Non-alcoholic fatty liver disease with obesity as an independent predictor for incident gastric and colorectal cancer: a population-based longitudinal study

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ABSTRACT

Background Colorectal cancer is known to be an extrahepatic complication of non-alcoholic fatty liver disease (NAFLD). However, the interaction of NAFLD with obesity for incident colorectal cancer has not been clarified yet. Moreover, the effect of NAFLD and obesity for incident gastric cancer has not been clarified yet. Thus, we investigated whether NAFLD with or without obesity would be a risk factor for incident gastric cancer as well as colorectal cancer.

Methods The study period was set from 2003 to 2016. NAFLD was diagnosed by abdominal ultrasonography using standardised criteria. We applied the Cox proportional hazards model to investigate the effect of NAFLD with or without obesity at baseline on incident gastric cancer as well as colorectal cancer. Age, sex, lifestyle factors including smoking states, alcohol consumption and exercise, and diabetes were used as covariates.

Results During the study period, 27 944 individuals (16 454 men and 11 490 women) were registered in the NAfld in Gifu Area, Longitudinal Analysis study. During the mean (SD) observational period of 2357 (1458) days, incident gastric cancers were diagnosed in 48 individuals (incident rate 0.48 per 1000 person-years) and incident colorectal cancers were diagnosed in 52 individuals (incident rate 0.51 per 1000 person-years). The adjusted HR of NAFLD with obesity for incident gastric cancer was 3.58 (95% CI 1.73 to 7.38, p=0.001) and that for incident colorectal cancer was 2.96 (95% CI 1.73 to 7.38, p=0.003).

Conclusion NAFLD with obesity was a risk factor for both incident gastric cancer and colorectal cancer in apparently healthy Japanese individuals.

Summary box

What is already known about this subject?

► Non-alcoholic fatty liver disease (NAFLD) has hepatic and extrahepatic complications. The risk of colorectal cancer has been known to increase in patients with NAFLD. However, the interaction of NAFLD and obesity for incident colorectal cancer as well as incident gastric cancer is unknown.

What are the new findings?

► NAFLD with obesity is a high-risk state for incident gastric cancer as well as colorectal cancer.

How might it impact on clinical practice in the foreseeable future?

► Obese individuals with NAFLD should be encouraged to receive screening examinations including upper gastrointestinal endoscopy for gastric cancer, in addition to occult blood tests for colorectal cancer.

BACKGROUND

Non-alcoholic fatty liver disease (NAFLD) includes non-alcoholic fatty liver and non-alcoholic steatohepatitis (NASH).[1] [2] Hepatocellular carcinoma (HCC) as well as chronic hepatitis and liver cirrhosis are often observed in patients with NAFLD, especially in those with NASH. In addition to HCC, patients with NAFLD might be at a high risk for colorectal cancer.[3] A recent meta-analysis of observational studies suggests that NAFLD is independently associated with a moderately increased prevalence and incidence of colorectal adenomas and cancer.[4] This is because NAFLD is a hepatic manifestation of metabolic syndrome, and metabolic syndrome is a well-known risk factor for colorectal cancer.[5–7] The mechanism underlying the link between NAFLD and colorectal cancer has not been fully elucidated, but it is likely to be similar to the putative mechanism underlying the link between metabolic syndrome and colorectal cancer.

Obesity is well-known risk factor for colorectal cancer.[8–10] Because overnutrition is a cause of development of NAFLD, the major part of individuals with NAFLD are obese or over weight individuals.[11] [12] Thus, NAFLD with obesity are thought to be a risk for incident colorectal cancer. However, a

part of individuals with NAFLD are lean.[13] We previously reported that NAFLD without obesity, as well as NAFLD with obesity, are risk factor for incident diabetes.[13] However, the association between NAFLD without obesity and incident colorectal cancer has not been clarified yet.

In addition to that, the risk of gastrointestinal cancer increases in individuals with metabolic syndrome.[14–17] Thus, the risk of gastric cancer would increase in patients with NAFLD. Indeed, a recent cross-sectional study reported that the prevalence of NAFLD was higher in patients with gastric cancer than in the general population.[18] Nonetheless, no study has revealed a direct association between NAFLD and incident gastric cancer. Moreover, the risk of NAFLD with or without obesity are still unknown.

To address this, we performed a longitudinal study to reveal the risk of NAFLD with or without obesity for the incidence of gastric cancer, as well as colorectal cancer, in apparently healthy Japanese individuals. We separated the study subjects according to the presence of NAFLD and/or obesity and investigated the incident rate of gastric cancer as well as colorectal cancer.

METHODS
Study population and design
We previously performed a longitudinal cohort study known as the NAGALA study (NAfld in the Gifu Area, Longitudinal Analysis) to reveal the impact of NAFLD on several types of chronic diseases or cancers.[7] In the NAGALA study, informed consent was obtained from individuals who participated in a nationwide health check-up programme known as Ningen Dokku, which translates roughly to 'human dock' (likening check-up patients to ships being repaired at dock). This nationwide programme promotes public health through the detection of chronic diseases—including gastrointestinal and other cancers—and their risk factors. Blood and urine examinations, upper gastrointestinal series or gastro-oesophageal endoscopy, abdominal ultrasonography and a faecal occult blood test are all part of the routine check-up.

For the NAGALA study, subjects participating in Ningen Dokku at the check-up centre of Murakami Memorial Hospital (Gifu, Japan), which was renamed to Asahi University Hospital since 2018, were recruited. This centre was founded in 1994, and more than 8000 individuals participated in the health check-up at this location each year.

Subjects were consisted with individuals who received health check-up programmes more than two times. Usually, they received health check-up programmes every year or every 2 years. We defined durations between the time when they registered and the time when they received the health-checkup programmes at the last time as observation period.

We provided an information packet to any check-up participant at Asahi University Hospital who was suggested to have a gastrointestinal cancer. The packet included a form that the doctors who performed the diagnostic examinations could use to provide their results to our team. The patients were notified by the information packet that a cancer was suggested by the health check-up programme and were encouraged to receive further examinations to diagnose it. We then collected the medical information on gastrointestinal cancers from the hospitals where the patients went for their additional examinations, again using standardised forms. Specialists in the field of gastrointestinal disease checked the collected information and defined each case as one of gastric cancer or colorectal cancer. We started this system on 1 January 2003 and set the study period as 1 January 2003–31 December 2016. The primary endpoint of the study was set to identify the hazard ratios of NAFLD with or without obesity at the baseline for the incident gastric cancer as well as colorectal cancer after adjusting sex, age and lifestyle factors including smoking habits, alcoholic consumption and physical activities and diabetes. In this study, if an individual was diagnosed with a cancer, the day when the individual was first suggested to have a cancer at the health check-up centre was defined as the incident day.

Individuals who participated in the health check-up programme from 1 January 2003 to 31 December 2016 and registered in the NAGALA study were included into the present study. The following individuals were excluded: (1) those with gastrointestinal cancer at baseline; (2) those receiving a medical treatment for diabetes, dyslipidaemia, hyperuricaemia or hypertension; (3) men who consumed alcohol of more than 210 g per week or females who consumed alcohol of more than 140 g per week[19]; and (4) those with known liver disease.[7 20] Known liver disease was defined as positivity for hepatitis B antigen or hepatitis C antibody, or a history of known liver disease, including viral, genetic, autoimmune or drug-induced liver disease.[21] We analysed the longitudinal data of individuals who participated in the health check-up programme more than two times.

Data collection and measurements
The detailed methods for data collection and measurements were described previously.[19] Briefly, we used a standardised self-administered questionnaire to acquire information on the medical history and lifestyle factors, including smoking habits, alcoholic consumption and physical activity.[7 19] Patients were categorised into three groups according to their smoking status (never smokers, ex-smokers and current smokers). Regarding exercise, if individuals participated in any kind of sports activity at least once a week on a regular basis, we categorised them as regular exercisers.[22] Body mass index (BMI) was calculated as weight (kg)/height (m) squared. The conventional criteria for Asian obesity (BMI ≥ 25 kg/m^2) were used.[13 23]

Definition of NAFLD

The definition of NAFLD was described previously.[19] Briefly, the cut-off level of alcohol consumption was set as 210 g/week for men and as 140 g/week for women.[19] Fatty liver was diagnosed based on the findings of ultrasonography. Among four known criteria, hepatorenal echo contrast and liver brightness are required for fatty liver.

Statistical analysis

P values of 0.05 or less were considered statistically significant. We analysed all data using SPSS software (V.25). We divided the individuals into four groups according to the presence of NAFLD and obesity. Categorical variables are expressed as percentages (n) and continuous variables are expressed as the means and SD. The HRs of the four groups for incident cancer were calculated by the Cox proportional hazards model, because there were censored cases and the follow-up duration was inconsistent. In the Cox proportional hazards model, the following potential cofactors were used as covariates: alcohol consumption, smoking status, exercise, sex and age at baseline examination.

RESULTS

From 1 January 2003 to 31 December 2016, 27 944 individuals (16 454 men and 11 490 women) were registered in the NAGALA study. At the baseline examinations, 51 individuals were diagnosed with gastrointestinal cancers (25 gastric cancers and 26 colorectal cancers). A total of 15 926 individuals (8585 men and 7341 women) who had participated in the health check-up programme two or more times were analysed (figure 1).

The characteristics of the study population are shown in table 1. During the mean (SD) observation period of 2357 (1458) days, 48 gastric cancers and 52 colorectal cancers were newly diagnosed. The prevalence of never smoker were lower in individuals with incident gastric cancer as well as colorectal cancer (table 1). The metabolic abnormalities, including diabetes, total cholesterol levels, triglycerides levels, low-density lipoprotein cholesterol levels and uric acid levels were higher, and high-density lipoprotein cholesterol levels are lower in individuals with incident gastric cancer as well as colorectal cancer. However, the indicator for advanced forms of NAFLD, such as FIB4 index or NAFLD fibrosis score, was not significantly higher in individuals with incident gastric cancer as well as colorectal cancer.

We evaluated the characteristics of subjects after stratification simultaneously for NAFLD and obesity status (table 2). The rate of male, exerciser, smoker or diabetes are not in the same level among these four groups separated by with or without NAFLD and obesity at the baseline.

The incidence rate of gastric cancer was 0.34 per 1000 person years in the non-NAFLD without obesity, 0.29 in the non-NAFLD with obesity, 0.83 in the NAFLD without obesity and 1.21 in the NAFLD with obesity group (table 3). The incidence rate of colorectal cancer was 0.37 per 1000 person years in the non-NAFLD without obesity, 0.72 in the non-NAFLD with obesity, 0.41 in the NAFLD without obesity and 1.49 in the NAFLD with obesity group.

The cumulative hazard curves for incident gastric cancer are shown in figure 2. The adjusted HR of NAFLD with obesity was 3.58 (95% CI 1.73 to 7.38, p=0.001) for gastric cancer and 2.96 (1.44–6.09, p=0.003) for colorectal cancer in comparison with non-NAFLD without obesity (table 4). In addition, the adjusted HR of NAFLD without obesity for gastric cancer was 1.96 (0.86–4.47, p=0.11), although it did not reach the level of statistical significance. Finally, the incidence rate of gastric cancer in the non-NAFLD patients with obesity was as low as that in the non-NAFLD patients without obesity.

DISCUSSION

This study clearly indicated that NAFLD with obesity at baseline was a high-risk state for gastric cancer, as well as colorectal cancer. There is no clear evidence that gastric cancer is one of the extrahepatic complications of NAFLD. Moreover, the risk of NAFLD with or without obesity for incident gastric cancer as well as colorectal cancer was unknown. However, this longitudinal study revealed, for the first time, that the risk of NAFLD with obesity for gastric cancer was statistically significantly high (HR 3.58, 95% CI 1.73 to 7.38, p=0.001). Additionally, that the risk of NAFLD with obesity for colorectal cancer was also statistically significantly high (HR 2.96, 95% CI 1.44 to 6.09, p=0.003).

Insulin resistance is pivotal for the progression of NAFLD.[24] Insulin resistance was thought to be higher in obese individuals with NAFLD than those in lean individuals with NAFLD, but it has not been clarified yet. The high concentration of insulin caused by insulin resistance is thought to promote the proliferation of cancers.[25] The insulin-like growth factor axis is upregulated in individuals with NAFLD, and this upregulation is thought to
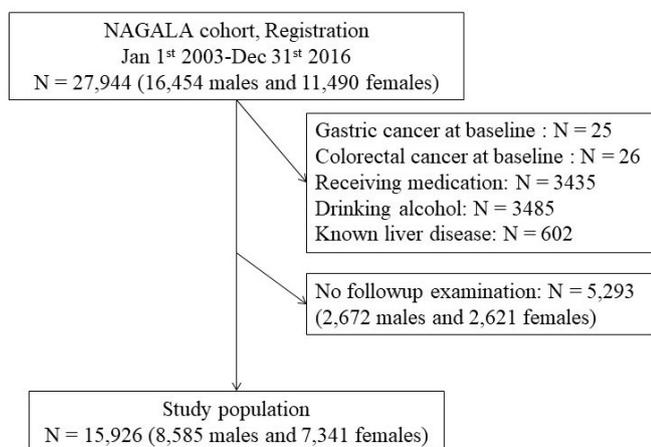

Figure 1 Inclusion and exclusion flow chart. NAGALA, NAfld in Gifu Area, Longitudinal Analysis.

Table 1 Basic characteristics of the study population with or without incident cancer

	Non-gastric cancer	Incident gastric cancer	P value	Non-colorectal cancer	Incident colorectal cancer	P value
Number	15 878	48		15 874	52	
Male, % (N)	53.9 (8553)	66.7 (32)	0.084	53.8 (8547)	73.1 (38)	0.006
Exerciser, % (N)	17.2 (2721)	18.8 (9)	0.70	17.2 (2722)	15.7 (8)	1.00
Never smoker, % (N)	59.5 (9419)	37.5 (18)	0.007	59.5 (9414)	44.2 (23)	0.08
Ex smoker, % (N)	18.8 (2979)	27.1 (13)		18.8 (2978)	26.9 (14)	
Current smoker, % (N)	21.7 (3440)	35.4 (17)		21.7 (3442)	28.8 (15)	
Diabetes, % (N)	1.9 (295)	8.3 (4)	0.012	1.9 (297)	3.8 (2)	0.26
Alcohol consumption, mg/week	32.5 (49.3)	38.5 (51.3)	0.41	32.4 (49.2)	54.9 (54.9)	0.002
Age, year	43.8 (9)	52.2 (8.3)	<0.001	43.8 (9)	45.3 (7.4)	0.23
BMI, kg/m^2	22.3 (3.2)	23 (3.5)	0.10	22.3 (3.2)	24.2 (3.8)	<0.001
Systolic blood pressure, mm Hg	114.7 (15.2)	118 (15.8)	0.13	114.7 (15.2)	117.1 (13.4)	0.25
Diastolic blood pressure, mm Hg	71.7 (10.5)	73.7 (10)	0.19	71.7 (10.5)	74.4 (9.1)	0.065
AST, IU/L	18.1 (9.4)	18.5 (5.1)	0.75	18.1 (9.4)	17.8 (5.7)	0.83
ALT, IU/L	20.7 (15.2)	22.7 (11.3)	0.35	20.7 (15.2)	24.2 (12.5)	0.097
GGT, IU/L	19.9 (17.5)	21.4 (16.3)	0.57	19.9 (17.5)	20.5 (12.8)	0.81
Alb, g/dL	4.33 (0.2)	4.31 (0.18)	0.53	4.33 (0.2)	4.29 (0.29)	0.13
Platelet, 10^3/mL	24.4 (5.6)	24.9 (6.1)	0.49	24.4 (5.6)	25.3 (5.2)	0.27
FIB4 index	0.79 (0.38)	0.89 (0.33)	0.057	0.79 (0.38)	0.7 (0.25)	0.11
NAFLD fibrosis score	1.07 (0.26)	1.1 (0.31)	0.34	1.07 (0.26)	1.08 (0.27)	0.78
Total cholesterol, mg/dL	200.8 (34.2)	217.6 (32.1)	0.001	200.8 (34.2)	213.4 (31.4)	0.009
Triglycerides, mg/dL	84 (64.7)	114.2 (57.3)	0.001	84 (64.5)	123.1 (108.3)	0.012
LDL cholesterol, mg/dL	128 (31.3)	145 (30.5)	<0.001	128 (31.3)	140.4 (34.8)	0.004
HDL cholesterol, mg/dL	55.9 (15.3)	49.7 (12.8)	0.002	55.9 (15.3)	51.3 (16.8)	0.029
Uric acid, mg/dL	4.81 (1.34)	5.27 (1.53)	0.018	4.81 (1.34)	5.62 (1.44)	<0.001
Fasting blood glucose, mg/dL	95.4 (13.2)	101.1 (18)	0.032	95.4 (13.2)	97.4 (11.8)	0.26
HbA1c, %	5.2 (0.49)	5.26 (0.69)	0.54	5.2 (0.49)	5.2 (0.45)	0.96

χ^2 test is applied to categorical variables and t test is applied to continuous variables. Categorical variables are expressed as percentages (n). Continuous variables are expressed as the means (SD).

ALT, alanineaminotransferase; AST, aspartateaminotransferase; Alb, albumin; FIB4, fibrosis-4index; GGT, gamma-glutamyltransferase; HDL, high-density lipoprotein; HbA1c, hemoglobinA1c; LDL, low-density lipoprotein; NAFLD, non-alcoholic fatty liver disease.

stimulate the formation of gastric cancer.[3] The abnormal hormonal action of enlarged adipocytes in patients with NAFLD could also stimulate the formation of gastric cancer.[26] Adipokines, inflammatory cytokines and chemokines produced by enlarged adipocytes in individuals with NAFLD is thought to modulate cellular proliferation and apoptosis.[26] Among them, adiponectin has anticarcinogenic effects and is one of the downregulated adipokines in individuals with NAFLD.[3] Adiponectin is thought to repress cell growth of carcinoma through AMPc-activated protein kinase.[3] Adiponectin also induces apoptosis through a caspase-dependent pathway in endothelial cells.[3] Tumour necrosis factor-alpha (TNF-α) is one of the upregulated adipokines in individuals with NAFLD. TNF-α was first identified as a cytotoxic factor produced by lymphocytes in the site of cancer.[27–29] However, TNF-α is also known to promote carcinogenesis.[30–32] Thus, insulin resistance, upregulated insulin-like growth factor axis and the abnormal hormonal actions accompanied by metabolic abnormality in individuals with NAFLD may be pivotal for the development of incident gastric cancer. However, future investigations will be needed to clarify whether there is a direct association between metabolic abnormality in individuals with NAFLD and incident gastric cancer.

Table 2 Basic characteristics of the study population with or without NAFLD or obesity

	Non-NAFLD without obesity	Non-NAFLD with obesity	NAFLD without obesity	NAFLD with obesity	P value among all four groups*
Total number	11 598	1117	1494	1717	
Incident gastric cancer, % (N)	0.22 (25)	0.18 (2)	0.54 (8)	0.76 (13)	
Incident colorectal cancer, % (N)	0.23 (27)	0.45 (5)	0.27 (4)	0.93 (16)	
Male, % (N)	45.4 (5270)	63.2 (706)	81.4 (1216)	81.1 (1393)	<0.001
Exerciser, % (N)	18.2 (2102)	15.5 (172)	14.9 (221)	13.7 (235)	<0.001
Never smoker, % (N)	63.9 (7393)	52.5 (586)	45.8 (682)	45.4 (776)	<0.001
Ex smoker, % (N)	16.6 (1916)	20.8 (232)	27.2 (405)	25.7 (439)	<0.001
Current smoker, % (N)	19.5 (2261)	26.7 (298)	27.1 (403)	29 (495)	<0.001
Diabetes, %(N)	0.6 (66)	1.7 (19)	4.6 (68)	8.5 (146)	<0.001

	Non-NAFLD without obesity #1	Non-NAFLD with obesity #2	NAFLD without obesity #3	NAFLD with obesity #4	P value between two groups†		
					#1 and #2	#1 and #3	#1 and #4
Alcohol consumption, mg/week	31.3 (48.4)	39.6 (53.8)	35.1 (51.3)	33.6 (49.6)	0.017	<0.001	0.225
Age, year	43.4 (9.1)	44.4 (8.7)	46.6 (8.6)	44.3 (8.3)	<0.001	<0.001	<0.001
BMI, kg/m^2	20.9 (2.1)	26.6 (1.6)	23.1 (1.4)	27.9 (2.6)	<0.001	<0.001	<0.001
Systolic blood pressure, mm Hg	111.3 (13.9)	122.5 (13.5)	120.3 (14.3)	128.1 (15)	<0.001	<0.001	<0.001
Diastolic blood pressure, mm Hg	69.4 (9.7)	76.8 (9.5)	75.8 (9.7)	80.8 (10.1)	<0.001	<0.001	<0.001
AST, IU/L	16.9 (8.2)	18.4 (13.1)	20 (7.8)	24.4 (12)	<0.001	<0.001	<0.001
ALT, IU/L	16.9 (11.2)	22.2 (12.2)	28.4 (14.5)	38.3 (23.5)	<0.001	<0.001	<0.001
GGT, IU/L	16.8 (13.5)	23.3 (19.7)	27.2 (21.6)	32.6 (25.8)	<0.001	<0.001	<0.001
Alb, g/dL	4.32 (0.2)	4.31 (0.19)	4.39 (0.2)	4.38 (0.2)	<0.001	0.247	<0.001
Platelet, 10^3/mL	24.1 (5.6)	25.1 (5.7)	24.9 (5.3)	25.2 (5.6)	<0.001	<0.001	<0.001
FIB4 index	0.8 (0.39)	0.75 (0.4)	0.76 (0.33)	0.75 (0.34)	0.001	<0.001	<0.001
NAFLD fibrosis score	1.05 (0.23)	1.11 (0.32)	1.07 (0.26)	1.14 (0.35)	0.010	<0.001	<0.001
Total cholesterol, mg/dL	196.9 (33.4)	206.2 (33.8)	212.1 (33.6)	214.3 (33.9)	<0.001	<0.001	<0.001
Triglycerides, mg/dL	68.9 (45.4)	97.9 (55.1)	123 (72.3)	144.5 (108.3)	<0.001	<0.001	<0.001
LDL cholesterol, mg/dL	123.7 (30.1	137 (30.7	140.1 (30.7	141.6 (32.3	<0.001	<0.001	<0.001
HDL cholesterol, mg/dL	59.4 (15.1)	49.5 (11.9)	47.3 (11.8)	44 (9.7)	<0.001	<0.001	<0.001
Uric acid, mg/dL	4.51 (1.22)	5.22 (1.32)	5.63 (1.14)	5.9 (1.3)	<0.001	<0.001	<0.001
Fasting blood glucose, mg/dL	92.9 (9.9)	97.7 (11.4)	101.6 (16.6)	105.1 (21.6)	<0.001	<0.001	<0.001
HbA1c, %	5.13 (0.39)	5.23 (0.46)	5.36 (0.63)	5.5 (0.79)	<0.001	<0.001	<0.001

Continued

Table 2 Continued

	Non-NAFLD without obesity #1	Non-NAFLD with obesity #2	NAFLD without obesity #3	NAFLD with obesity #4	P value between two groups†		
					#1 and #2	#1 and #3	#1 and #4

Categorical variables are expressed as percentages (n). Continuous variables are expressed as the means (SD).
*The difference of the ratio among all four groups is tested by χ^2 test.
†The difference between each group (#2, #3 or #4) and non-NAFLD without obesity group (#1) is tested by to Dunnett's test.
ALT, alanineaminotransferase; AST, aspartateaminotransferase; Alb, albumin; BMI, body mass index; FIB4, fibrosis-4index; GGT, gamma-glutamyltransferase; HDL, high-density lipoprotein; HbA1c, hemoglobinA1c; LDL, low-density lipoprotein; NAFLD, non-alcoholic fatty liver disease.

The strengths of the present study include its population-based design and longitudinal analysis. In addition, the gastrointestinal cancer cases collected in this study were identified reliably through systemic surveillance. However, several limitations should also be noted. First, the state of *Helicobacter pylori* infection was not available as a potential confounder. Second, the diagnosis of NAFLD was done using ultrasonography, rather than liver biopsy. Nonetheless, ultrasonography has a high sensitivity and specificity for diagnosing fatty liver, has been validated and is reasonable noninvasive surrogate measure for use in clinical settings.[33][34] Although it may provide a less accurate diagnosis than liver biopsy, it would be impossible to perform liver biopsy in such a large number of healthy individuals. Third, subjects received health check-up programmes every year or every 2 years. We defined durations between the time when they registered and the time when they received the health-checkup programmes at the last time as observation period. Gastric cancer or colorectal cancer might occur after the last visit. However, the mean observation period was not different with or without NAFLD or obesity. When cases were diagnosed and/or treated outside our facilities, we collected the medical information via letters. However, if cases died before carcinoma occurred, we treated them as censored cases. Fourth, we have no anatomopathological data. Thus, we have not assessed anatomopathological features of gastric cancer or colorectal cancer between subjects with or without NAFLD. Fifth, we have no detailed data regarding physical activity, body composition or diet. These states have remained as a potential confounders for incident colorectal cancer and gastric cancer. Lastly, the generalisability of our study to non-Japanese populations is uncertain.

In conclusion, NAFLD with obesity at baseline is a risk factor for gastric cancer as well as colorectal cancer. Obese individuals with NAFLD should be encouraged to receive screening examinations for gastric cancer, including upper gastrointestinal endoscopy, in addition to occult blood tests for colorectal cancer. Future investigations are needed to reveal the efficacy of lifestyle modification in obese individuals with NAFLD to prevent incident gastric cancer.

Table 3 Incident rate of gastric cancer or colorectal cancer

	N	Incident gastric cancer		Incident colorectal cancer	
		Cases	Incidence rate (per 1000 person-year)	Cases	Incidence rate (per 1000 person-year)
Non-NAFLD without obesity	11 598	25	0.34	27	0.37
Non-NAFLD with obesity	1117	2	0.29	5	0.72
NAFLD without obesity	1494	8	0.83	4	0.41
NAFLD with obesity	1717	13	1.21	16	1.49

The incidence rate are shown as cases per 1000 person-years.
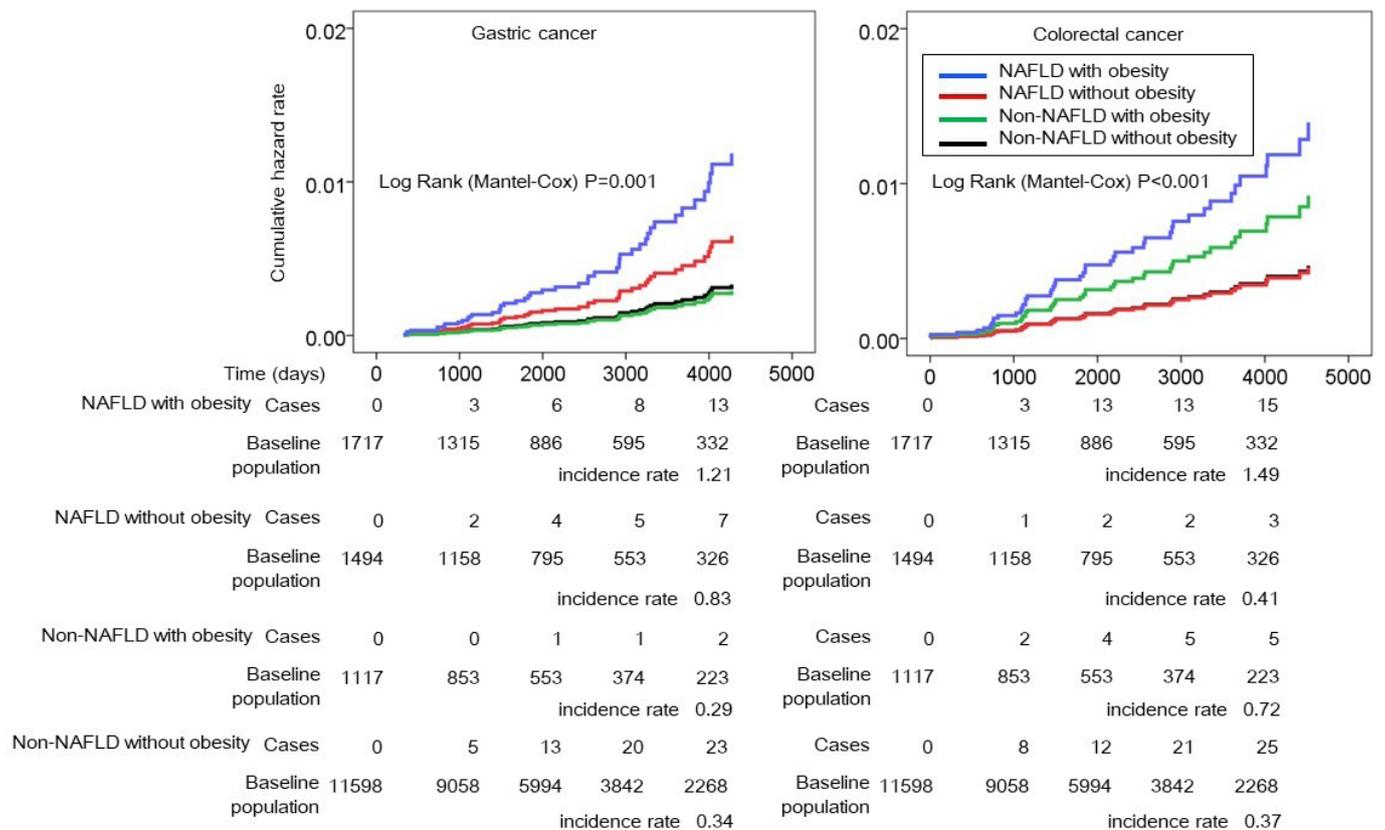NAFLD, non-alcoholic fatty liver disease.

Gastric cancer — Log Rank (Mantel-Cox) P=0.001

Colorectal cancer — Log Rank (Mantel-Cox) P<0.001

Legend:
- NAFLD with obesity
- NAFLD without obesity
- Non-NAFLD with obesity
- Non-NAFLD without obesity

Gastric cancer

Time (days)	0	1000	2000	3000	4000	5000
NAFLD with obesity Cases	0	3	6	8	13	
Baseline population	1717	1315	886	595	332	
incidence rate				1.21		
NAFLD without obesity Cases	0	2	4	5	7	
Baseline population	1494	1158	795	553	326	
incidence rate				0.83		
Non-NAFLD with obesity Cases	0	0	1	1	2	
Baseline population	1117	853	553	374	223	
incidence rate				0.29		
Non-NAFLD without obesity Cases	0	5	13	20	23	
Baseline population	11598	9058	5994	3842	2268	
incidence rate				0.34		

Colorectal cancer

Time (days)	0	1000	2000	3000	4000	5000
NAFLD with obesity Cases	0	3	13	13	15	
Baseline population	1717	1315	886	595	332	
incidence rate				1.49		
NAFLD without obesity Cases	0	1	2	2	3	
Baseline population	1494	1158	795	553	326	
incidence rate				0.41		
Non-NAFLD with obesity Cases	0	2	4	5	5	
Baseline population	1117	853	553	374	223	
incidence rate				0.72		
Non-NAFLD without obesity Cases	0	8	12	21	25	
Baseline population	11598	9058	5994	3842	2268	
incidence rate				0.37		

Figure 2 HRs of NAFLD with or without obesity for incident gastric cancer and colorectal cancer. The vertical axis shows the cumulative hazard rate for gastric cancer and colorectal cancer, and the horizontal axis indicates the observational time in days. The blue lines represent NAFLD with obesity, the red lines indicate NAFLD without obesity, the green lines indicate non-NAFLD with obesity and the black lines indicate non-NAFLD without obesity. NAFLD, non-alcoholic fatty liver disease.

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Table 4 The adjusted hazard risk of individuals with or without NAFLD and obesity for incident gastric cancer or colorectal cancer

	HR (95% CI)	P value	HR (95% CI)	P value
Incident gastric cancer	Model 1		Model 2	
Non-NAFLD without obesity	Ref		Ref	
NAFLD without obesity	1.96 (0.86 to 4.47)	0.11	1.84 (0.8 to 4.23)	0.15
Non-NAFLD with obesity	0.88 (0.21 to 3.73)	0.86	0.86 (0.2 to 3.67)	0.84
NAFLD with obesity	3.58 (1.73 to 7.38)	0.001	3.3 (1.57 to 6.9)	0.002
Exerciser	1.00 (0.48 to 2.10)	1.00	1.01 (0.48 to 2.13)	0.97
Alcohol consumption	1.00 (0.99 to 1.00)	0.6	1 (0.99 to 1)	0.59
Male	0.7 (0.31 to 1.6)	0.4	0.69 (0.3 to 1.57)	0.37
Age	1.13 (1.1 to 1.17)	< 0.001	1.13 (1.1 to 1.17)	0
Never smoker	Ref		Ref	
Ex-smoker	1.64 (0.67 to 4.01)	0.28	1.65 (0.68 to 4.03)	0.27
Current smoker	2.71 (1.2 to 6.11)	0.016	2.75 (1.22 to 6.19)	0.014
Diabetes			2.19 (0.76 to 6.31)	0.15
Incident colorectal cancer	Model 1		Model 2	
Non-NAFLD without obesity	Ref		Ref	
NAFLD without obesity	0.98 (0.33 to 2.88)	0.97	0.99 (0.34 to 2.93)	0.99
Non-NAFLD with obesity	1.96 (0.74 to 5.17)	0.17	1.97 (0.75 to 5.2)	0.17
NAFLD with obesity	2.96 (1.44 to 6.09)	0.003	3.04 (1.47 to 6.3)	0.003
Exerciser	0.83 (0.37 to 1.89)	0.66	0.83 (0.37 to 1.88)	0.66
Alcohol consumption	1 (1 to 1.01)	0.12	1 (1 to 1.01)	0.12
Male	1.33 (0.57 to 3.14)	0.51	1.34 (0.57 to 3.15)	0.5
Age	1.04 (1 to 1.07)	0.053	1.04 (1 to 1.07)	0.049
Never smoker	Ref		Ref	
Ex smoker	1.40 (0.62 to 3.15)	0.42	1.39 (0.62 to 3.14)	0.43
Current smoker	1.33 (0.6 to 2.94)	0.48	1.33 (0.6 to 2.93)	0.49
Diabetes			0.64 (0.09 to 4.81)	0.67

The HRs of the four group for incident gastric cancer and colorectal cancer are calculated by the Cox proportional hazards model. In model 1, exerciser, alcohol consumption, male, age, smoking sates are used as covariates. In addition to them, diabetes is used as a covariate in model 2.
NAFLD, non-alcoholic fatty liver disease.

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