Impact of metabolically healthy obesity on the risk of incident gastric cancer: a population-based cohort study

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Abstract

Background Previous meta-analyses revealed that obesity confers a risk of gastric cancer. On the other hand, metabolically healthy obese (MHO) individuals, who are healthier than metabolically abnormal obese (MAO) individuals, have lower risks of colon cancer and breast cancer. However, the association between MHO and incident gastric cancer is unclear. Methods This historical cohort study included 19,685 Japanese individuals who participated in health-checkup programs from 2003 to 2016. Each subject was classified as metabolically healthy (MH) (no metabolic abnormalities) or metabolically abnormal (MA) (one or more metabolic abnormalities), according to four metabolic factors (hypertension, impaired fasting glucose, hypertriglyceridemia and low high density lipoprotein-cholesterol). Obese (O) or non-obese (NO) was classified by a body mass index cutoff of 25.0 kg/m2. Hazard ratios of metabolic phenotypes for incident gastric cancer were calculated by the Cox proportional hazard model with adjustments for age, sex, alcohol consumption, smoking and exercise. Results Over the median follow-up period of 5.5 years, 78 participants developed gastric cancer. Five-years cumulative incident rate of gastric cancer was 0.2% (case/n = 17/8,331) in MHNO, 0.2% (1/653) in MHO, 0.5% (35/7,276) in MANO and 0.7% (25/3,425) in MAO. Compared with MHNO, the adjusted hazard ratios for development of gastric cancer were 0.69 (95%CI 0.04–3.39, p = 0.723) in MHO, 1.16 (95%CI 0.63–2.12, p = 0.636) in MANO and 2.09 (95%CI 1.10–3.97, p = 0.024) in MAO. Conclusions This study shows that individuals with MAO, but not those with MHO, had an elevated risk for incident gastric cancer.

Background

Gastric cancer is a major global health concern and was the third leading cause of cancer death worldwide in 2012 [1] and gastric cancer is the third leading cause of cancer death in 2016 in Japan [2]. Previous meta-analyses showed that obesity was a risk factor for incident gastric cancer, especially gastric cardia cancer [3], although an umbrella review revealed the effect of obesity on gastric cancer was smaller than that on other obesity-related cancers, such as colon and breast cancers [4].

On the other hand, obesity is also known as a risk factor for type 2 diabetes mellitus (T2DM) [5], chronic kidney disease (CKD) [6] and cardiovascular disease (CVD) [7]. The subgroup of individuals with metabolically healthy obesity (MHO)—i.e., obesity without metabolic abnormalities—are knowns as lower risk of T2DM, CKD and CVD than individuals with metabolic abnormalities obese [8-11]. However, these studies also revealed that individuals with the MHO phenotype were at higher risk of T2DM, CKD and CVD than individuals with metabolically healthy non-obese [8,10,11]. In addition, there is accumulating evidence that metabolically abnormal obesity (MAO), but not MHO, confers an elevated risk of incident colon cancer [12] and breast cancer [13]. To our knowledge, however, no previous studies have clarified the relation between MHO and incident gastric cancer. Thus, the aim of this study was to elucidate the impact of MHO on incident gastric cancer.

Methods

1.1.Study population

This was an historical cohort study of participants who received a medical health-checkup at Asahi University Hospital (the **NAGALA** (**NA**fld in **G**ifu **A**rea, **L**ongitudinal **A**nalysis) study, Gifu, Japan) [14]. The purpose of medical health-checkup was to promote public health by early detection of chronic diseases and their risk factors, and about 60-70% examiners received the examinations, repeatedly. The medical data of all individuals who agreed to participate in the study were stored in a database after removing all personally identifiable information. For the current study, we used the results of individuals who participated in the health-checkup program for at least one year between 2003 and 2016. The exclusion criteria of this study were as follows: the presence of gastric cancer at baseline examination, missing covariate data

(body weight, high-density lipoprotein (HDL) cholesterol, and lifestyle factors) and no follow-up health-checkup programs. Informed consent was obtained from each participant. The study was approved by the ethics committee of Murakami Memorial Hospital and was conducted in accordance with the Declaration of Helsinki.

1.2.Data collection

A self-administered questionnaire was used for gathering the medical history and lifestyle factorsof participants [14]. In regard to alcohol consumption, participants were asked the type and amounts of alcoholic beverages consumed per week over the past month, and then the mean ethanol intake per week was estimated [15]. For smoking status, the participants were categorized into three groups: never-, ex- and current smokers. In addition, pack-years were calculated by multiplying the number of cigarette packs smoked per day by the number of years of smoking [16]. For exercise, participants were asked to describe the type, duration and frequency of sports or recreational activities [17]. Based on the results, we defined regular exercisers as the participants who performed any kind of sports activity at least once a week on a regular basis [15]. Body mass index (BMI) (kg/m^2) was calculated as body weight (kg) divided by height (m) squared. Waist circumference was measured as the abdominal circumference around the navel. Fasting plasma glucose, triglycerides, or HDL cholesterol was measured using the venous blood after an overnight fast. We also performed an upper gastrointestinal series or gastro-esophageal endoscopy and fecal occult blood test. If gastrointestinal cancer was suspected, we contacted and encouraged the participants to receive further examinations to diagnose it. We then collected the medical information about gastrointestinal cancers by sending a standardized letter to the hospital where the subject received the additional examinations. Specialists in the field of gastrointestinal disease checked the collected information and defined each cases as esophageal cancer, gastric cancer, or colorectal cancer. The first standardized questionnaires were sent on Jan 1^{st} 2003; thus, we set the study period as Jan 1^{st} 2003 to Dec 31^{st} 2016. The primary endpoint of this study was hazard risk (HR) of MHO for gastric cancer after adjusting for sex, age, and lifestyle factors including smoking habits, alcoholic consumption and physical activities.

1.3.Definitions of metabolic phenotypes

We used body mass index >25.0 kg/m^2 to identify the individual with obesity. This value has been proposed as a cutoff for the diagnosis of individual with obesity in Asian people [18] and has often been used in Japan [19,20]. Four metabolic factors (fasting plasma glucose, triglycerides, HDL cholesterol and blood pressure) were used to divide participants into metabolically healthy or metabolically abnormal subgroups [9]. Impaired fasting plasma glucose and/or diabetes was defined as fasting plasma glucose >5.6 mmol/L and/or current medical treatment. Hypertension was defined as systolic blood pressure >130 mmHg and/or diastolic blood pressure >85 mmHg or current medical treatment. Elevated triglycerides were defined as triglycerides >1.7 mmol/L or treatment for hyperlipidemia. Low HDL-cholesterol was defined as <1.0 mmol/L in men and <1.3 mmol/L in women. When none of these four metabolic factors were present, we defined the participants as metabolically healthy (MH) and when one or more of these four metabolic factors were present, we defined the participants as metabolically abnormal (MA) [21]. Then, participants were categorized at the baseline examination into 4 phenotypes: metabolically healthy non-obesity (MHNO), metabolically healthy obesity (MHO); metabolically abnormal non-obesity (MANO), and metabolically abnormal obesity (MAO).

1.4.Statistical analysis

The study participants were divided into four groups based on metabolic phenotypes. Continuous variables were expressed as the means ± standard deviation or median (interquartile range) and categorical variables were expressed as numbers. The clinical characteristics at baseline examination of the four groups were compared; continuous variables of groups were evaluated by one-way ANOVA and Tukey's Honestly Significant Difference Test or Kruskal-Wallis Test and Steel-Dwass Test, and categorical variables of groups were evaluated by Pearson's Chi-Squared Test. Because of the

censored cases and inconsistent follow-up duration, we used the Cox Proportional Hazards Model to calculate the HR of the four groups. We considered five potential confounders as covariates: age, sex, alcohol consumption, pack-years, and exercise. Because alcohol consumption and pack-years were skewed variables, logarithmic transformation was carried out before performing the Cox Proportional Hazard Model analysis.

The statistical analyses were performed using JMP version 13.2 software (SAS Institute Inc., Cary, NC). A p value <0.05 was considered statistically significant.

Results

We included 27,944 participants from the NAGALA database (Figure 1). Among them, 8,259 participants were excludedThus, 19,685 participants were eligible for this cohort study. The baseline characteristics of the participants are shown in Table 1. Both BMI and metabolic parameters, including blood pressure, fasting plasma glucose, triglycerides and HDL cholesterol, were different among the four metabolic phenotype groups.

Over the median follow-up period of 5.5 (2.9-9.4) years, 78 participants developed gastric cancer. The 5-year cumulative incidence rates of gastric cancer were 0.2% (cases/total subjects = 17/8331) in MHNO, 0.2% (1/653) in MHO, 0.5% (35/7276) in MANO and 0.7% (25/3425) in MAO.

The results of the Cox proportional hazard model are shown in Table 2. Compared with the MHNO phenotype, the MAO phenotype (adjusted HR 2.09, 95%CI 1.10–3.97, p = 0.024) was associated with a higher risk for development of gastric cancer after adjusting for covariates, whereas the MHO phenotype (adjusted HR 0.69, 95%CI 0.04–3.39, p = 0.723) was not.

Discussion

This cohort study of apparently healthy Japanese people is the first to reveal an association between MHO and incident gastric cancer. Previous studies revealed that the risk of incident colorectal cancer [12] and incident breast cancer [13], both of which have been shown to be related to obesity [4], was not high in subjects with MHO. In addition, another study revealed that the risk of obesity-related cancer in MHO was lower than that in MAO [22]. However, no previous study has revealed an association between MHO and incident gastric cancer. In this study, we revealed that MAO, but not MHO, was associated with a higher risk of incident gastric cancer.

As to why MAO, but not MHO, was associated with a higher risk of incident gastric cancer, there were several possible explanations. Inflammation, as represented by elevation of the pro-inflammatory cytokines tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6), and monocyte chemoattractant protein-1 (MCP-1), is known to be closely associated with obesity [23]. Inflammation leads to the development of gastric cancer by stimulating proliferation and inhibiting apoptosis of human gastric cancer cells [24]. In addition, tumor cell progression is stimulated by enhancing the mTOR signaling pathways through an increase in insulin-like growth factor 1 (IGF-1) [25]. On the other hand, it has been reported that the levels of inflammation and IGF-1 in MHO were lower than those in MAO [26,27]. Moreover, it has been reported that metabolic syndrome is associated with gastric cancer [28]. Collectively, these results could explain why the MAO phenotype, but not the MHO phenotype, was associated with a higher risk of incident gastric cancer.

Some limitations of our study should be noted. First, there was a possibility of selection bias, because we only included the participants who were re-examined in the health-checkup program. Second, we did not have data on *H. pylori* infection, which is known to pose a risk for gastric cancer [29]. In fact, many Japanese, especially elderly people, are infected with *H. pylori* [30]. Therefore, the results of this study might have been affected by the status of *H. pylori* infection. Third, we did not have detailed data on gastric cancer according to the anatomic location of the lesion, such as

gastric non-cardia cancer and gastric cardia cancer. A previous study revealed that gastric cardia cancer showed a greater association with obesity than non-cardia cancer [1]. Lastly, the generalizability of our study to non-Japanese populations is uncertain.

Conclusions

In conclusion, our study showed that MAO individuals, not but MHO individuals, had a higher risk of incident gastric cancer. Thus, to prevent future gastric cancer, we should focus on metabolic abnormalities.

Declarations

Ethics approval and consent to participate: Informed consent was obtained from each participant. The study was approved by the ethics committee of Murakami Memorial Hospital.

Consent for publication: Not applicable.

Availability of data and material: The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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Authors' Contributions: Y.H. designed the study, analyzed and interpreted the data, and wrote the manuscript. M.H. originated the study, researched and interpreted the data, and reviewed and edited the manuscript. A.O. and T.K. originated the study, researched the data and reviewed the manuscript. M.F. designed the study, interpreted the data, and reviewed the manuscript. M.H. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. All authors have approved the final draft submitted.

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Tables

Table 1. Characteristics of study participants at the baseline examination

	ALL	MHNO	MHO	MANO	MAO	*p*
N	19,685	8,331	653	7,276	3,425	—
Age (years)	45.5 ± 9.5	42.6 ± 8.7	43.8 ± 8.3 *	48.3 ± 9.7 *†	47.0 ± 9.0 *†‡	<0.001
Sex (men/women)	11,782/7,903	3,496/4,835	424/229	5,088/2,188	2,774/651	<0.001
BMI (kg/m^2)	22.6 ± 3.3	20.7 ± 2.1	26.7 ± 1.7 *	22.1 ± 1.9 *†	27.6 ± 2.5 *†‡	<0.001
Waist circumference (cm)	78.0 ± 9.6	72.3 ± 7.0	86.9 ± 6.0 *	77.9 ± 6.8 *†	90.6 ± 7.2 *†‡	<0.001
SBP (mmHg)	117.5 ± 16.3	108.0 ± 10.7	116.1 ± 8.9 *	122.2 ± 16.2 *†	130.8 ± 15.2 *†‡	<0.001
DBP (mmHg)	73.7 ± 11.2	67.2 ± 7.8	72.6 ± 6.7 *	76.9 ± 11.0 *†	82.6 ± 10.1 *†‡	<0.001
FPG (mmol/L)	5.4 ± 0.9	5.0 ± 0.3	5.1 ± 0.3 *	5.6 ± 1.0 *†	6.0 ± 1.3 *†‡	<0.001
Triglycerides (mmol/L)	0.8 (0.5–1.2)	0.6 (0.4–0.8)	0.8 (0.6–1.2) *	1.0 (0.6–1.5) *†	1.3 (0.9–1.9) *†‡	<0.001
HDL cholesterol (mmol/L)	1.4 ± 0.4	1.6 ± 0.4	1.4 ± 0.3 *	1.3 ± 0.4 *†	1.2 ± 0.3 *†‡	<0.001
Exercise	1,6111/3,574	6,781/1,550	540/113	5,911/1,365	2,879/546	0.002
Never-/Ex-/Current smoker	10,480/4,405/4,776	5,414/1,331/1,375	346/153/154	3,342/1,897/2,029	1,378/1,024/1,018	<0.001
Pack-year	0 (0–305)	0 (0–120)	0 (0–300) *	50 (0–420) *†	150 (0–460) *†‡	<0.001
Alcohol consumption (g/wk)	4.2 (0–90)	1 (0–54)	1 (0–66) *	12 (0–126) *†	12 (1–126) *†	0.070

MHNO, Metabolically healthy non-obesity; MHO, Metabolically healthy obesity; MANO, Metabolically abnormal non-obesity; MAO, Metabolically abnormal obesity; BMI, Body mass index; SBP, Systolic blood pressure; DBP, Diastolic blood pressure; FPG, Fasting plasma glucose; HDL, High-density lipoprotein. Data are the number, mean ± standard deviation, or median (interquartile range). The analyses of continuous variables to assess differences among the four groups were performed using one-way ANOVA or Kruskal-Wallis Test, followed by Tukey's Honestly Significant Difference Test or Steel-Dwass Test. The analyses of categorical variables among the four groups were determined by Pearson's Chi-Squared Test. *, p <0.05 vs. MHNO; †, p <0.05 vs. MHO; and ‡, p <0.05 vs. MANO.

Table 2. Hazard ratio of metabolic phenotype for incident gastric cancer

	Model 1		Model 2	
	Hazard ratio (95% CI)	*p* value	Hazard ratio (95% CI)	*p* value
Age, years	1.12 (1.10–1.15)	<0.001	1.12 (1.09–1.15)	<0.001
Men	1.83 (1.02–3.27)	0.043	0.91 (0.43–1.92)	0.811
Metabolic phenotype				
Metabolically healthy non-obesity	Ref	—	Ref	—
Metabolically healthy obesity	0.68 (0.04–3.32)	0.691	0.69 (0.04–3.39)	0.723
Metabolically abnormal non-obesity	1.19 (0.66–2.23)	0.567	1.16 (0.63–2.12)	0.636
Metabolically abnormal obesity	2.16 (1.14–4.09)	0.018	2.09 (1.10–3.97)	0.024
Exercise, yes	—	—	0.91 (0.53–1.58)	0.745
Log (alcohol consumption +1)	—	—	1.04 (0.94–1.16)	0.412
Log (pack-year + 1)	—	—	1.16 (1.04–1.28)	0.005

CI, Confidence interval; Log, logarithmic. For determination of the metabolic phenotype, metabolically healthy non-obesity was used as a reference.

Figures

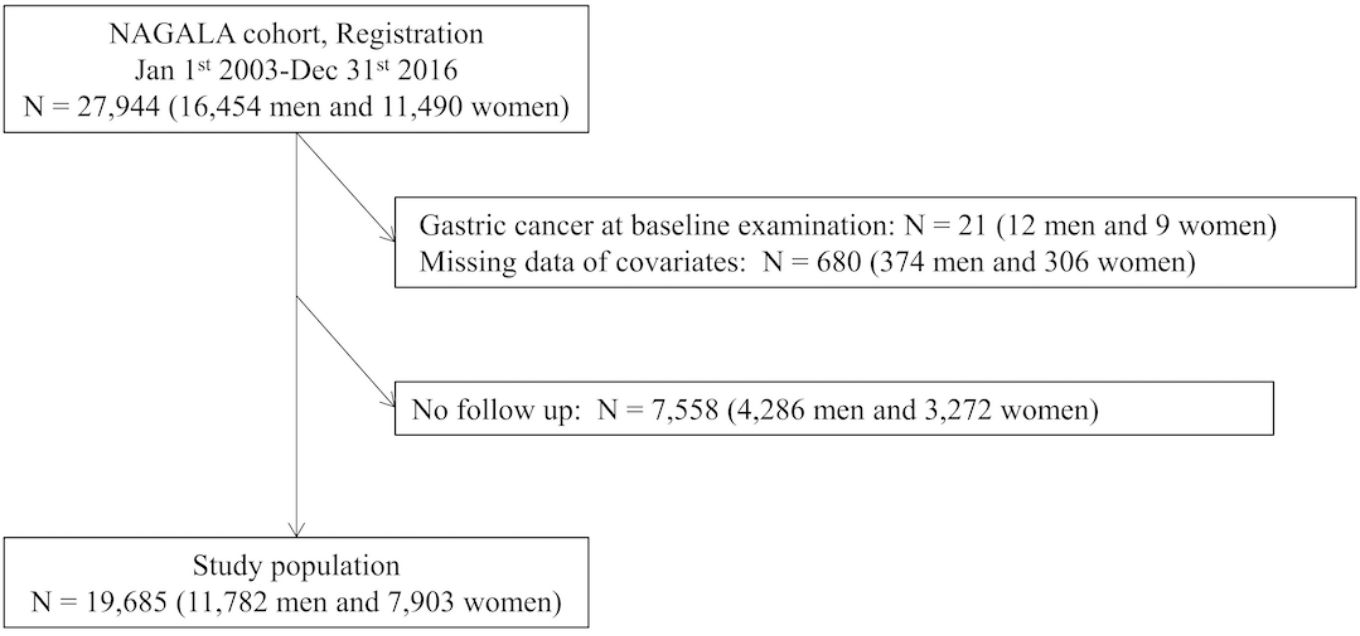

Figure 1

Inclusion and exclusion flow chart. NAGALA: NAfld in Gifu Area, Longitudinal Analysis