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Body mass index and lung cancer risk: Pooled analysis of 10 prospective cohort studies in Japan

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Abstract

Mounting evidence suggests that body mass index (BMI) is inversely associated with the risk of lung cancer. However, relatively few studies have explored this association in Asian people, who have a much lower prevalence of obesity than Caucasians. We pooled data from 10 prospective cohort studies involving 444,143 Japanese men and women to address the association between BMI and the risk of lung cancer. Study-specific hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated in each cohort using the Cox proportional hazards model. A meta-analysis was undertaken by combining the results from each cohort. Heterogeneity across studies was evaluated

Abbreviations: 8-OHdG, 8-hydroxy-2-deoxyguanosine; BMI, body mass index; CI, confidence interval; HR, hazard ratio; MR, Mendelian randomization; PY, pack year.

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using Cochran's Q and I^2 statistics. During 5,730,013 person-years of follow-up, 6454 incident lung cancer cases (4727 men and 1727 women) were identified. Baseline BMI was inversely associated with lung cancer risk in men and women combined. While leanness (BMI <18.5) was associated with a higher risk of lung cancer (HR 1.35; 95% CI, 1.16–1.57), overweight and obesity were associated with a lower risk, with HRs of 0.77 (95% CI, 0.71–0.84) and 0.69 (95% CI, 0.45–1.07), respectively. Every 5 kg/m^2 increase in BMI was associated with a 21% lower risk of lung cancer (HR 0.79; 95% CI, 0.75–0.83; $p < 0.0001$). Our pooled analysis indicated that BMI is inversely associated with the risk of lung cancer in the Japanese population. This inverse association could be partly attributed to residual confounding by smoking, as it was more pronounced among male smokers.

KEYWORDS
body mass index, inverse association, lung cancer risk, pooled analysis, smoking

1 | INTRODUCTION

Obesity, as defined by BMI, is known to increase the risk of a wide range of diseases, including type 2 diabetes, cardiovascular disease, and cancer.[1] Over the past several decades, there has been growing interest in exploring the associations of BMI with cancer incidence and mortality. According to the 2018 working group report of the IARC, obesity has been shown to increase the risk of at least 13 different types of cancer.[2] However, one notable exception appears to be lung cancer, which is the leading cause of cancer deaths in developed countries such as Japan. Numerous observational studies in different ethnic groups have almost consistently shown that BMI is inversely associated with the risk of lung cancer.[3–10]

Due to the nature of observational studies, it remains controversial whether the inverse association between BMI and lung cancer is causal or merely spurious. Some previous studies reported that this association could be due in part to methodological weaknesses, as it disappeared after restricting analyses to never-smokers and/or properly adjusting for cigarette smoking (the dominant risk factor for lung cancer).[8,10] However, increasing evidence supports the existence of an inverse association, with a 2019 pooled analysis of 12 cohort studies from the United States, Europe, and Asia demonstrating that high BMI was associated with a decreased risk of lung cancer in both smokers and never smokers after excluding cases diagnosed during the first 5 years of follow-up.[3] As concluded by the authors of this pooled analysis, "the inverse BMI–lung cancer association is not entirely due to smoking and reverse causation."

Fewer studies have explored the association between BMI and lung cancer in Asian people, who are known to have a lower prevalence of obesity than Caucasians, as well as different body composition. In Japan, three cohort studies[7,11,12] and two case–control studies[13,14] examined the relationship between BMI and lung cancer incidence or mortality, but their findings were inconclusive. Of note, the Japan Public Health Center–based Prospective Study followed 92,098 men and women for an average of 19.1 years and found that after adjustment for smoking and other confounders, lower BMI (<19) at baseline was associated with a 48% increased risk of lung cancer in men.[7] The individual studies mentioned above, however, did not undertake stratified analyses by smoking status, perhaps because of the small number of lung cancer cases in never smokers. This limitation points to the need to conduct a pooled analysis of available cohort study data to further address confounding by smoking.

To better understand the associations between BMI and lung cancer risk, we pooled data from 10 prospective cohort studies with a total of 444,143 participants (including 6454 lung cancer cases). This constituted the largest sample size ever established in the Japanese population. Additionally, we aimed to stratify the associations by sex, smoking status, and histological type.

2 | MATERIALS AND METHODS

2.1 | Study population

This analysis is part of an ongoing project aiming to elucidate the associations of major cancers with lifestyle factors in Japanese people by pooling data from ongoing cohort studies. A detailed description of the pooling project was provided elsewhere.[15] Briefly, we pooled data from 10 prospective cohort studies that met the predefined criteria: namely the Japan Public Health Center–based Prospective Study (JPHC-I and JPHC-II),[16] the Japan Collaborative Cohort Study (JACC),[17] the Miyagi Cohort Study (MIYAGI),[18] the Three-Prefecture Cohort Study in Miyagi (3-Pref MIYAGI),[19] the Three-Prefecture Cohort Study in Aichi (3-Pref AICHI),[19] the Three-Prefecture Cohort Study in Osaka (3-Pref OSAKA),[19] the Ohsaki Cohort Study (OHSAKI),[20] the Takayama Study (TAKAYAMA),[21] and the Life Span Study (LSS).[22] Each cohort enrolled more than 30,000 participants in the 1980s–1990s and used validated questionnaires to collect baseline information on height, weight, cigarette smoking, alcohol consumption, and other lifestyle factors. Selected characteristics of these cohort studies are shown in Table 1.

TABLE 1 Characteristics of cohort studies included in the present pooled analysis to determine associations between body mass index (BMI) and lung cancer.

							For the present pooled analysis							
											Baseline cohort size		Lung cancer cases	
Study	Cohort participants	Age at baseline survey (years)	Baseline survey (year)	Cohort size	Response rate of the baseline questionnaire (%)	Outcome ascertainment	Age (years)	Date of last follow-up	Mean duration of follow-up (years)	Mean of BMI (SD)	Men	Women	Men	Women
JPHC-I	Japanese residents of five public health center areas in Japan	40–59	1990	61,595	82	Cancer registry and death certificate	40–59	Dec 31, 2013	20.8	23.6 (3.0)	20,155	21,673	584	219
JPHC-II	Japanese residents of six public health center areas in Japan	40–69	1993-1994	78,825	80	Cancer registry and death certificate	40–69	Dec 31, 2013 (Suita, Osaka is only until Dec 31, 2012)	17.2	23.4 (3.0)	28,874	31,966	894	330
JACC	Residents from 45 areas throughout Japan	40–79	1988-1990	110,792	83	Cancer registry (selected areas: 24) and death certificate	40–79	2009	13.2	22.8 (3.0)	46,395	64,190	646	226
MIYAGI	Residents of 14 municipalities in Miyagi Prefecture, Japan	40–64	1990	47,605	92	Cancer registry and death certificate	40–64	Dec 31, 2014	21.5	23.7 (2.9)	21,094	22,657	800	303
OHSAKI	Beneficiaries of National Health Insurance among residents of 14 municipalities in Miyagi Prefecture, Japan	40–79	1994	54,996	95	Cancer registry and death certificate	40–79	Mar 31, 2008	10.8	23.6 (3.1)	21,514	23,209	583	179
TAKAYAMA	Residents of Takayama, Gifu Prefecture, Japan	≥35	1992	31,552	92	Cancer registry and death certificate	35–101	Mar 31, 2008	13.7	22.2 (2.8)	13,409	15,573	266	104
3-Pref MIYAGI	Residents of three municipalities in Miyagi Prefecture, Japan	40+	1984	31,345	94	Cancer registry and death certificate	40+	Dec 31, 1992	7.7	23.2 (3.1)	13,010	15,944	154	56
3-Pref AICHI	Residents of two municipalities in Aichi Prefecture, Japan	40+	1985	33,529	90	Cancer registry and death certificate	40–103	Dec 31, 2000	11.6	22.1 (2.9)	15,746	17,783	298	115
3-Pref OSAKA	Residents of four municipalities in Osaka Prefecture, Japan	40+	1983	35,755	82	Cancer registry and death certificate	40–97	Jan 31, 2000	12.3	22.4 (3.0)	15,919	17,973	333	108
LSS	Atomic bomb survivors in Hiroshima and Nagasaki, Japan	46–104	1991	20,147	100	Cancer registry and death certificate	46–100	Dec 31, 2003	10.9	22.4 (3.2)	6541	10,518	169	87
Total											202,657	241,486	4727	1727

Abbreviations: 3-Pref AICHI, Three-Prefecture Study – Aichi portion; 3-Pref MIYAGI, Three-Prefecture Study – Miyagi portion; 3-Pref OSAKA, Three-Prefecture Study – Osaka portion; JACC, Japan Collaborative Cohort Study; JPHC, Japan Public Health Center–based prospective Study; LSS, Life Span Study; MIYAGI, Miyagi Cohort Study; OHSAKI, Ohsaki National Health Insurance Cohort Study; TAKAYAMA, Takayama Study.

2.2 | Body mass index assessment

Self-reported data on weight and height at baseline were collected from all cohort participants. Body mass index, calculated as weight (kg) divided by the square of height (m), was categorized into six groups: <18.5, 18.5–20.9, 21.0–22.9, 23.0–24.9, 25.0–29.9, and ≥30. Based on the WHO classifications, a BMI of <18.5 is defined as underweight, 18.5–22.9 as normal weight, 25.0–29.9 as overweight, and ≥30 as obese. Individuals with an extreme BMI (<14 or >40) were excluded from the analyses. The validity of self-reported height and weight was examined in some of the cohorts included in this pooled analysis, with correlation coefficients between self-reported and measured values ranging from 0.85 to 0.97.[23–26]

2.3 | Follow-up and outcome ascertainment

Follow-up and outcome ascertainment were carried out according to each cohort's protocol. Cancer diagnoses were confirmed mainly through linkage with cancer registries, review of medical records, or a combination of the two. Lung cancer was ascertained by the International Classification of Diseases (162 in ICD-9 and C34 in ICD-10), and was further classified into squamous cell carcinoma (8050–8078, 8083–8084), adenocarcinoma (8140, 8211, 8230–8231, 8250–8260, 8323, 8480–8490, 8550–8552, 8570–8574, 8576), and small-cell carcinoma (8041–8045) according to the histological grouping proposed by the IARC.[27]

2.4 | Statistical analysis

Our two-stage analysis followed the same analytical approach as the one used in the previously mentioned study.[15] In the first stage, individuals were excluded from analyses if they reported a history of any cancer at baseline and had missing data on body weight and/or height. Life Span Study participants with an atomic bomb radiation dose ≥100 mGy were also excluded. We calculated study-specific HRs of lung cancer in relation to various BMI categories for each participating cohort. Individuals with a BMI of 21.0–22.9 served as the reference group. Hazard ratios and 95% CIs were estimated from Cox proportional hazards regression models. The BMI–lung cancer associations were examined in overall as well as sex-specific analyses. Assuming a log-linear dose–response relationship, BMI was also modeled as a continuous variable; HRs were estimated for each 5 kg/m^2 increase in BMI. All multivariate models were adjusted for age at baseline, PY of cigarette smoking (men: never, former and current [PY 0< and ≤20], former and current [PY 20< and ≤30], former and current [PY 30< and ≤40], former and current [PY >40]; women: never, former and current [PY 0< and ≤20], former and current [PY 20< and ≤30], former and current [PY >30]), and alcohol consumption (never, occasional, current <23 g/day of ethanol, and current ≥23 g/day of ethanol), with model 3 further adjusting for physical activity if available. For former smokers, we further adjusted for years since quitting smoking (<5, 5 to <10, 10 to <15, and ≥15 years).

In the second stage, we undertook a random-effects meta-analysis combining results (β and SE) from each cohort. Heterogeneity across studies was evaluated using Cochran's Q and I^2 statistics. The effect size values were log-transformed prior to the pooled analysis in order to resolve the asymmetry of the confidence intervals, and then exponentially transformed to obtain the combined values.

In subgroup analyses, we evaluated BMI–lung cancer associations by smoking status (current, former, and never) and histological type (adenocarcinoma, squamous cell carcinoma, and small-cell carcinoma). The three histological subtypes account for approximately 90% of lung cancers in Japanese patients.[28,29] The interaction between smoking and low BMI (<21) in influencing lung cancer risk was evaluated using likelihood tests with the addition of an interaction term. To address reverse causation, we undertook sensitivity analyses that excluded lung cancer cases diagnosed during the first 5 years of follow-up.

Statistical tests were two-sided, and a p value <0.05 was considered statistically significant. Analyses were carried out using SAS (version 9.4; SAS Institute) and Stata 17 (StataCorp).

3 | RESULTS

Table 1 presents the baseline characteristics of each cohort study included in the current pooled analysis. The mean BMI at baseline ranged from 22.1 to 23.7, and the follow-up duration ranged from 7.7 to 21.5 years. During 5,730,013 person-years of follow-up, 6454 incident lung cancer cases (4727 men and 1727 women) were identified.

Overall, BMI was inversely associated with lung cancer risk; while underweight (BMI <18.5) was associated with a higher risk of lung cancer (HR 1.35; 95% CI, 1.16–1.57), overweight (BMI 25.0–29.9) and obesity (BMI ≥30) were associated with a lower risk, with HRs of 0.77 (95% CI, 0.71–0.84) and 0.69 (95% CI, 0.45–1.07), respectively (Table 2). This inverse association was consistently observed across cohorts included in the pooled analysis, with no significant heterogeneity in risk in the lowest BMI category (BMI <18.5) compared with the reference category (BMI 21.0–22.9). In multivariable-adjusted models, every 5 kg/m^2 increase in BMI was associated with a 21% decrease in the risk of lung cancer (HR 0.79; 95% CI, 0.75–0.83; p <0.0001). Stratification by sex indicated that the inverse BMI–lung cancer association was similar between men and women, except that the increased risk in underweight (BMI <18.5) women was not statistically significant.

Table 3 shows the sex-specific associations between BMI and lung cancer risk by smoking status. Overall, higher BMI was associated with a lower risk of lung cancer regardless of smoking status, with never, former, and current smokers showing 10%, 22%, and 16% decreases in risk, respectively, per 5 kg/m^2 increase in BMI. Notably, overweight (BMI 25.0–29.9) was significantly associated with decreased lung cancer risk in both never-smokers and

TABLE 2 Associations between body mass index (BMI) and lung cancer by sex in the Japanese population ($N=444,143$).

		<18.5	18.5 to <21	21 to <23	23 to <25	25 to <30	≥30	Heterogeneity for lowest category		Trend (per 5 kg/m^2)		Heterogeneity for trend	
	Total	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	I^2 (%)	Cochran's Q test	HR (95% CI)	p	I^2 (%)	Cochran's Q test
Both sexes													
Participants, n	392,533	21,407	79,331	104,316	94,931	84,448	8100	–	–	–	–	–	–
Person-years	5,733,351	254,390	1,104,802	1,527,754	1,430,791	1,292,930	122,685	–	–	–	–	–	–
Cases, n	6454	478	1464	1816	1469	1139	88	–	–	–	–	–	–
HR1 (model 1)[a]		1.43 (1.29–1.59)	1.12 (1.04–1.21)	1 (Ref.)	0.85 (0.80–0.91)	0.76 (0.71–0.83)	0.73 (0.54–1.01)	0.0	$p=0.38$	0.75 (0.71–0.79)	<0.0001	30.5	$p=0.16$
HR2 (model 2)[b]		1.37 (1.23–1.52)	1.11 (1.02–1.20)	1 (Ref.)	0.87 (0.81–0.93)	0.77 (0.71–0.83)	0.72 (0.52–1.00)	0.0	$p=0.31$	0.77 (0.73–0.81)	<0.0001	32.2	$p=0.15$
HR3 (model 3)[c]		1.35 (1.16–1.57)	1.06 (0.98–1.14)	1 (Ref.)	0.87 (0.81–0.93)	0.77 (0.71–0.84)	0.69 (0.45–1.07)	31.0	$p=0.13$	0.79 (0.75–0.83)	<0.0001	26.6	$p=0.23$
Men													
Participants, n	180,495	8299	35,616	48,928	46,885	38,021	2746	–	–	–	–	–	–
Person-years	2589,596	92,967	482,489	700,211	696,356	576,191	41,382	–	–	–	–	–	–
Cases, n	4727	336	1144	1371	1065	760	51	–	–	–	–	–	–
HR1 (model 1)		1.46 (1.28–1.66)	1.16 (1.06–1.26)	1 (Ref.)	0.81 (0.75–0.89)	0.73 (0.66–0.79)	0.83 (0.61–1.14)	3.0	$p=0.26$	0.71 (0.66–0.76)	<0.0001	36.1	$p=0.11$
HR2 (model 2)		1.40 (1.23–1.60)	1.14 (1.05–1.25)	1 (Ref.)	0.83 (0.77–0.91)	0.74 (0.67–0.81)	0.84 (0.61–1.15)	7.6	$p=0.18$	0.73 (0.68–0.78)	<0.0001	34.1	$p=0.11$
HR3 (model 3)		1.43 (1.19–1.71)	1.10 (1.01–1.20)	1 (Ref.)	0.83 (0.75–0.91)	0.74 (0.67–0.81)	0.84 (0.57–1.25)	34.4	$p=0.11$	0.74 (0.68–0.80)	<0.0001	45.8	$p=0.07$
Women													
Participants, n	212,038	13,108	43,715	55,388	48,046	46,427	5354	–	–	–	–	–	–
Person-years	3,143,755	161,423	622,312	827,542	734,435	716,739	81,303	–	–	–	–	–	–
Cases, n	1727	142	320	445	404	379	37	–	–	–	–	–	–
HR1 (model 1)		1.44 (1.17–1.76)	0.98 (0.85–1.13)	1 (Ref.)	0.99 (0.86–1.13)	0.93 (0.77–1.13)	0.83 (0.55–1.24)	0.0	$p=0.32$	0.86 (0.79–0.95)	0.003	32.1	$p=0.08$
HR2 (model 2)		1.34 (1.10–1.65)	0.96 (0.83–1.11)	1 (Ref.)	1.00 (0.87–1.14)	0.92 (0.76–1.11)	0.78 (0.52–1.18)	1.0	$p=0.24$	0.87 (0.79–0.96)	0.0072	39.1	$p=0.05$
HR3 (model 3)		1.20 (0.95–1.53)	0.91 (0.78–1.07)	1 (Ref.)	0.99 (0.86–1.15)	0.96 (0.76–1.22)	0.71 (0.43–1.20)	0.0	$p=0.40$	0.92 (0.84–1.01)	0.0766	23.2	$p=0.23$

Note: The interaction between smoking (never vs. ever) and BMI (<21 vs. ≥21) was not statistically significant ($p=0.07$ for men and women combined, $p=0.09$ for men, and $p=0.12$ for women).

Abbreviations: CI, confidence interval; HR, hazard ratio; I^2, inconsistency index; p, probability; Ref. reference.

[a]Adjustment for age (year, continuous) and area (for Japan Public Health Center–based prospective Study [JPHC]-I, JPHC-II, Japan Collaborative Cohort Study, and Life Span Study).

[b]Further adjustment for smoking (men: never, former and current [pack years (PY) 0< and ≤20], former and current [PY 20< and ≤30], former and current [PY 30< and ≤40], former and current [PY >40]; women: never, former and current [PY 0< and ≤20], former and current [PY 20< and ≤30], former and current [PY >30]), drinking (noncurrent drinkers [never- or ex-drinker], occasional drinkers [less than once per week], regular drinkers [<23 g/day], regular drinkers [≥23 g/day]) and history of diabetes (no, yes) to model 1.

[c]Further adjustment for exercise to model 2.

TABLE 3 Associations between body mass index and lung cancer by smoking status in the Japanese population ($N = 444,143$).

		<18.5	18.5 to <21	21 to <23	23 to <25	25 to <30	≥30	Heterogeneity for lowest category		Trend (per 5 kg/m^2)		Heterogeneity for trend	
	Total	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	I^2 (%)	Cochran's Q test	HR (95% CI)	p	I^2 (%)	Cochran's Q test
Both sexes													
Never smokers													
Participants, n	200,921	10,752	39,546	52,800	48,037	45,080	4706	–	–	–	–	–	–
Person-years	3,058,481	136,156	575,205	806,960	751,826	714,960	73,374	–	–	–	–	–	–
Cases, n	1457	74	235	402	391	331	24	–	–	–	–	–	–
HR1 (model 1)[a]	–	1.10 (0.84–1.43)	0.87 (0.74–1.03)	1 (Ref.)	0.96 (0.84–1.10)	0.85 (0.75–0.96)	0.70 (0.49–1.00)	18.7	$p = 0.17$	0.91 (0.83–0.98)	0.019	12.4	$p = 0.34$
HR2 (model 2)[b]	–	1.09 (0.84–1.40)	0.87 (0.74–1.03)	1 (Ref.)	0.96 (0.84–1.10)	0.85 (0.75–0.96)	0.69 (0.49–0.99)	15.0	$p = 0.19$	0.90 (0.83–0.98)	0.015	10.3	$p = 0.37$
HR3 (model 3)[c]	–	1.14 (0.88–1.47)	0.85 (0.71–1.03)	1 (Ref.)	0.95 (0.82–1.10)	0.84 (0.74–0.95)	0.70 (0.49–1.00)	8.4	$p = 0.45$	0.90 (0.83–0.98)	0.014	11.0	$p = 0.54$
Former smokers													
Participants, n	48,543	2512	9013	12,788	12,773	10,652	805	–	–	–	–	–	–
Person-years	678,471	26,351	119,463	178,914	184,698	156,691	12,353	–	–	–	–	–	–
Cases, n	765	63	186	208	168	131	9	–	–	–	–	–	–
HR1 (model 1)	–	1.56 (1.15–2.10)	1.26 (1.02–1.56)	1 (Ref.)	0.81 (0.63–1.04)	0.75 (0.60–0.94)	1.16 (0.59–2.28)	0.0	$p = 0.71$	0.75 (0.66–0.86)	<0.0001	0.0	$p = 0.69$
HR2 (model 2)	–	1.42 (1.05–1.91)	1.20 (0.91–1.57)	1 (Ref.)	0.83 (0.69–1.01)	0.75 (0.61–0.93)	1.09 (0.60–1.96)	0.0	$p = 0.47$	0.78 (0.68–0.88)	0.0001	8.2	$p = 0.39$
HR3 (model 3)	–	1.38 (0.90–2.11)	1.05 (0.77–1.44)	1 (Ref.)	0.83 (0.67–1.03)	0.72 (0.57–0.90)	0.91 (0.48–1.73)	39.9	$p = 0.13$	0.78 (0.67–0.91)	0.0012	20.4	$p = 0.26$
Current smokers													
Participants, n	108,972	6250	24,366	30,113	26,041	20,508	1694	–	–	–	–	–	–
Person-years	1,552,638	72,604	331,253	429,282	385,705	308,687	25,108	–	–	–	–	–	–
Cases, n	3830	318	954	1087	818	606	47	–	–	–	–	–	–
HR1 (model 1)	–	1.42 (1.23–1.65)	1.11 (1.01–1.21)	1 (Ref.)	0.89 (0.81–0.98)	0.88 (0.79–0.97)	1.00 (0.72–1.40)	17.7	$p = 0.29$	0.81 (0.76–0.87)	<0.0001	27.9	$p = 0.24$
HR2 (model 2)	–	1.40 (1.21–1.63)	1.11 (1.01–1.22)	1 (Ref.)	0.89 (0.81–0.98)	0.87 (0.79–0.97)	1.00 (0.72–1.40)	17.9	$p = 0.26$	0.82 (0.76–0.88)	<0.0001	29.5	$p = 0.23$
HR3 (model 3)	–	1.37 (1.12–1.69)	1.08 (0.98–1.19)	1 (Ref.)	0.89 (0.84–0.94)	0.89 (0.80–0.99)	0.98 (0.66–1.44)	39.9	$p = 0.11$	0.84 (0.78–0.91)	<0.0001	24.8	$p = 0.25$
Men													
Never smokers													
Participants, n	34,481	1157	5471	8614	9683	8846	710	–	–	–	–	–	–
Person-years	491,202	13,966	78,120	131,337	151,293	108,787	7699	–	–	–	–	–	–
Cases, n	265	8	33	72	94	53	5	–	–	–	–	–	–
HR1 (model 1)	–	1.06 (0.46–2.45)	0.75 (0.49–1.15)	1 (Ref.)	1.16 (0.82–1.64)	0.75 (0.52–1.09)	1.21 (0.47–3.10)	0.0	$p = 0.89$	0.98 (0.79–1.22)	0.87	0.0	$p = 0.45$
HR2 (model 2)	–	0.89 (0.38–2.11)	0.73 (0.48–1.13)	1 (Ref.)	1.17 (0.84–1.65)	0.77 (0.53–1.11)	1.20 (0.47–3.09)	0.0	$p = 0.93$	1.02 (0.82–1.26)	0.88	0.0	$p = 0.47$
HR3 (model 3)	–	0.66 (0.22–2.01)	0.71 (0.44–1.12)	1 (Ref.)	1.09 (0.77–1.55)	0.72 (0.49–1.06)	1.18 (0.46–3.04)	0.0	$p = 0.99$	0.99 (0.79–1.24)	0.92	0.0	$p = 0.67$

(Continues)

TABLE 3 (Continued)

	Total	<18.5	18.5 to <21	21 to <23	23 to <25	25 to <30	≥30	Heterogeneity for lowest category		Trend (per 5 kg/m^2)		Heterogeneity for trend	
		HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	I^2 (%)	Cochran's Q test	HR (95% CI)	p	I^2 (%)	Cochran's Q test
Former smokers													
Participants, *n*	41,326	1884	7349	11,025	11,326	9167	575	–	–	–	–	–	–
Person-years	575,961	19,218	96,515	153,428	163,411	134,585	8805	–	–	–	–	–	–
Cases, *n*	668	51	159	192	150	109	7	–	–	–	–	–	–
HR1 (model 1)	–	1.47 (1.00–2.17)	1.19 (0.93–1.52)	1 (Ref.)	0.78 (0.61–0.99)	0.70 (0.55–0.89)	1.32 (0.62–2.83)	21.5	$p=0.30$	0.74 (0.64–0.85)	<0.0001	0.0	$p=0.63$
HR2 (model 2)	–	1.42 (1.01–1.98)	1.18 (0.89–1.50)	1 (Ref.)	0.82 (0.67–1.00)	0.77 (0.61–0.96)	1.12 (0.59–2.13)	10.2	$p=0.4$	0.78 (0.68–0.90)	0.0005	10.4	$p=0.33$
HR3 (model 3)	–	1.55 (1.05–2.29)	1.05 (0.76–1.46)	1 (Ref.)	0.82 (0.66–1.02)	0.73 (0.56–0.95)	0.88 (0.43–1.80)	15.4	$p=0.3$	0.77 (0.65–0.91)	0.0016	21.5	$p=0.25$
Current smokers													
Participants, *n*	95,222	4861	21,320	26,953	23,297	17,546	1245	–	–	–	–	–	–
Person-years	1,374,002	56,775	294,761	389,834	348,290	265,890	18,452	–	–	–	–	–	–
Cases, *n*	3529	263	905	1029	759	537	36	–	–	–	–	–	–
HR1 (model 1)	–	1.36 (1.17–1.57)	1.11 (1.00–1.22)	1 (Ref.)	0.89 (0.81–0.97)	0.87 (0.78–0.97)	1.06 (0.69–1.63)	7.6	$p=0.38$	0.82 (0.77–0.88)	<0.0001	7.8	$p=0.4$
HR2 (model 2)	–	1.34 (1.15–1.55)	1.11 (1.00–1.23)	1 (Ref.)	0.89 (0.81–0.97)	0.86 (0.78–0.96)	1.06 (0.70–1.63)	8.4	$p=0.32$	0.82 (0.77–0.88)	<0.0001	10.5	$p=0.37$
HR3 (model 3)	–	1.33 (1.08–1.64)	1.07 (0.97–1.18)	1 (Ref.)	0.88 (0.80–0.97)	0.87 (0.78–0.98)	1.11 (0.66–1.85)	33.9	$p=0.12$	0.84 (0.79–0.90)	<0.0001	3.5	$p=0.32$
Women													
Never smokers													
Participants, *n*	166,440	9595	34,075	44,186	38,354	36,234	3996	–	–	–	–	–	–
Person-years	2,530,699	122,190	497,086	675,623	600,533	572,880	62,387	–	–	–	–	–	–
Cases, *n*	1192	66	202	330	297	278	19	–	–	–	–	–	–
HR1 (model 1)	–	1.04 (0.79–1.37)	0.86 (0.71–1.04)	1 (Ref.)	0.97 (0.83–1.14)	0.94 (0.78–1.14)	0.70 (0.43–1.14)	0.0	$p=0.19$	0.93 (0.85–1.02)	0.1400	0.0	$p=0.14$
HR2 (model 2)	–	1.04 (0.79–1.37)	0.86 (0.71–1.04)	1 (Ref.)	0.97 (0.83–1.13)	0.94 (0.77–1.14)	0.69 (0.43–1.13)	0.0	$p=0.20$	0.93 (0.85–1.02)	0.1100	0.0	$p=0.13$
HR3 (model 3)	–	1.09 (0.80–1.48)	0.85 (0.68–1.05)	1 (Ref.)	0.98 (0.82–1.18)	0.94 (0.75–1.20)	0.70 (0.43–1.13)	0.0	$p=0.60$	0.91 (0.83–1.01)	0.0700	0.0	$p=0.74$
Former smokers													
Participants, *n*	7217	628	1664	1763	1447	1485	230	–	–	–	–	–	–
Person-years	102,509	7133	22,948	25,486	21,287	22,106	3549	–	–	–	–	–	–
Cases, *n*	97	12	27	16	18	22	2	–	–	–	–	–	–
HR1 (model 1)	–	3.62 (0.56–23.52)	1.32 (0.59–2.95)	1 (Ref.)	1.21 (0.53–2.80)	1.22 (0.50–2.96)	1.90 (0.34–10.68)	56.2	$p=0.11$	0.81 (0.57–1.15)	0.2300	16.4	$p=0.37$
HR2 (model 2)	–	2.22 (0.07–76.10)	0.55 (0.22–1.37)	1 (Ref.)	1.20 (0.53–2.76)	0.66 (0.25–1.73)	1.19 (0.24–5.94)	77.9	$p=0.03$	0.98 (0.67–1.42)	0.9000	14.2	$p=0.25$
HR3 (model 3)	–	2.37 (0.05–104.50)	0.58 (0.22–1.50)	1 (Ref.)	1.20 (0.44–3.26)	0.67 (0.21–2.15)	1.37 (0.20–9.16)	80.3	$p=0.02$	1.13 (0.79–1.60)	0.5100	0.0	$p=0.36$

TABLE 3 (Continued)

	Total	<18.5	18.5 to <21	21 to <23	23 to <25	25 to <30	≥30	Heterogeneity for lowest category		Trend (per 5 kg/m^2)		Heterogeneity for trend	
		HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	I^2 (%)	Cochran's Q test	HR (95% CI)	*p*	I^2 (%)	Cochran's Q test
Current smokers													
Participants, *n*	15,695	1605	3956	3918	2898	2851	467	-	-	-	-	-	-
Person-years	215,053	19,044	53,128	54,131	40,691	41,167	6893	-	-	-	-	-	-
Cases, *n*	270	54	61	53	42	51	9	-	-	-	-	-	-
HR1 (model 1)	-	2.17 (1.45–3.26)	1.18 (0.81–1.72)	1 (Ref.)	1.06 (0.70–1.62)	1.10 (0.73-1.64)	1.62 (0.72–3.63)	0.0	*p* = 0.95	0.82 (0.66–1.02)	0.0700	33.4	*p* = 0.17
HR2 (model 2)	-	2.16 (1.44–3.25)	1.19 (0.81–1.73)	1 (Ref.)	1.07 (0.70–1.62)	1.08 (0.72-1.61)	1.56 (0.69–3.52)	0.0	*p* = 0.93	0.82 (0.65–1.02)	0.0800	35.5	*p* = 0.14
HR3 (model 3)	-	1.98 (1.20–3.28)	1.27 (0.82–1.96)	1 (Ref.)	1.00 (0.61–1.63)	1.17 (0.74-1.84)	1.18 (0.46–3.05)	0.0	*p* = 0.83	0.86 (0.65–1.14)	0.3000	45.4	*p* = 0.09

Abbreviations: CI, confidence interval; HR, hazard ratio; I^2, inconsistency index; *p*, probability; Ref., reference.

[a]Adjustment for sex, age (year, continuous) and area (for Japan Public Health Center–based prospective Study [JPHC]-I, JPHC-II, Japan Collaborative Cohort Study, and Life Span Study).

[b]Further adjustment for drinking (noncurrent drinkers [never- or ex-drinker], occasional drinkers [less than once per week], regular drinkers [<23 g/day], regular drinkers [≥23 g/day]), history of diabetes (no, yes) and years since quitting smoking (<5, 5 to <10, 10 to <15, and ≥15 years) to model 1.

[c]Further adjustment for exercise to model 2.

ever-smokers (former and current smokers), with HRs ranging from 0.72 to 0.89. Decreased risk was also observed in obese people regardless of smoking status, but the associations were not statistically significant. Further sex-stratified analyses by smoking status showed significant, inverse associations between BMI and lung cancer risk in male current and former smokers, but not in male never smokers. In women, no significant, inverse associations were noted in either never smokers or ever smokers (former and current smokers). In addition, we found no statistically significant interaction between smoking and low BMI ($p = 0.07$ for men and women combined, $p = 0.09$ for men, and $p = 0.13$ for women).

In analyses stratified by histological subtype, an inverse association between BMI and lung cancer risk was evident for adenocarcinoma and squamous cell carcinoma (Table 4), but it was attenuated for small-cell carcinoma. In further stratification by sex, the associations seemed to vary between men and women. Among the three major subtypes, underweight (BMI <18.5) was significantly associated with an increased risk of adenocarcinoma only among men (HR 1.73; 95% CI, 1.24–2.43), whereas it was significantly associated with an increased risk of squamous cell carcinoma only among women (HR 3.33; 95% CI, 1.60–6.91).

To address the effect of reverse causation, we repeated the analyses, this time excluding lung cancer cases diagnosed during the first 5 years of follow-up. Overall, the inverse associations persisted for both men and women; however, further analyses stratified by smoking status suggested that the associations were more apparent in male former and current smokers, with no significant trend in female nonsmokers (Tables S1–S3).

4 | DISCUSSION

In this pooled analysis of 10 prospective cohort studies, we observed an overall inverse association between BMI and the risk of lung cancer in Japanese people, with each 5 kg/m^2 increase in BMI associated with 21% decreased risk. This estimate was consistent with a number of previous cohort studies, meta-analyses, and pooled analyses that included ethnically diverse populations.[3–10] Notably, our estimate of a 21% decreased risk per 5 kg/m^2 increase in BMI was larger than that (11%) reported in the 2018 pooled analysis of 30 prospective cohort studies involving more than 1.6 million individuals from the United States, Europe, and Asia.[3]

While obesity has been causally linked with at least 13 cancer sites, its causal relationship with lung cancer remains inconclusive. Although almost all observational studies (including ours) have consistently shown an inverse association, it remains controversial whether this was due to a real cause–effect relation or whether it merely represents a spurious association stemming from confounding, reverse causation, or other sources of bias. Among confounding factors that could distort BMI–lung cancer associations, cigarette smoking is a major concern because current smokers are well known to weigh less and have a substantially higher risk of developing lung cancer than never smokers. Previous studies that

TABLE 4 Associations between body mass index and lung cancer by histologic type in the Japanese population ($N = 444,143$).

		<18.5	18.5 to <21	21 to <23	23 to <25	25 to <30	≥30	Heterogeneity for lowest category		Trend (per 5 kg/m^2)		Heterogeneity for trend	
	Total	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	I^2 (%)	Cochran's Q test	HR (95% CI)	p	I^2 (%)	Cochran's Q test
Overall													
Adenocarcinoma													
Participants, n	363,579	19,921	73,821	96,792	87,954	77,709	7382	–	–	–	–	–	–
Person-years	5,511,723	244,219	1,063,848	1,470,446	1,376,351	1,239,807	117,051	–	–	–	–	–	–
Cases, n	2120	112	396	601	534	445	32	–	–	–	–	–	–
HR1 (model 1)[a]	–	1.34 (1.08–1.66)	1.03 (0.87–1.21)	1 (Ref.)	0.99 (0.84–1.18)	0.77 (0.67–0.87)	0.72 (0.43–1.21)	0	$p = 0.74$	0.83 (0.76–0.90)	<0.0001	13.95	$p = 0.55$
HR2 (model 2)[b]	–	1.34 (1.08–1.66)	1.02 (0.87–1.20)	1 (Ref.)	0.95 (0.84–1.07)	0.82 (0.70–0.95)	0.76 (0.44–1.31)	0	$p = 0.39$	0.83 (0.76–0.91)	<0.0001	17.89	$p = 0.48$
HR3 (model 3)[c]	–	1.38 (1.10–1.73)	1.03 (0.87–1.23)	1 (Ref.)	0.93 (0.82–1.05)	0.84 (0.71–0.98)	0.77 (0.45–1.32)	0	$p = 0.27$	0.83 (0.75–0.91)	0.0001	23.41	$p = 0.4$
Squamous cell carcinoma													
Participants, n	363,579	19,921	73,821	96,792	87,954	77,709	7382	–	–	–	–	–	–
Person-years	5511,723	244,219	1063,848	1470,446	1376,351	1239,807	117,051	–	–	–	–	–	–
Cases, n	1223	75	284	361	284	201	18	–	–	–	–	–	–
HR1 (model 1)	–	1.41 (1.05–1.90)	1.20 (0.95–1.52)	1 (Ref.)	0.79 (0.67–0.93)	0.72 (0.61–0.86)	0.91 (0.56–1.46)	15.01	$p = 0.38$	0.74 (0.65–0.85)	<0.0001	30.08	$p = 0.08$
HR2 (model 2)	–	1.35 (1.02–1.78)	1.19 (0.94–1.51)	1 (Ref.)	0.81 (0.69–0.96)	0.74 (0.62–0.88)	0.88 (0.54–1.42)	3.89	$p = 0.51$	0.77 (0.69–0.85)	<0.0001	0	$p = 0.1$
HR3 (model 3)	–	1.40 (1.04–1.87)	1.09 (0.87–1.35)	1 (Ref.)	0.82 (0.69–0.96)	0.72 (0.60–0.86)	0.81 (0.50–1.33)	5.16	$p = 0.38$	0.77 (0.69–0.86)	<0.0001	0	$p = 0.15$
Small-cell carcinoma													
Participants, n	363,579	19,921	73,821	96,792	87,954	77,709	7382	–	–	–	–	–	–
Person-years	5,511,723	244,219	1,063,848	1,470,446	1,376,351	1,239,807	117,051	–	–	–	–	–	–
Cases, n	529	31	119	153	109	107	10	–	–	–	–	–	–
HR1 (model 1)	–	1.60 (1.05–2.45)	1.15 (0.89–1.48)	1 (Ref.)	0.74 (0.57–0.95)	0.87 (0.67–1.12)	1.19 (0.62–2.29)	0	$p = 0.60$	0.78 (0.65–0.94)	0.009	20.14	$p = 0.30$
HR2 (model 2)	–	1.52 (0.99–2.33)	1.11 (0.86–1.44)	1 (Ref.)	0.74 (0.57–0.95)	0.9 (0.69–1.16)	1.16 (0.60–2.24)	0	$p = 0.39$	0.81 (0.67–0.97)	0.0244	16.72	$p = 0.27$
HR3 (model 3)	–	1.48 (0.93–2.36)	1.10 (0.85–1.44)	1 (Ref.)	0.77 (0.59–1.01)	0.86 (0.66–1.12)	1.17 (0.61–2.26)	0	$p = 0.25$	0.81 (0.65–1.00)	0.0496	31.89	$p = 0.07$
Men													
Adenocarcinoma													
Participants, n	167,485	7734	33,136	45,330	43,466	35,255	2564	–	–	–	–	–	–
Person-years	2,491,941	89,176	464,280	673,248	670,166	555,060	40,011	–	–	–	–	–	–
Cases, n	1185	69	256	333	297	214	16	–	–	–	–	–	–
HR1 (model 1)	–	1.63 (1.25–2.14)	1.20 (1.01–1.42)	1 (Ref.)	0.91 (0.77–1.06)	0.74 (0.62–0.88)	0.94 (0.54–1.64)	0	$p = 0.40$	0.72 (0.65–0.80)	<0.0001	0	$p = 0.95$
HR2 (model 2)	–	1.58 (1.10–2.26)	1.18 (1–1.4)	1 (Ref.)	0.92 (0.78–1.08)	0.75 (0.63–0.90)	0.93 (0.53–1.61)	30.78	$p = 0.14$	0.73 (0.66–0.82)	<0.0001	0	$p = 0.79$
HR3 (model 3)	–	1.73 (1.24–2.43)	1.19 (1–1.42)	1 (Ref.)	0.91 (0.77–1.08)	0.76 (0.63–0.91)	0.93 (0.53–1.62)	18.35	$p = 0.24$	0.73 (0.65–0.82)	<0.0001	0	$p = 0.48$

TABLE 4 (Continued)

		<18.5	18.5 to <21	21 to <23	23 to <25	25 to <30	≥30	Heterogeneity for lowest category		Trend (per 5 kg/m^2)		Heterogeneity for trend	
	Total	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	I^2 (%)	Cochran's Q test	HR (95% CI)	p	I^2 (%)	Cochran's Q test
Squamous cell carcinoma													
Participants, *n*	167,485	7734	33,136	45,330	43,466	35,255	2564	–	–	–	–	–	–
Person-years	2,491,941	89,176	464,280	673,248	670,166	555,060	40,011	–	–	–	–	–	–
Cases, *n*	1110	60	258	334	262	180	16	–	–	–	–	–	–
HR1 (model 1)	–	1.25 (0.88–1.76)	1.17 (0.91–1.49)	1 (Ref.)	0.78 (0.66–0.93)	0.79 (0.58–1.09)	1.02 (0.62–1.67)	23.36	$p=0.31$	0.77 (0.66–0.91)	0.0020	40.31	$p=0.05$
HR2 (model 2)	–	1.21 (0.86–1.70)	1.16 (0.90–1.49)	1 (Ref.)	0.81 (0.69–0.96)	0.74 (0.61–0.89)	0.94 (0.57–1.56)	18.38	$p=0.36$	0.79 (0.71–0.89)	<0.0001	0	$p=0.1$
HR3 (model 3)	–	1.23 (0.85–1.78)	1.07 (0.85–1.34)	1 (Ref.)	0.81 (0.69–0.97)	0.72 (0.59–0.87)	0.95 (0.57–1.57)	24.46	$p=0.25$	0.8 (0.71–0.9)	0.0002	0	$p=0.13$
Small-cell carcinoma													
Participants, *n*	167,485	7734	33,136	45,330	43,466	35,255	2564	–	–	–	–	–	–
Person-years	2,491,941	89,176	464,280	673,248	670,166	555,060	40,011	–	–	–	–	–	–
Cases, *n*	459	26	101	137	97	91	7	–	–	–	–	–	–
HR1 (model 1)	–	1.59 (1.02–2.49)	1.07 (0.81–1.40)	1 (Ref.)	0.74 (0.56–0.97)	0.88 (0.67–1.15)	1.16 (0.53–2.53)	0	$p=0.88$	0.78 (0.65–0.93)	0.0070	6.47	$p=0.67$
HR2 (model 2)	–	1.43 (0.90–2.26)	1.03 (0.78–1.36)	1 (Ref.)	0.73 (0.56–0.96)	0.88 (0.66–1.16)	1.17 (0.54–2.56)	0	$p=0.86$	0.80 (0.67–0.96)	0.0174	4.25	$p=0.47$
HR3 (model 3)	–	1.45 (0.88–2.38)	1.02 (0.76–1.36)	1 (Ref.)	0.76 (0.58–1.01)	0.90 (0.68–1.19)	1.18 (0.54–2.58)	0	$p=0.58$	0.82 (0.68–0.99)	0.0409	4.2	$p=0.36$
Women													
Adenocarcinoma													
Participants, *n*	196,094	12,187	40,685	51,462	44,488	42,454	4818	–	–	–	–	–	–
Person-years	3,019,783	155,044	599,569	797,198	706,185	684,747	77,041	–	–	–	–	–	–
Cases, *n*	934	43	140	268	237	231	15	–	–	–	–	–	–
HR1 (model 1)	–	1.14 (0.81–1.60)	0.83 (0.66–1.03)	1 (Ref.)	1.11 (0.84–1.46)	0.98 (0.74–1.29)	0.67 (0.39–1.17)	0	$p=0.91$	0.97 (0.84–1.11)	0.6110	29.21	$p=0.16$
HR2 (model 2)	–	1.15 (0.81–1.63)	0.81 (0.64–1.02)	1 (Ref.)	1.16 (0.85–1.57)	1.02 (0.73–1.41)	0.66 (0.38–1.16)	0	$p=0.68$	0.96 (0.84–1.09)	0.5376	22.83	$p=0.21$
HR3 (model 3)	–	1.10 (0.76–1.60)	0.86 (0.64–1.16)	1 (Ref.)	1.08 (0.78–1.50)	1.14 (0.75–1.74)	0.67 (0.38–1.19)	0	$p=0.65$	0.99 (0.85–1.15)	0.8497	38.77	$p=0.11$
Squamous cell carcinoma													
Participants, *n*	196,094	12,187	40,685	51,462	44,488	42,454	4818	–	–	–	–	–	–
Person-years	3,019,783	155,044	599,569	797,198	706,185	684,747	77,041	–	–	–	–	–	–
Cases, *n*	113	15	26	27	22	21	2	–	–	–	–	–	–
HR1 (model 1)	–	3.22 (1.67–6.22)	1.57 (0.92–2.67)	1 (Ref.)	0.83 (0.47–1.47)	0.94 (0.54–1.63)	2.97 (0.63–13.92)	0	$p=0.67$	0.60 (0.44–0.83)	0.002	9.73	$p=0.45$
HR2 (model 2)	–	3.04 (1.51–6.12)	1.11 (0.6–2.04)	1 (Ref.)	0.87 (0.47–1.61)	0.76 (0.41–1.42)	2.74 (0.52–14.47)	0	$p=0.95$	0.64 (0.46–0.9)	0.0103	9.87	$p=0.49$
HR3 (model 3)	–	3.33 (1.60–6.91)	1.10 (0.58–2.1)	1 (Ref.)	0.90 (0.48–1.71)	0.77 (0.40–1.46)	1.72 (0.17–17.20)	0	$p=0.96$	0.6 (0.42–0.87)	0.0065	12.26	$p=0.45$

(Continues)

TABLE 4 (Continued)

	Total	<18.5	18.5 to <21	21 to <23	23 to <25	25 to <30	≥30	Heterogeneity for lowest category		Trend (per 5 kg/m^2)		Heterogeneity for trend	
		HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	I^2 (%)	Cochran's Q test	HR (95% CI)	p	I^2 (%)	Cochran's Q test
Small-cell carcinoma													
Participants, n	196,094	12,187	40,685	51,462	44,488	42,454	4818	-	-	-	-	-	-
Person-years	3,019,783	155,044	599,569	797,198	706,185	684,747	77,041	-	-	-	-	-	-
Cases, n	70	5	18	16	12	16	3	-	-	-	-	-	-
HR1 (model 1)	-	2.42 (0.87–6.75)	2.28 (1.15–4.51)	1 (Ref.)	0.72 (0.33–1.53)	1.19 (0.62–2.30)	2.39 (0.61–9.35)	0	$p=1.00$	0.81 (0.51–1.29)	0.3790	35	$p=0.11$
HR2 (model 2)	-	1.73 (0.42–7.13)	2.18 (0.72–6.60)	1 (Ref.)	0.87 (0.38–1.99)	0.91 (0.4–2.07)	1.95 (0.48–7.99)	0	$p=0.83$	0.91 (0.56–1.46)	0.6855	33.53	$p=0.15$
HR3 (model 3)	-	1.71 (0.33–8.86)	2.25 (0.72–7.00)	1 (Ref.)	0.87 (0.38–1.99)	0.75 (0.33–1.7)	1.95 (0.48–7.98)	0	$p=0.47$	0.83 (0.41–1.67)	0.5936	55.86	$p=0.07$

Abbreviations: CI, confidence interval; HR, hazard ratio; I^2, inconsistency index; p, probability; Ref., reference.

[a]Adjustment for age (year, continuous) and area (for JPHC-I, JPHC-II, JACC, and LSS).

[b]Further adjustment for smoking (men: never, former and current [pack-years (PY) 0< and ≤20], former and current [PY 20< and ≤30], former and current [PY 30< and ≤40], former and current [PY >40]; women: never, former and current [PY 0< and ≤20], former and current [PY 20< and ≤30], former and current [PY >30]), drinking (noncurrent drinkers [never- or ex-drinker], occasional drinkers [less than once per week], regular drinkers [<23 g/day], regular drinkers [≥23 g/day]) and history of diabetes (no, yes) to model 1.

[c]Further adjustment for exercise to model 2.

sought to control for smoking yielded mixed findings, with some showing the attenuation or even disappearance of inverse associations in analyses restricted to never-smokers.[8,10] The 2018 pooled analysis provided evidence supporting the inverse association in both smokers and never smokers.[3] Our findings showing an overall inverse association in men and women combined were largely consistent with the results of the 2018 pooled analysis. However, further sex-specific analyses revealed that the increased risk associated with low BMI was apparent only in male current and former smokers, and was attenuated or absent in male never smokers. Among women, low BMI was associated with an increased risk of lung cancer, but this association was not statistically significant. One possible reason for the different results between sexes is the limited statistical power of the sex-specific analyses. Together, our findings suggest that the overall inverse associations between BMI and lung cancer risk may be partly driven by current and former male smokers. In addition, we examined the interaction between BMI and smoking in influencing lung cancer risk and found no statistically significant interaction between low BMI and ever smoking. Given that previous studies have shown increased levels of 8-OHdG (endogenous oxidative damage to DNA) in lean smokers and an inverse association between weight loss and 8-OHdG levels,[30,31] leanness may contribute to reduced biological functions against smoking-induced oxidative DNA damage. Further studies are needed to address biological or statistical interactions between smoking and BMI in modulating lung cancer risk.

Another possible explanation for the observed inverse associations is reverse causation, which refers to the fact that undiagnosed lung carcinoma or other chronic medical conditions precede and cause weight loss.[32] To evaluate the effect of reverse causation on risk estimates, we repeated the analyses but excluded cases diagnosed during the first 5 years of follow-up. The results remained materially unchanged when compared to the main analyses, thereby implying that the observed inverse associations could not be explained by pre-existing illness.

Even with careful attempts to address confounding and reverse causation, establishing an inverse causal relationship between BMI and lung cancer risk remains challenging because of the nature of observational studies as well as the lack of mechanistic understanding. The emergence of MR—an approach using genetic variants as instrumental variables to approximate environmental exposure—has offered a solution to circumvent the limitations (confounding and reverse causation) that are inherent in observational studies.[33] Several MR studies revealed that genetically predicted BMI was associated with an increased risk of lung cancer of all types,[34–38] a finding that contrasts with the inverse association seen in observational studies. One interpretation is that MR studies evaluated the association of lung cancer with static, genetically determined BMI throughout one's lifetime, while observational studies often examined associations with one single baseline BMI measurement in adulthood. Another reason may be that BMI-associated genetic variants used in these MR studies were derived from genome-wide association studies involving populations of European ancestry, making it uncertain

whether the results can be generalized to populations of East Asian ancestry. Further MR analyses using genetic variants associated with BMI in the Japanese population are warranted to corroborate or refute BMI–lung cancer associations.

Whether the association of BMI with lung cancer differs by histological subtype has been explored in both observational and MR studies, but the findings are inconclusive. The 2018 pooled analysis found inverse associations for adenoma and squamous cell carcinoma, but identified a positive association for small-cell lung cancer.[3] In our pooled analysis, similar inverse associations were observed for adenocarcinoma and squamous cell carcinoma; however, no significant associations were noted for small-cell lung cancer. In addition, the results of MR studies were not entirely consistent, with inverse association documented for lung adenocarcinoma in some studies.[34,39] These findings indicate that BMI may exert differential effects on lung cancer histological subtypes in different ethnic groups.

A major strength of our study is that the number of lung cancer cases in the Japanese population was larger than that in any previous study. By pooling data, we were able to use the same BMI categories and covariate definitions, analyzing the associations between BMI and the risk of lung cancer according to sex, smoking status, and histological type. In addition, we were able to address the effect of confounding by adjusting for PY of smoking and restricting the analysis to never-smokers.

Our study also has limitations. First, BMI is known to be an imperfect measurement of adiposity; it does not distinguish between adipose tissue and lean body mass, nor does it reflect metabolic or endocrine disruptions associated with obesity.[40] However, few studies have explored whether other measures of fatness and body composition, such as waist circumference and waist-to-hip ratio, are associated with the risk of lung cancer in Japan.[7] Second, we were only able to analyze a single baseline BMI measurement for each individual; it is possible that changes in weight and height over time may have influenced the observed associations. Third, we acknowledge the lack of statistical power for certain subgroup analyses, such as histological type, because of the small number of cases. The possibility that some of the results of these analyses were due to chance cannot be ruled out. Fourth, despite our best efforts to address confounders, the confounding effect of smoking may have persisted, in particular in lean male smokers, and other unknown confounders might also have distorted the observed associations. Finally, compared with current smokers, the precise risk estimate for underweight never smokers is still challenging because they are thought to be a heterogeneous group; their BMI is thought to be influenced by various factors, including genetics, passive smoking, underlying medical conditions, culture, and socioeconomic status.[41] Further refinement in risk estimates is needed for this group.

In summary, our findings add to the evidence that low BMI is inversely associated with an increased risk of lung cancer. This may be driven by current and former smokers, and warrants further investigation of never-smokers in additional studies.

AUTHOR CONTRIBUTIONS

Sayo Kawai: Conceptualization; data curation; formal analysis; methodology; writing – original draft; writing – review and editing. **Yingsong Lin:** Conceptualization; data curation; methodology; project administration; supervision; writing – original draft; writing – review and editing. **Hiroshi Tsuge:** Formal analysis; methodology; resources; writing – review and editing. **Hidemi Ito:** Data curation; resources; supervision; writing – review and editing. **Keitaro Matsuo:** Data curation; investigation; project administration; supervision; validation; writing – review and editing. **Keiko Wada:** Data curation; formal analysis; investigation; project administration; resources; validation; writing – review and editing. **Chisato Nagata:** Investigation; project administration; resources; supervision; validation; writing – review and editing. **Nobuhiro Narii:** Data curation; formal analysis; validation; writing – review and editing. **Tetsuhisa Kitamura:** Data curation; investigation; project administration; supervision; validation; writing – review and editing. **Mai Utada:** Data curation; formal analysis; investigation; project administration; resources; validation; writing – review and editing. **Ritsu Sakata:** Investigation; project administration; resources; validation. **Takashi Kimura:** Data curation; formal analysis; validation; writing – review and editing. **Akiko Tamakoshi:** Data curation; investigation; project administration; resources; supervision; writing – review and editing. **Yumi Sugawara:** Data curation; formal analysis; validation; writing – review and editing. **Ichiro Tsuji:** Investigation; project administration; resources; supervision; writing – review and editing. **Seitaro Suzuki:** Data curation; formal analysis; validation; writing – review and editing. **Norie Sawada:** Investigation; project administration; resources; supervision; writing – review and editing. **Shoichiro Tsugane:** Investigation; project administration; resources; supervision; writing – review and editing. **Tetsuya Mizoue:** Conceptualization; methodology; supervision; writing – review and editing. **Isao Oze:** Investigation; project administration; supervision; validation; writing – review and editing. **Sarah Krull Abe:** Conceptualization; methodology; supervision; validation; writing – review and editing. **Manami Inoue:** Conceptualization; funding acquisition; project administration; resources; supervision; validation; writing – review and editing.

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CONFLICT OF INTEREST STATEMENT

Inoue Manami, Keitaro Matsuo, Chisato Nagata, and Norie Sawada are Editorial Board Members of *Cancer Science*. The other authors have no conflict of interest.

DATA AVAILABILITY STATEMENT

The data underlying this manuscript cannot be shared publicly due to the privacy of study participants. A collaboration with each participating cohort study is required to access the data.

ETHICS STATEMENT

Approval of the research protocol by an institutional review board: Approval of institutional review boards was obtained for each participating study included in the pooled analysis.

Informed consent: Informed consent was obtained from participants of each cohort study.

Registry and the registration no. of the study/trial: N/A.

Animal studies: N/A.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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