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ORIGINAL ARTICLE

Body mass index and esophageal and gastric cancer: A pooled analysis of 10 population-based cohort studies in Japan

Yuriko N. Koyanagi[1] | Keitaro Matsuo[2,3] | Hidemi Ito[1,4] | Chaochen Wang[5] | Akiko Tamakoshi[6] | Yumi Sugawara[7] | Ichiro Tsuji[7] | Ayami Ono[8] | Shoichiro Tsugane[9,10] | Norie Sawada[9] | Keiko Wada[11] | Chisato Nagata[11] | Taro Takeuchi[12] | Tetsuhisa Kitamura[12] | Mai Utada[13] | Ritsu Sakata[13] | Tetsuya Mizoue[14] | Sarah Krull Abe[8] | Manami Inoue[8] | Research Group for the Development and Evaluation of Cancer Prevention Strategies in Japan

[1]Division of Cancer Information and Control, Aichi Cancer Center Research Institute, Nagoya, Japan

[2]Division of Cancer Epidemiology and Prevention, Aichi Cancer Center Research Institute, Nagoya, Japan

[3]Department of Cancer Epidemiology, Nagoya University Graduate School of Medicine, Nagoya, Japan

[4]Division of Descriptive Cancer Epidemiology, Nagoya University Graduate School of Medicine, Nagoya, Japan

[5]Japan Value, Evidence and Outcomes, Japan Drug Development and Medical Affairs Eli Lilly Japan K.K., Kobe, Japan

[6]Department of Public Health, Hokkaido University Faculty of Medicine, Sapporo, Japan

[7]Division of Epidemiology, Department of Public Health and Forensic Medicine, Tohoku University Graduate School of Medicine, Sendai, Japan

[8]Division of Prevention, National Cancer Center Institute for Cancer Control, Tokyo, Japan

[9]Division of Cohort Research, National Cancer Center Institute for Cancer Control, Tokyo, Japan

[10]National Institute of Health and Nutrition, National Institutes of Biomedical Innovation, Health and Nutrition, Tokyo, Japan

[11]Department of Epidemiology and Preventive Medicine, Gifu University Graduate School of Medicine, Gifu, Japan

[12]Department of Environmental Medicine and Population Sciences, Graduate School of Medicine, Osaka University, Suita, Japan

[13]Department of Epidemiology, Radiation Effects Research Foundation, Hiroshima, Japan

[14]Department of Epidemiology and Prevention, Center for Clinical Sciences, National Center for Global Health and Medicine, Tokyo, Japan

Correspondence
Keitaro Matsuo, Division of Cancer Epidemiology and Prevention, Department of Preventive Medicine, Aichi Cancer Research Institute, 1-1 Kanokoden Chikusa-ku, Nagoya, AIC 464-8681, Japan.
Email: kmatsuo@aichi-cc.jp

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Abstract

The effect of body mass index (BMI) on esophageal and gastric carcinogenesis might be heterogeneous, depending on subtype or subsite. However, findings from prospective evaluations of BMI associated with these cancers among Asian populations have been inconsistent and limited, especially for esophageal adenocarcinoma and gastric cardia cancer. We performed a pooled analysis of 10 population-based cohort studies to examine this association in 394,247 Japanese individuals. We used Cox proportional hazards regression to estimate study-specific hazard ratios (HRs)

Abbreviations: aHR, adjusted hazard ratio; AICHI, Three-Prefecture Cohort Study in Aichi; BMI, body mass index; CI, confidence interval; HR, hazard ratio; ICD-O-3, International Classification of Diseases for Oncology, third edition; ICD-O-3-M, ICD-O-3 morphology; ICD-O-3-T, ICD-O-3 tomography; JACC, Japan Collaborative Cohort Study; JPHC- I, Japan Public Health Center- based Prospective Study I; JPHC- II, Japan Public Health Center- based Prospective Study II; LSS, Life Span Study; MIYAGI-I, Miyagi Cohort Study; MIYAGI-II, Three-Prefecture Cohort Study in Miyagi; OHSAKI, Ohsaki Cohort Study; OSAKA, Three-Prefecture Cohort Study in Osaka; RR, relative risk; TAKAYAMA, Takayama Study.

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and 95% confidence intervals (CIs), then pooled these estimates to calculate summary HRs with a random effects model. During 5,750,107 person-years of follow-up, 1569 esophageal cancer (1038 squamous cell carcinoma and 86 adenocarcinoma) and 11,095 gastric (728 cardia and 5620 noncardia) cancer incident cases were identified. An inverse association was observed between BMI and esophageal squamous cell carcinoma (HR per 5-kg/m^2 increase 0.57, 95% CI 0.50–0.65), whereas a positive association was seen in gastric cardia cancer (HR 1.15, 95% CI 1.00–1.32). A nonsignificant and significant positive association for overweight or obese (BMI ≥25 kg/m^2) relative to BMI <25 kg/m^2 was observed with esophageal adenocarcinoma (HR 1.32, 95% CI 0.80–2.17) and gastric cardia cancer (HR 1.24, 95% CI 1.05–1.46), respectively. No clear association with BMI was found for gastric noncardia cancer. This prospective study—the largest in an Asian country—provides a comprehensive quantitative estimate of the association of BMI with upper gastrointestinal cancer and confirms the subtype- or subsite-specific carcinogenic impact of BMI in a Japanese population.

KEYWORDS
body mass index, esophageal cancer, gastric cancer, large-scale population-based cohort studies, pooled analysis

1 | INTRODUCTION

Esophageal and gastric cancers remain common worldwide, affecting more than 604,000 and 1,089,000 people in 2020, respectively.[1] Incidence rates are highest in Asian countries, among which Japan showed the third- and second-largest number of new cases (~26,000 and ~138,000 cases), respectively.[1] The etiologies of these cancers are heterogeneous, depending on subtype or subsite. Of the two most common histological subtypes of esophageal cancer, squamous cell carcinoma is the predominant histological subtype in Asians, and is strongly associated with alcohol drinking and smoking.[2,3] The other most common subtype, esophageal adenocarcinoma, is more common in Caucasians, and the major risk factors are obesity and smoking.[2,3] For gastric cancer, the most common subtype is adenocarcinoma, but etiology differs between subsites: gastric cardia cancer appears to share a common etiology with esophageal adenocarcinoma and is associated with obesity and smoking, whereas noncardia cancer—the most prevalent subsite in Asia—is associated with *Helicobacter pylori* infection and smoking.[4–6]

A number of epidemiological studies have confirmed a positive association between body mass index (BMI) and esophageal adenocarcinoma and gastric cardia cancer.[7–9] The World Cancer Research Fund and American Institute of Cancer Research accordingly concluded that this association was "convincing" for esophageal adenocarcinoma and "probable" for gastric cardia cancer.[3,4] One plausible mechanism for this association is that the development of gastroesophageal reflux disease or inflammation of the esophagus promoted by greater body fatness induces Barrett's esophagus, resulting in increased risk of esophageal adenocarcinoma and gastric cardia cancer.[10,11] In contrast, however, epidemiological evidence has shown an inverse association between BMI and esophageal squamous cell carcinoma,[7] and no clear association between BMI and gastric noncardia cancer.[9]

Given that Asians generally have greater adiposity with the same BMI[12] and different dietary activities and lifestyles compared with Caucasians, it is crucial to assess whether the magnitude and direction of the associations between BMI and risk of upper gastrointestinal cancer in Asians are comparable to those in Caucasians. Several epidemiological studies have evaluated the association between BMI and esophageal and gastric cancer risk among Asian populations,[13–20] but the findings were inconsistent and limited, particularly with regard to esophageal adenocarcinoma and gastric cardia cancer. A recent large-scale pooled analysis in Asian countries with more than 800,000 individuals reported that underweight (BMI <18.5 kg/m^2) and extreme obesity (BMI ≥35 kg/m^2) were associated with the mortality risk of overall esophageal and esophageal squamous cell carcinoma, but showed no clear association between esophageal adenocarcinoma and BMI.[20] A second pooled analysis including more than 500,000 Asian individuals showed a U-shaped association between BMI and incidence risk of overall gastric and gastric noncardia cancer, but failed to confirm increased risk of gastric cardia cancer incidence in overweight and obese people.[19] These findings suggest that the association between BMI and these cancers shows different patterns between populations. However, considering that lifestyle and environmental factors are strongly associated with both BMI as well as esophageal and gastric cancer risk, unmeasured confounders due to the pooling of various populations with heterogeneous lifestyle and environmental factors might bias the results.

Here, we conducted a pooled analysis of 10 population-based prospective cohort studies in Japan comprising approximately 400,000 subjects and evaluated the association of BMI with esophageal and gastric cancers by subtype or subsite with unified BMI

categories. This study included general Japanese populations sharing a similar lifestyle and living environment, used incidence rather than mortality as an end point, and adjusted for several important covariates uniformly across cohorts, making it possible to increase the generalizability of the results and identify the risk contribution of BMI directly.

2 | METHODS

2.1 | Study population

To evaluate the association between lifestyle factors and cancer risk, the Research Group for the Development and Evaluation of Cancer Prevention Strategies in Japan has been evaluating the association between lifestyle factors and cancer risk by conducting pooled analyses using original data from large-scale population-based cohort studies in Japan that met inclusion criteria described elsewhere.[21] The present study included 10 studies: the Japan Public Health Center-based Prospective Study (JPHC-I and -II),[22] the Japan Collaborative Cohort Study (JACC),[23] the Miyagi Cohort Study (MIYAGI-I),[24] the Three-Prefecture Cohort Study in Miyagi (MIYAGI-II),[25] the Three-Prefecture Cohort Study in Aichi (AICHI),[25] the Takayama Study (TAKAYAMA),[26] the Ohsaki Cohort Study (OHSAKI),[27] the Three-Prefecture Cohort Study in Osaka (OSAKA),[25] and the Life Span Study (LSS)[28] (Table 1). We excluded subjects with a past history of cancer at baseline, subjects with unknown information on BMI, subjects with extreme values of BMI (BMI <14 or >40 kg/m^2), and subjects with estimated radiation doses from the atomic bombings of ≥100 mGy (for LSS). All studies were reviewed and approved by their relevant institutional ethics review boards. The JPHC-I and -II,[17,18] MIYAGI-II,[15] and TAKAYAMA[16] studies have already evaluated the association between BMI and esophageal or gastric cancer risk in their respective cohorts. We reanalyzed the association using the updated datasets of these studies.

2.2 | Assessment of exposure

Each study collected information on height and weight at baseline using a custom-developed self-administered questionnaire. BMI was calculated as weight in kilograms divided by height in meters squared. A number of studies conducted validation studies on BMI that had been estimated from self-reported weight and height. These reported correlation coefficients between BMI estimated from the questionnaire and BMI estimated from actually measured values for weight and height of 0.89 in men and 0.90 in women for JPHC-I and -II,[29] 0.91 in the two sexes for MIYAGI-I,[30] and 0.88 in the two sexes for OHSAKI.[31] Correlation coefficients for self-reported versus measured height and weight values in both sexes were 0.93 and 0.97 for TAKAYAMA, respectively.[32] In contrast, JACC, MIYAGI-II, AICHI, OSAKA, and LSS did not provide information on the validation of BMI, but JACC used the same questions on height and weight as MIYAGI-I while MIYAGI-II, AICHI, OSAKA, and LSS used similar questions on height and weight to JPHC-I and -II. Important covariates for esophageal and gastric cancers—cumulative smoking exposure,[6] alcohol consumption,[3,4,33] history of diabetes,[34–36] vegetable and fruit intake,[3,37] salt intake,[38] green tea intake,[39] and physical activity[3]—were also collected via self-administered questionnaire.

2.3 | Follow-up and outcome assessment

As shown in Table 1, participants had been followed from baseline survey to last follow-up date in all studies. Residential status, survival, date of death, and date of moving out were confirmed using residential registries managed by municipalities in the respective study areas. Incident cancer cases were identified using local cancer registries or via direct access with main regional hospitals. Esophageal cancer was identified by the International Classification of Diseases for Oncology, third edition (ICD-O-3)[40] tomography (ICD-O-3-T) codes of C15.0-C15.9. Esophageal squamous cell carcinoma included ICD-O-3 morphology (ICD-O-3-M) 8050–8078 and 8083–8084.[41] Esophageal adenocarcinoma included ICD-O-3-M 8140–8141, 8143–8145, 8190–8231, 8260–8265, 8310, 8401, 8480–8490, 8550–8552, 8570–8574, and 8576.[41] Gastric cancer included ICD-O-3-T C16.0-C16.9, with cancers of the cardia including ICD-O-3-T C16.0 and those of the noncardia stomach including ICD-O-3-T C16.1–C16.6.

2.4 | Statistical analysis

A Cox proportional hazards regression model was used to estimate study-specific hazard ratios (HRs) and their two-sided 95% confidence intervals (CIs) for the incidence of esophageal or gastric cancer per 5-kg/m^2 increase in BMI. We calculated person-years of follow-up from the date of the baseline survey to the first occurrence of the date of diagnosis, date of death, date of loss to follow-up (migration from the study area), or date of termination of follow-up. All studies estimated two types of HR: model 1 adjusted for sex, age at baseline, and area (for multicentric studies, i.e., JPHC-I, JPHC-II, JACC, and LSS), and model 2 adjusted for covariates in model 1 as well as cumulative smoking exposure (pack-years: 0, 0< and ≤20, >20), alcohol consumption (nondrinker, occasional drinker [<1 day/week], and current drinker [1 to 4 days/week, ≥5 days/week and <23 ethanol g/day, ≥5 days/week and ≥23 ethanol g/day]), and history of diabetes (no, yes). Pack-years were established as the product of the number of packs smoked per day by the number of years of smoking.

Among the six studies with available information on total energy intake, vegetable intake, fruit intake, salt intake, consumption of green tea, and physical activity (JPHC-I, JPHC-II, JACC, MIYAGI-I, TAKAYAMA, and OHSAKI), we also estimated HRs by making the same adjustments as in model 2, but also with adjustment for total energy intake (quartiles), vegetable intake (quartiles), fruit intake

TABLE 1 Characteristics of the cohort studies included in the present pooled analysis

Study	Initial population	Age range at baseline (years)	Follow-up (start)	Follow-up (end)	Average follow-up period (years)	Number of subjects		Number of cases						Remarks
						Male	Female	EC (M, F)	GC (M, F)	ESCC	EA	GCC	GNCC	
JPHC-I	Japanese residents of five public health center areas in Japan	40–59	1990	2013	20.9	20,383	22,201	221, 22	991, 394	201	13	76	1105	Subjects of one public health center area were excluded due to lack of incidence data
JPHC-II	Japanese residents of six public health center areas in Japan	40–69	1993	2013	17.2	29,150	32,673	276, 29	1235, 498	243	8	101	1121	
JACC	Residents from 45 areas throughout Japan	40–79	1988	2009	13.2	24,755	35,659	149, 21	1091, 614	73	14	79	633	22 selected areas with cancer incidence follow-up data were used in this analysis
MIYAGI-I	Residents of 14 municipalities in Miyagi Prefecture, Japan	40–64	1990	2014	21.3	21,094	22,657	259, 31	1432, 567	213	32	191	1331	
MIYAGI-II	Residents of three municipalities in Miyagi Prefecture, Japan	40+	1984	1992	7.6	13,027	15,956	60, 8	332, 140	0	0	67	107	
AICHI	Residents of two municipalities in Aichi Prefecture, Japan	40–103	1985	2000	11.6	15,217	16,863	60, 7	405, 187	29	1	27	24	
TAKAYAMA	Residents of Takayama city, Gifu Prefecture, Japan	35–101	1992	2008	13.6	13,398	15,568	57, 10	411, 218	49	3	10	81	
OHSAKI	Residents of 14 municipalities in Miyagi Prefecture, Japan	40–79	1994	2008	10.7	21,498	23,196	175, 38	954, 375	160	13	131	746	
OSAKA	Residents of four municipalities in Osaka Prefecture, Japan	40–97	1983	1998–2000	11.4	15,920	17,973	80, 10	537, 265	24	2	21	158	
LSS	Atomic bomb survivors in Hiroshima and Nagasaki, Japan	46–104	1991	2003	10.8	6541	10,518	45, 11	263, 186	46	0	25	314	LSS originally started in 1950 This analysis included subjects who responded to the 1991 survey
Total						**180,983**	**213,264**	**1382, 187**	**7651, 3444**	**1038**	**86**	**728**	**5620**	

Abbreviations: AICHI, The Three-Prefecture Cohort Study in Aichi; EA, esophageal adenocarcinoma; EC, esophageal cancer; ESCC, esophageal squamous cell carcinoma; F, female; GC, gastric cancer; GCC, gastric cardia cancer; GNCC, gastric noncardia cancer; JACC, The Japan Collaborative Cohort Study; JPHC, The Japan Public Health Center-based Prospective Study; LSS, Life Span Study; M, male; MIYAGI-I, The Miyagi Cohort Study; MIYAGI-II, The Three-Prefecture Cohort Study in Miyagi; OHSAKI, The Ohsaki Cohort Study; Osaka, The Three-Prefecture Cohort Study in Osaka; TAKAYAMA, The Takayama Study. In ESCC and EA, we excluded MIYAGI-II, in which no information on histological type was available.

(quartiles), salt intake (quartiles), consumption of green tea (<1 cup/day, 1–2 cups/day, 3–4 cups/day, ≥5 cups/day), and physical activity (seldom, sometimes, frequently) (model 3). Consumption of vegetables, fruit, and salt was adjusted for total energy intake by the residual method[42] and classified into quartiles using sex- and cohort-specific cutoff points. Because the questionnaires were not homogeneous across the studies, we created a variable for physical activity using broad exposure categories as follows: seldom (JPHC-I, JPHC-II, JACC, MIYAGI-I, and OHSAKI: seldom; TAKAYAMA: never), sometimes (JPHC-I and JPHC-II: <5 days/week; JACC, MIYAGI-I, TAKAYAMA, and OHSAKI: <5 h/day), frequently (JPHC-I and JPHC-II: almost every day; JACC, MIYAGI-I, TAKAYAMA, and OHSAKI: ≥5 h/day).

HRs with exclusion of cases diagnosed in the first 3 years of follow-up were estimated to examine possible reverse causation. To investigate whether the effect of BMI was homogeneous within strata of smoking status and sex, we performed stratified analyses according to smoking status (never, ever) and sex. Furthermore, with the same covariate adjustment, we evaluated the impact of overweight (25 to <30 kg/m^2) or obese (≥30 kg/m^2) on esophageal and gastric cancer risks relative to <25 kg/m^2. Subjects were additionally classified into the following six categories (<18.5, 18.5 to <21, 21 to <23, 23 to <25, 25 to <30, and ≥30 kg/m^2) and HR was estimated for each category relative to a reference category of 21 to <23 kg/m^2. Among covariates, the ratio of missing data was 9.3% for cumulative smoking exposure (n = 36,772), 7.8% for alcohol consumption (n = 30,633), 9.4% for history of diabetes (n = 37,126), 6.9% for energy intake (n = 19,352), 2.2% for vegetable intake (n = 6072), 2.2% for fruit intake (n = 6281), 5.5% for consumption of green tea (n = 15,474), and 5.9% for physical activity (n = 16,606). Missing data for each covariate were coded as indicator terms.

Additionally, we pooled study-specific results using a random effects model.[43] The degree of between-study heterogeneity was analyzed with Cochran's Q-statistic and I^2-statistic.[44] The proportional hazards assumption was evaluated graphically with log-negative-log plots, which revealed no major violations of the proportional hazards assumption. All analyses were performed using SAS version 9.4 (SAS Institute, Inc.) or STATA version 17.0 (Stata Corporation). Two-sided p values of <0.05 were considered statistically significant.

3 | RESULTS

This study included 394,247 subjects (180,983 males and 213,264 females) with 5,750,107 person-years of follow-up (average follow-up: 13.8 years). In total, we identified 1569 incident esophageal cancer cases (1382 males and 187 females), including 1038 esophageal squamous cell carcinoma and 86 esophageal adenocarcinoma cases, and 11,095 incident gastric cancer cases (7651 males and 3444 females), including 728 gastric cardia cancer and 5620 gastric noncardia cancer cases (Table 1).

Figure 1 shows adjusted (model 2) HRs (aHRs) per 5-kg/m^2 increase in BMI. A significant inverse association was observed between BMI and risk of overall esophageal cancer (aHR 0.59, 95% CI 0.52–0.67). Stratification by subtype demonstrated that the inverse association was restricted to squamous cell carcinoma (aHR 0.57, 95% CI 0.50–0.65), with no association seen in adenocarcinoma (aHR 1.01, 95% CI 0.69–1.48). Furthermore, these inverse associations observed in overall esophageal cancer and esophageal squamous cell carcinoma were stronger in ever smokers (esophageal cancer: aHR 0.52, 95% CI 0.46–0.58; esophageal squamous cell carcinoma: aHR 0.49, 95% CI 0.43–0.57). For gastric cancer, although we observed a significant inverse association of BMI with overall gastric cancer (aHR 0.96, 95% CI 0.93–1.00), stratification by subsite demonstrated a positive association in gastric cardia cancer (aHR 1.15, 95% CI 1.00–1.32) and no association in gastric noncardia cancer (aHR 0.99, 95% CI 0.94–1.03). The inverse association in overall gastric cancer became slightly stronger in ever smokers (aHR 0.93, 95% CI 0.89–0.98) and unclear in never smokers (aHR 0.99, 95% CI 0.94–1.06), but consistent results across each stratum of smoking status were observed for both gastric cardia and noncardia cancers.

Figure 2 shows aHRs for being overweight or obese (BMI ≥25 kg/m^2) relative to BMI <25 kg/m^2. Being overweight or obese was inversely associated with the risk of overall esophageal cancer (aHR 0.64, 95% CI 0.56–0.73) and esophageal squamous cell carcinoma (aHR 0.56, 95% CI 0.47–0.67). In contrast, we observed a nonsignificant and significant positive association of overweight or obesity with esophageal adenocarcinoma (aHR 1.32, 95% CI 0.80–2.17) and gastric cardia cancer (aHR 1.24, 95% CI 1.05–1.46), respectively.

Risks of esophageal and gastric cancers by six BMI categories are shown in Table 2. A nonlinear association was suggested for gastric cardia cancer due to a nonsignificant positive association in underweight (BMI <18.5 kg/m^2, aHR 1.16, 95% CI 0.79–1.70) and overweight (25 to <30 kg/m^2, aHR 1.12, 95% CI 0.92–1.37) or obese (≥30 kg/m^2, aHR 1.04, 95% CI 0.57–1.87). On stratification by smoking status (Table 2), results indicated U-shaped associations in overall esophageal cancer, esophageal squamous cell carcinoma, overall gastric cancer, and gastric cardia cancer among never smokers, although some estimates which included only a small number of cases were unstable. No between-study heterogeneity was observed in most estimates (Figures 1 and 2, and Table 2).

Results remained largely unchanged after additional adjustment for total energy intake, vegetable intake, fruit intake, salt intake, consumption of green tea, and physical activity (model 3) and the exclusion of cases diagnosed early within 3 years after enrollment (Tables S1–S3). Further analyses stratified by sex are shown in Table S4. We did not perform analyses by subtype or subsite in females due to the small number of female cases. The results were mostly consistent between sexes in overall esophageal and gastric cancers, but we observed a greater decrease in HR per 5-kg/m^2 for overall esophageal cancer in males (aHR 0.56, 95% CI 0.49–0.64) than in females (aHR 0.74, 95% CI 0.59–0.94).

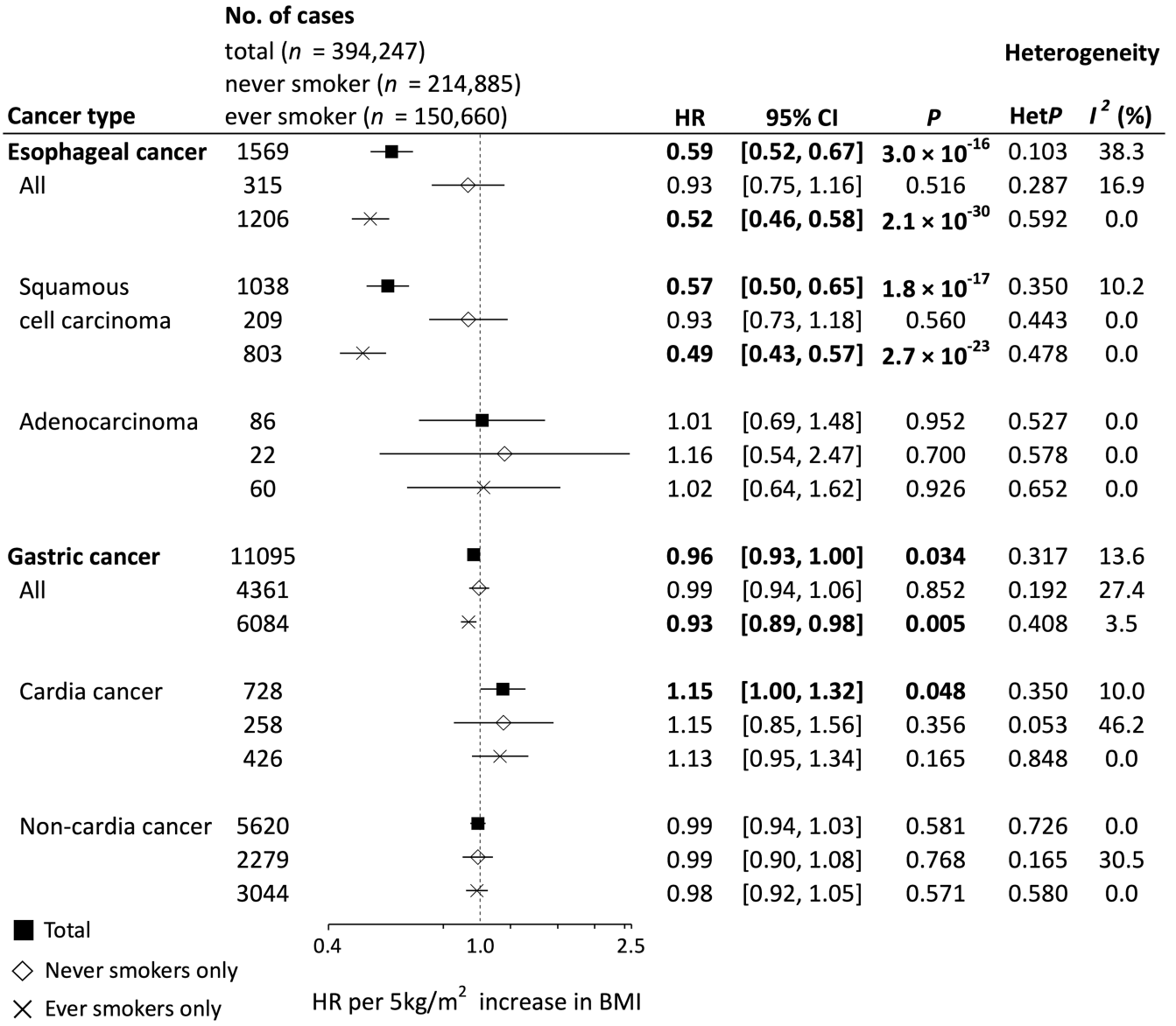

FIGURE 1 Forest plot of hazard ratios (HRs) and 95% confidence intervals (CIs) for each cancer per 5-kg/m^2 increase in body mass index (BMI). HRs were calculated by a random effects model by pooling study-specific HR adjusted for sex, age, area (for multicentric studies, namely JPHC-I, JPHC-II, JACC, and LSS), pack-years (0, 0< and ≤20, >20), alcohol consumption (nondrinker, occasional drinker [<1 day/week], and current drinker [1–4 days/week, ≥5 days/week and <23 ethanol g/day, ≥5 days/week and ≥23 ethanol g/day]), and history of diabetes. Between-study heterogeneity for the risk estimate by trend analysis was evaluated using the *Q*-statistic and the I^2-statistic. The *Q*-statistic was considered statistically significant when $p < 0.10$ and 0% of the I^2-statistic represented no heterogeneity. HR values in bold show statistical significance ($p < 0.05$). For esophageal squamous cell carcinoma and esophageal adenocarcinoma, we excluded MIYAGI-II, in which no information on histological type was available. JACC, Japan Collaborative Cohort Study; JPHC, Japan Public Health Center-based Prospective Study; TAKAYAMA, Takayama Study; LSS, Life Span Study.

4 | DISCUSSION

Using data from 10 population-based cohort studies comprising a total of 394,247 Japanese subjects, we evaluated the association between BMI and risk of upper gastrointestinal cancer incidence by subtype and subsite in an Asian population, where evidence to date has been inconsistent.[13–20] This is one of the largest prospective analyses in an Asian country, with 1569 incident esophageal cancer cases (1038 esophageal squamous cell carcinoma and 86 esophageal adenocarcinoma cases) and 11,095 incident gastric cancer cases (728 gastric cardia and 5620 gastric noncardia cases). The results enabled us to confirm the heterogeneous impact of BMI on upper gastrointestinal cancer according to subtype or subsite[3,4] in an Asian population, as is also seen in Caucasians. Specifically, a significant inverse association was observed between BMI and risk of esophageal squamous cell carcinoma (HR per 5-kg/m^2 increase in BMI 0.57, 95% CI 0.50–0.65), whereas a significant positive association was seen in gastric cardia cancer (HR 1.15, 95% CI 1.00–1.32). The magnitude of the effect of BMI on these cancers was equivalent to that observed in the previous

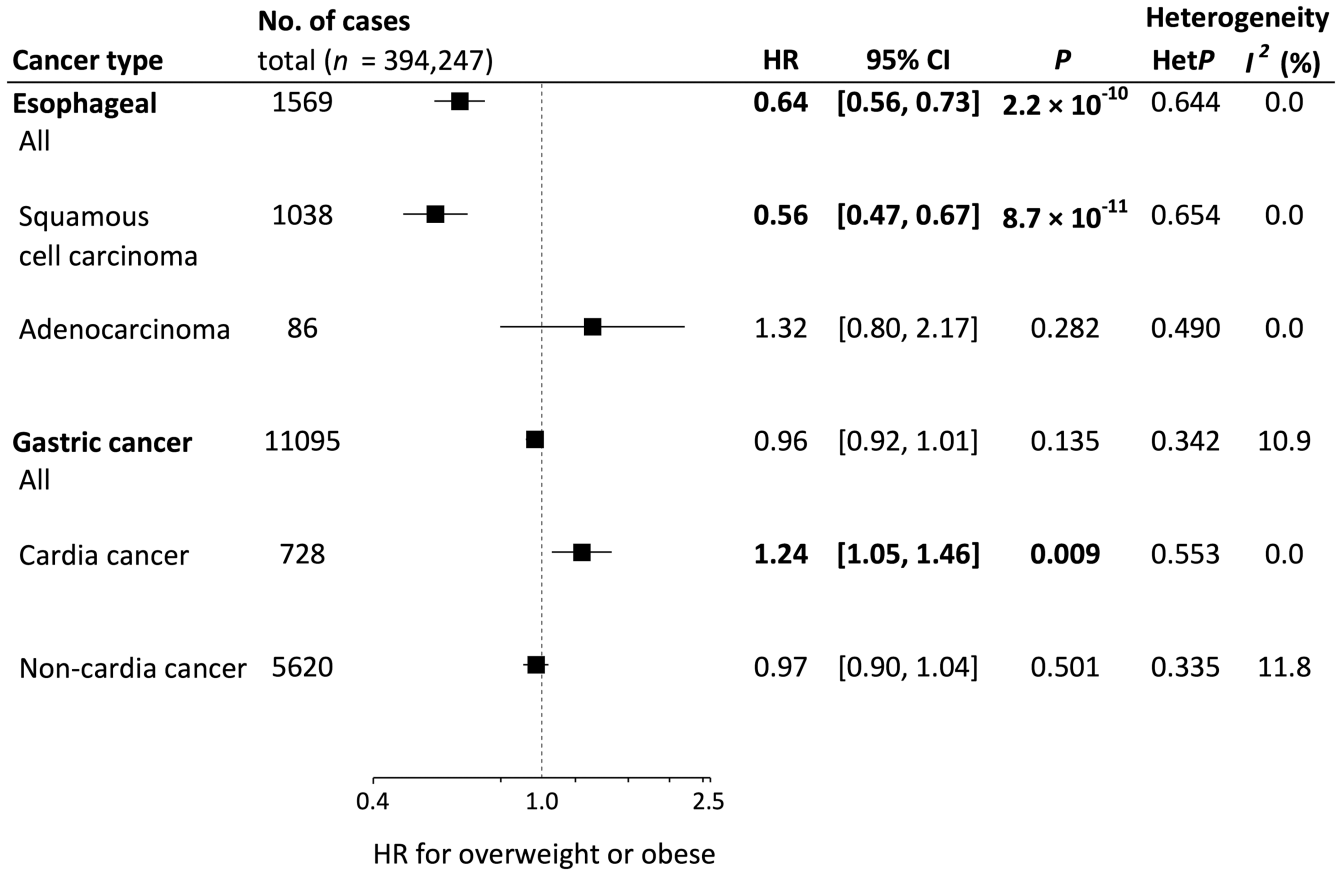

FIGURE 2 Forest plot of hazard ratios (HRs) and 95% confidence intervals (CIs) for overweight or obese (body mas index [BMI] ≥25 kg/m^2) relative to BMI <25. HRs were calculated by a random effects model by pooling study-specific HR adjusted for sex, age, area (for multicentric studies, namely JPHC-I, JPHC-II, JACC, and LSS), pack-years (0, 0 < and ≤20, >20), alcohol consumption (nondrinker, occasional drinker [<1 day/week], and current drinker [1–4 days/week, ≥5 days/week and <23 ethanol g/day, ≥5 days/week and ≥23 ethanol g/day]), and history of diabetes. Between-study heterogeneity for the risk estimate by trend analysis was evaluated using the *Q*-statistic and the I^2-statistic. The *Q*-statistic was considered statistically significant when $p < 0.10$ and 0% of the I^2-statistic represented no heterogeneity. HRs values in bold show statistical significance ($p < 0.05$). For esophageal squamous cell carcinoma and esophageal adenocarcinoma, we excluded MIYAGI-II, in which no information on histological type was available. JACC, Japan Collaborative Cohort Study; JPHC, Japan Public Health Center-based Prospective Study; TAKAYAMA, Takayama Study; LSS, Life Span Study.

meta-analyses conducted mainly in Caucasians (relative risk [RR] of 5-kg/m^2 increase in BMI 0.64, 95% CI 0.56–0.73 for esophageal squamous cell carcinoma; RR 1.23, 95% CI 1.07–1.40 for gastric cardia cancer).[3,11] Being overweight or obese (BMI ≥25 kg/m^2) relative to BMI <25 kg/m^2 was inversely associated with the risk of esophageal squamous cell carcinoma (HR 0.56, 95% CI 0.47–0.67). In contrast, we observed a nonsignificant and significant positive association of overweight or obesity with esophageal adenocarcinoma (HR 1.32, 95% CI 0.80–2.17) and gastric cardia cancer (HR 1.24, 95% CI 1.05–1.46), respectively. In addition, we found no clear association of gastric noncardia cancer with BMI, consistent with a previous meta-analysis.[9]

This study included the largest number of incident cases of esophageal squamous cell carcinoma to date and provides the strongest evidence yet that leanness is a risk factor for esophageal squamous cell carcinoma. Increased risks among lean subjects have been consistently observed in other smoking-associated cancer sites,[45] including lung[46,47] and head and neck,[48] making this relationship more convincing. Given that smoking decreases appetite[49] and that smokers accordingly tend to be leaner than nonsmokers, confounding by smoking has been one of the primary explanations for this association. To disentangle the effects of leanness and smoking on risk of esophageal squamous cell carcinoma epidemiologically, five studies[20,50–53] evaluated consistency in the inverse association with BMI by smoking status. Three reported a consistent inverse association with BMI in never and ever smokers.[50–52] Consistent with these, the present study suggests that risk is elevated in those with low BMI within both strata of smoking status (Table 2). With respect to other sites, one large prospective study showed the association of higher BMI with reduced risk of lung cancer only in ever smokers,[47] whereas large collaborative analyses involving multiple cohort studies and case–control studies showed the association of leanness with lung cancer[46] and head and neck cancer,[48] respectively, regardless of smoking status. Taken together, the effect of low BMI on never smokers is also likely to be carcinogenic, although this study could

TABLE 2 Risks of esophageal and gastric cancers by BMI category

			Esophageal cancer											
			All				Squamous cell carcinoma				Adenocarcinoma			
BMI kg/m^2	Subjects (*n*)	Person- years	Ca (*n*)	HR	95% CI	Het*P*, I^2	Ca (*n*)	HR	95% CI	Het*P*, I^2	Ca (*n*)	HR	95% CI	Het*P*, I^2
All subjects														
<18.5	21,466	254,959	129	**1.48**	**1.14–1.91**	0.3, 20	51	1.31	0.90–1.90	0.2, 28	0	ND		–
18.5 to <21	79,688	1,108,234	394	**1.31**	**1.15–1.50**	0.9, 0	284	**1.30**	**1.10–1.53**	0.9, 0	19	0.91	0.48–1.72	0.9, 0
21 to <23	104,714	1,531,131	471	1.00	Reference	–	320	1.00	Reference		27	1.00	Reference	–
23 to <25	95,164	1,431,439	326	**0.75**	**0.61–0.91**	0.1, 40	231	**0.76**	**0.62–0.93**	0.3, 19	16	0.91	0.46–1.82	0.7, 0
25 to <30	85,053	1,300,950	235	**0.64**	**0.55–0.76**	0.4, 0	143	**0.56**	**0.46–0.68**	0.5, 0	23	0.95	0.52–1.71	0.6, 0
≥30	8162	123,394	14	0.64	0.37–1.10	0.8, 0	9	0.54	0.28–1.05	0.9, 0	1	1.19	0.15–9.22	–
Never smokers														
<18.5	11,174	139,846	12	1.69	0.82–3.50	0.6, 0	6	1.60	0.62–4.14	0.9, 0	0	ND		–
18.5 to <21	41,595	601,085	55	1.02	0.71–1.45	0.5, 0	34	0.92	0.59–1.45	0.5, 0	4	0.84	0.21–3.37	0.6, 0
21 to <23	56,251	852,112	85	1.00	Reference	–	61	1.00	Reference		7	1.00	Reference	–
23 to <25	51,834	803,621	83	0.93	0.68–1.27	0.4, 0	57	0.90	0.62–1.30	0.8, 0	2	1.18	0.11–13.05	–
25 to <30	48,999	770,799	75	0.83	0.60–1.14	0.5, 0	46	0.72	0.49–1.07	0.8, 0	9	0.65	0.20–2.14	0.8, 0
≥30	5032	78,149	5	1.28	0.49–3.33	0.5, 0	5	1.76	0.65–4.75	0.4, 0	0	ND		–
Ever smokers														
<18.5	8772	99,452	83	**1.60**	**1.22–2.09**	0.3, 14	44	1.44	0.96–2.15	0.2, 28	0	ND		–
18.5 to <21	32,780	442,798	363	**1.36**	**1.17–1.57**	1, 0	245	**1.37**	**1.15–1.64**	1, 0	14	0.90	0.43–1.91	0.9, 0
21 to <23	41,232	586,281	366	1.00	Reference	–	254	1.00	Reference		19	1.00	Reference	–
23 to <25	36,736	537,031	228	**0.69**	**0.57–0.85**	0.2, 23	166	**0.71**	**0.57–0.89**	0.3, 13	13	1.23	0.54–2.77	0.9, 0
25 to <30	28,814	433,142	157	**0.58**	**0.48–0.71**	0.6, 0	90	**0.51**	**0.40–0.65**	0.7, 0	13	0.99	0.46–2.11	0.7, 0
≥30	2326	34,802	9	0.86	0.33–2.21	0.2, 42	4	0.71	0.26–1.92	0.8, 0	1	2.88	0.34–24.24	–
			Gastric cancer											
			All				Cardia cancer				Noncardia cancer			
BMI kg/m^2	Subjects (*n*)	Person- years	Ca (*n*)	HR	95% CI	Het*P*, I^2	Ca (*n*)	HR	95% CI	Het*P*, I^2	Ca (*n*)	HR	95% CI	Het*P*, I^2
All subjects														
<18.5	21,466	254,959	597	1.07	0.96–1.20	0.2, 32	32	1.16	0.79–1.70	0.9, 0	203	0.97	0.84–1.13	0.5, 0
18.5 to <21	79,688	1,108,234	2293	1.05	0.99–1.12	0.3, 19	106	**0.78**	**0.61–0.99**	0.5, 0	1058	1.04	0.96–1.13	0.5, 0
21 to <23	104,714	1,531,131	2975	1.00	Reference		206	1.00	Reference	–	1517	1.00	Reference	–
23 to <25	95,164	1,431,439	2715	0.98	0.91–1.05	0.1, 45	176	0.89	0.69–1.14	0.2, 24	1446	0.98	0.91–1.05	0.5, 0

TABLE 2 (Continued)

25 to <30	85,053	1,300,950	2304	0.96	0.90–1.03	0.2, 30	196	1.12	0.92–1.37	0.5, 0	1275	0.96	0.89–1.03	0.6, 0
≥30	8162	123,394	211	1.05	0.88–1.25	0.2, 22	12	1.04	0.57–1.87	0.5, 0	121	1.04	0.76–1.43	0.1, 48
Never smokers														
<18.5	11,174	139,846	238	**1.22**	**1.02–1.45**	0.2, 26	12	1.90	0.96–3.76	0.9, 0	81	1.02	0.75–1.41	0.1, 37
18.5 to <21	41,595	601,085	788	1.07	0.94–1.23	0.04, 48	33	0.92	0.59–1.41	0.9, 0	389	1.08	0.92–1.27	0.2, 25
21 to <23	56,251	852,112	1066	1.00	Reference		61	1.00	Reference	–	577	1.00	Reference	–
23 to <25	51,834	803,621	1085	1.04	0.94–1.15	0.2, 21	68	1.08	0.76–1.54	0.7, 0	574	0.97	0.86–1.09	0.6, 0
25 to <30	48,999	770,799	1074	1.05	0.96–1.15	0.4, 5	76	1.19	0.83–1.68	0.6, 0	595	0.99	0.88–1.11	0.6, 0
≥30	5032	78,149	110	1.14	0.91–1.43	0.3, 12	8	1.94	0.85–4.43	0.6, 0	63	1.19	0.85–1.66	0.2, 27
Ever smokers														
<18.5	8772	99,452	326	1.00	0.87–1.15	0.2, 23	19	1.23	0.74–2.06	0.8, 0	111	0.93	0.72–1.21	0.2, 30
18.5 to <21	32,780	442,798	1388	1.04	0.97–1.12	0.7, 0	67	**0.72**	**0.53–0.97**	0.6, 0	625	1.02	0.92–1.14	0.4, 7
21 to <23	41,232	586,281	1739	1.00	Reference		136	1.00	Reference	–	866	1.00	Reference	–
23 to <25	36,736	537,031	1483	0.96	0.86–1.06	0.01, 50	95	0.83	0.63–1.08	0.5, 0	797	0.99	0.89–1.11	0.3, 15
25 to <30	28,814	433,142	1066	0.90	0.79–1.02	0.03, 58	108	1.14	0.88–1.47	0.7, 0	597	0.94	0.85–1.05	0.6, 0
≥30	2326	34,802	82	1.05	0.84–1.32	0.8, 0	1	0.77	0.10–5.71	–	48	1.24	0.92–1.67	0.8, 0

Note: HRs were calculated by a random effects model by pooling study-specific HR adjusted for sex, age, area (for multicentric studies, namely JPHC-I, JPHC-II, JACC, and LSS), pack-years (0, 0< and ≤20, >20), alcohol consumption (nondrinker, occasional drinker [<1 day/week], and current drinker [1–4 days/week, ≥5 days/week and <23 ethanol g/day, ≥5 days/week and ≥23 ethanol g/day]), and history of diabetes. HRs values in bold show statistical significance ($p < 0.05$). In esophageal squamous cell carcinoma and esophageal adenocarcinoma, we excluded MIYAGI-II, in which no information on histological type was available.

Abbreviations: BMI, body mass index; Ca, cases; CI, confidence interval; Het*P*, *P* value from test of heterogeneity; HR, hazard ratio; JACC, Japan Collaborative Cohort Study; JPHC, Japan Public Health Center-based Prospective Study; LSS, Life Span Study; ND, no cases in this stratum.

not provide conclusive evidence on never smokers despite having the largest number of esophageal squamous cell carcinoma cases.

It is important to note that, judging from the significantly higher inverse effect among ever smokers than never smokers (Figure 1), significant effect modification between BMI and smoking on the risk of esophageal squamous cell carcinoma is likely present. Studies evaluating biomarkers showed increased levels of DNA adducts[54] and an oxidative stress marker[55] among lean smokers compared with nonlean smokers, suggesting a biological connection between esophageal squamous cell carcinoma and leanness among smokers. Furthermore, the recent Mendelian randomization analysis demonstrated a complex bidirectional relation between obesity and smoking.[56] We therefore consider that our results highlight the importance of jointly considering both smoking and BMI in reducing the risk of esophageal squamous cell carcinoma. Still, although we included pack-years as a covariate in the stratified analysis by smoking status to obviate concerns about residual confounding, we cannot completely deny the possibility that the impact of residual confounding remains. The underlying mechanisms of this association may be heterogeneous by smoking status,[57] and further biological studies are needed.

One of the considerable strengths of this study was that it included a very large number of general Japanese participants and a substantial number of incident cases. This allowed us to perform a comprehensive evaluation of BMI effects on upper gastrointestinal cancers, including stratified analyses by subtype or subsite, investigation of nonlinearity, and effect modification. In addition, we unified the categories of BMI and multiple important covariates across cohorts. Together, these various factors allow us to ignore any potential heterogeneity that can occur in meta-analyses of published studies.

Several limitations of this study also warrant mention. First, we did not perform analyses for abdominal obesity, such as waist circumference and waist-to-hip ratio, because our study is an aggregation of cohort studies and not all studies had such information. Although findings for the association between abdominal obesity and esophageal or gastric cancer risk were inconsistent,[50,53,58–60] the European Prospective Investigation into Cancer and Nutrition, a multicenter prospective cohort study, suggested positive associations for both waist circumference and waist-to-hip ratio on adjustment of BMI, even in esophageal squamous cell carcinoma.[50,53] Abdominal obesity might therefore be an important risk factor for upper gastrointestinal cancer independent of BMI. Second, we conducted our analysis using only the baseline questionnaire and were therefore unable to account for changes in BMI or other covariate exposure status that occurred after enrollment. Third, we did not observe any significant HRs for esophageal adenocarcinoma. The number of esophageal adenocarcinoma cases was only 86, and the estimates for adenocarcinoma were accordingly unstable. Therefore, the nonsignificant results and smaller magnitude of the dose-dependent effect of BMI in this study (HR 5-kg/m^2 increase in BMI 1.01, 95% CI 0.69–1.48) than in the previous meta-analysis (RR 5-kg/m^2 increase in BMI 1.48, 95% CI 1.35–1.62)[11] on esophageal adenocarcinoma can be considered partially due to the small sample size. Further studies to evaluate the impact of BMI on esophageal adenocarcinoma among Asians with a larger sample size are needed. Lastly, although we took account of important potential confounders, the possibility of residual confounders remains.

In summary, this study—the largest prospective study conducted in an Asian country to date—obtained a comprehensive quantitative estimate of the association between BMI and upper gastrointestinal cancer incidence. Our results confirm the subtype- or subsite-specific effect of BMI, and therefore carry important implications for primary prevention strategies against upper gastrointestinal cancer incidence.

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CONFLICT OF INTEREST STATEMENT

The authors declare no potential conflicts of interest.

ETHICS STATEMENT

All studies obtained written informed consent from all participants and were approved by their respective institutional review boards.

Registry and the Registration No. of the study/trial: N/A.

Animal Studies: N/A.

ORCID

Yuriko N. Koyanagi https://orcid.org/0000-0002-5675-3429
Keitaro Matsuo https://orcid.org/0000-0003-1761-6314
Hidemi Ito https://orcid.org/0000-0002-8023-4581
Yumi Sugawara https://orcid.org/0000-0002-0197-6772
Norie Sawada https://orcid.org/0000-0002-9936-1476
Keiko Wada https://orcid.org/0000-0002-5467-8592
Taro Takeuchi https://orcid.org/0000-0002-9900-9608
Sarah Krull Abe https://orcid.org/0000-0003-3991-2739
Manami Inoue https://orcid.org/0000-0003-1276-2398

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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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APPENDIX 1

Research group member (as of April 2023)

Manami Inoue (Principal investigator); Sarah Krull Abe, Norie Sawada (National Cancer Center); Takashi Kimura (Hokkaido University); Yumi Sugawara (Tohoku University); Shuhei Nomura (The University of Tokyo); Hidemi Takimoto (National Institutes of Biomedical Innovation, Health and Nutrition); Hidemi Ito; Isao Oze (Aichi Cancer Center); Yingsong Lin (Aichi Medical University); Keiko Wada (Gifu University); Tetsuhisa Kitamura (Osaka University); Mai Utada (Radiation Effects Research Foundation).

Past members:

Akihisa Hidaka, Mayo Hirabayashi, Motoki Iwasaki, Yuri Kitamura, Keitaro Matsuo, Tetsuya Mizoue, Nagisa Mori, Michihiro Muto, Chisato Nagata, Mariko Naito, Tomio Nakayama, Yoshikazu Nishino, Atsuko Sadakane, Eiko Saito, Ritsu Sakata, Shizuka Sasazuki, Taichi Shimazu, Hiroyuki Shimizu, Kemmyo Sugiyama, Hidekazu Suzuki, Akiko Tamakoshi, Keitaro Tanaka, Shiori Tanaka, Yoshitaka Tsubono, Ichiro Tsuji, Shoichiro Tsugane, Kenji Wakai, Yoko Yamagiwa, Taiki Yamaji