous variable.
‡Multivariate HR has been adjusted for age (continuous variables), weight at the baseline (quintiles, kg), family history of cancer (yes or no), level of educational (junior high school or less, high school, or college/university or higher), smoking status (ex-smoker, 1-19 cigarettes/day, or ≥ 20 cigarettes/day), dinking status (never drinkers, ex-drinkers, current drinkers), time spent walking (≤ 0.5 hour/day, 0.5-1.0 hour/day, or ≥ 1 hour/day), vegetable consumption (quartiles, g/day), and fruit consumption (quartiles, g/day).

covariates included in Table 2. However, we did not find any statistically significant effect modifications between adult height and any of the covariates.

Discussion

In this population-based prospective cohort study conducted in Japan, we found a significant association between adult height and the incidence of lung cancer in men, but no such association in women. Furthermore, stratified analysis showed that adult height was significantly associated with an increased risk of lung cancer in ever smokers, but not in never smokers.

Many previous studies have shown that adult height is associated with an increased risk of lung cancer in men. In the Asia region, two studies from Korea and China have reported a positive association between height and the risk of lung cancer among men (Sung et al. 2009; Tang et al. 2012). Our results for a Japanese population were consistent with those previous findings. The study from Korea also reported that each 10 cm increase in body height was associated with a 14% increased risk of lung cancer among men (Sung et al. 2009). The study from China also found that each 10 cm increase in body height was associated with a 19% increased risk of lung cancer in men (Tang et al. 2012). Similarly, we found that each 10 cm increase in adult height was associated with a 26% increased risk of lung cancer among Japanese men. Meanwhile, in women, some previous studies have reported that adult height was not associated with the incidence of lung cancer, and the present findings are consistent with those studies.

In addition, a prospective study from the USA had reported a positive association between height during adulthood and lung cancer incidence for men who had ever smoked (Kabat et al. 2014). In the present study, we investigated the association between adult height and the risk of lung cancer according to smoking status among Japanese men. However, the results were largely similar to those for Western men, despite the difference in genetic and lifestyle factors. Our results suggested that the association between height and the incidence of lung cancer might be stronger in individuals who have ever smoked. One of the reasons why the association between adult height and lung cancer risk were higher for ever smoker men than for never smoker might be serum IGF and IGF-binding protein levels. A lung cancer case-control study reported that both IGF-I and IGF-binding protein-3 (IGFBP-3) levels were higher in cases than in controls (Spitz et al. 2002). In addition, the associated between IGFBP-3 level and the risk of lung cancer tended to be higher in current smokers. The increased risk seen in smokers may be due to the increased risk of small cell lung cancer or squamous cell carcinoma. Previous studies have reported that small cell carcinoma and squamous cell carcinoma were strongly associated with smoking (Sobue et al. 2002; Wakai et al. 2006). We therefore examined the association between adult height and risk of lung cancer according to histological type (adenocarcinoma, small cell carcinoma, squamous cell carcinoma, or other). As a result, adult height was associated with an increased risk of small cell lung cancer and squamous cell carcinoma related to smoking. In our study, the increased risk in smokers was consistent with these findings.

We found a significant positive association between

Table 5. Cox proportional hazard ratios (HRs) and 95% confidence intervals (CI) for Lung cancer incidence stratified by histological types in men.

	Height (cm)						
	≤159.9	160.0-162.9	163.0-165.0	165.1-169.9	≥ 170.0	p for trend†	10-cm Increment
Number	4,122	3,961	5,075	3,597	4,328		
Adenocarcinoma							
Person-years	83,675	82,567	106,208	76,629	91,173		
No. of cases (n = 260)	58	57	58	36	51		
Age-adjusted RR	1.0	1.18(0.82-1.70)	1.00(0.69-1.45)	0.96(0.63-1.47)	1.28(0.87-1.89)	0.50	1.05(0.85-1.28)
Multivariate HR‡	1.0	1.26(0.86-1.83)	1.09(0.74-1.60)	1.10(0.70-1.72)	1.53(0.99-2.38)	0.16	1.16(0.92-1.47)
Small cell lung cancer							
Person-years	83,850	82,808	106,411	76,706	91,283		
No. of cases (n = 102)	24	15	22	20	21		
Age-adjusted RR	1.0	0.79(0.42-1.52)	1.01(0.56-1.81)	1.48(0.81-2.71)	1.52(0.83-2.78)	0.06	1.36(0.99-1.89)
Multivariate HR‡	1.0	0.86(0.44-1.65)	1.10(0.60-2.02)	1.67(0.87-3.19)	1.73(0.87-3.19)	< 0.05	1.48(1.03-2.14)
Squamous cell carcinoma							
Person-years	83,671	82,689	106,192	76,634	91,223		
No. of cases (n = 249)	58	49	64	44	34		
Age-adjusted RR	1.0	1.10(0.75-1.62)	1.25(0.87-1.79)	1.39(0.93-2.08)	1.06(0.69-1.64)	0.36	1.19(0.97-1.47)
Multivariate HR‡	1.0	1.10(0.75-1.63)	1.19(0.81-1.73)	1.35(0.898-2.08)	1.06(0.66-1.72)	0.46	1.24(0.98-1.58)
Other							
Person-years	83,854	82,789	106,445	76,702	91,288		
No. of cases (n = 50)	13	11	8	8	10		
Age-adjusted RR	1.0	0.96(0.43-2.16)	0.57(0.24-1.40)	0.86(0.35-2.12)	0.97(0.41-2.30)	0.80	0.94(0.59-1.50)
Multivariate HR‡	1.0	1.17(0.51-2.69)	0.70(0.27-1.78)	1.10(0.41-2.93)	1.32(0.49-3.59)	0.71	1.13(0.67-1.93)

†*p*-trend were calculated by treating each of the categories of adult height as continuous variable.
‡Multivariate HR has been adjusted for age (continuous variables), weight at the baseline (quintiles, kg), family history of cancer (yes or no), level of educational (junior high school or less, high school, or college/university or higher), smoking status (ex-smoker, 1-19 cigarettes/day, or ≥ 20 cigarettes/day), dinking status (never drinkers, ex-drinkers, current drinkers), time spent walking (≤ 0.5 hour/day, 0.5-1.0 hour/day, or ≥ 1 hour/day),vegetable consumption (quartiles, g/day), and fruit consumption (quartiles, g/day).

adult height and the risk of lung cancer incidence in men, but not in women. This sex difference might be attributed to difference in baseline characteristics, such as smoking status. We therefore investigated the association between adult height and the risk of lung cancer according to smoking status (never smoker or ever smoker) in women, but no such association was observed for either never or ever smokers. This null association among women who had ever smoked would be partly explained by the fact that only 37 developed lung cancer, leading to insufficient statistical power (Table 4). In the present study, the highest quintile group for women (≥ 157.0 cm) corresponded to the lowest quintile group for men (< 160.0 cm), and we were unable to evaluate the association between adult height and the incidence of lung cancer for women who were taller than this. In addition, according to the World Cancer Research Fund and the American Institute for Cancer Research (WCRF/AICR), consumption of vegetables and fruit might decrease the risk of lung cancer (World Cancer Research Fund International 2018). In fact, for women, those in the higher adult height category were more likely to consume green and yellow vegetables and fruit, and this may have been associated with a decreased risk of lung cancer (Table1).

Although the biological mechanism underlying the association between adult height and the risk of lung cancer incidence is not clear, several hypotheses can be considered. One common link between height and cancer incidence is that taller individuals have larger organs (Chirachariyavej et al. 2006; Nunney 2018), and therefore a greater number of cells that can undergo neoplastic change at each of these sites. Moreover, body height is determined by conditions during the embryonic period and childhood nutrition, but it has also been suggested that insulin-like growth factor-1 (IGF-1), a major regulator of childhood growth, has an impact on cancer risk (Aune et al. 2012). High levels of IGF-1 have been found to be associated with an increased risk of prostate cancer (Chan et al. 1998), premenopausal breast cancer (Hankinson et al. 1998; Schernhammer et al. 2005), colorectal cancer (Ma et al. 1999; Giovannucci et al. 2000), and lung cancer (Wu et al. 2000).

The present study had several strengths. First, it was a prospective cohort study targeting a large number of community-dwelling Japanese, and the follow-up period was long (mean period, 24.5 years) in comparison to recent prospective studies. Second, the rate of response to the questionnaire was high at 91.7%, and the internal validity was considered high. Third, the validity of the self-reported questionnaire using anthropometric measures was high (Pearson's correlation coefficient: body height; 0.85, body weight 0.97) (Kuriyama et al. 2004). Fourth, the incidence of lung cancer was confirmed through verification using regional cancer registration.

There were also some limitations to our research. First, the proportion of smokers tended to be high in the top highest category group, but even when this influence of smoking was corrected for, an increased risk of lung cancer incidence was still observed in the top height group. However, stratification analysis based on smoking status showed that the increase in the risk of lung cancer was greater in the highest category group for both past smokers and current smokers. Second, as there was no information on the smoking status of parents and smoke in the workplace, the influence of passive smoking could not be ruled out. Third, the influence of other possible confounders such as genetic factors, parental height, and socioeconomic factors could not be verified. Fourth, cigarette smoking is the main cause of lung cancer (Centers for Disease Control and Prevention 2004; World Health Organization 2012). A residual confounding effect on our results likely remains, although we adjusted for smoking status in the multivariate model.

In conclusion, this population-based, prospective cohort study conducted in Japan has demonstrated a positive association between adult height and the risk of lung cancer incidence among men. The results for Japanese men were largely similar to those of studies in Western countries, despite the difference in genetic and lifestyle factors. On the basis of these results, we consider it important to promote lung cancer prevention in men who are taller, greater height, especially those who are past or present smokers.

Author Contributions

M.M., Y.S., and I.T. designed the research; Y.S., S.K., A.F., and I.T. performed the research; M.M., and Y.S., analyzed the data; M.M., Y.S., and I.T. wrote the paper; M.M., Y.S., Y.T., S.K., A.F., and I.T. had primary responsibility for the final content.

Acknowledgments

This study was supported by the National Cancer Center Research and Development Fund (30-A-15).

Conflict of Interest

The authors declare no conflict of interest.

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