Original article

The Significance of Comprehensive Metabolic Phenotypes in Cancer Risk: A Japan Multi-Institutional Collaborative Cohort (J-MICC) Study

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Abbreviations list

J-MICC: Japan Multi-Institutional Collaborative Cohort

BMI: Body mass weight

MUHO: Metabolically unhealthy obese/obesity

MHO: Metabolically healthy obese/obesity

MUNW: Metabolically unhealthy normal weight

MHNW: Metabolically healthy normal weight

MetS: Metabolic syndrome

CVD: Cardiovascular disease

ICD-10: International Classification of Diseases, 10th revision

METs: metabolic equivalent of tasks

NAFLD: Nonalcoholic fatty liver disease

Conflict of Interest

All authors declare no potential conflicts of interest with respect to the authorship and/or publication of this article.

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Abstract (229 word)

The present study investigated the relationship between metabolic phenotypes and the risk of cancer in a Japanese population using the criteria of metabolic phenotypes based on an examination and those based on questionnaires. We used data from 25,357 subjects for examination-based analyses and those from 53,042 subjects for questionnaire-based analyses in the Japan Multi-Institutional Collaborative Cohort Study. Metabolic phenotypes were defined by classifying subjects according to their BMI (obesity: BMI $\geq$25 kg/m^2; normal weight: BMI <25 kg/m^2) and the number of metabolic abnormalities. Metabolic abnormalities were defined according to metabolic syndrome components of the Joint Interim Statement Criteria for examination-based analyses and self-reported histories of diabetes, dyslipidemia, and hypertension for questionnaire-based analyses. Cox proportional hazards regression analyses adjusted for potential confounders were performed for total and site-specific cancer incidence according to metabolic phenotypes. Metabolically unhealthy obesity (MUHO) was significantly associated with cancer incidence in both examination-based [HR (95% CI): 1.17 (1.01-1.36)] and questionnaire-based analyses [HR (95% CI): 1.15 (1.04-1.26)]. Regarding site-specific cancer in questionnaire-based analyses, metabolically healthy obesity and MUHO were associated with colorectum and liver cancers in all subjects and with breast cancer in female subjects. Subjects with a metabolically unhealthy normal weight had a higher risk of pancreatic cancer. Moreover, MUHO was associated with corpus uteri cancer in female subjects. This prospective

cohort study suggests that metabolic phenotypes are important risk factors for total and some site-specific cancers in Japanese adults.

Significance

The prospective cohort study in a large Japanese population suggested that metabolic phenotypes are important risk factors for total and some site-specific cancers in Japanese adults. Moreover, the risk of each site-specific cancer may differ according to metabolic phenotypes.

Keywords: Cancer incidence, cohort study, metabolic syndrome, metabolically unhealthy obesity, Japanese.

Introduction

Obesity is a serious public health issue worldwide [1] and the number of people living with obesity is increasing both globally [2] and in Japan [3]. Obesity and other cardiovascular risks, i.e., hypertension, hyperglycemia, and dyslipidemia, form the complex called metabolic syndrome (MetS) [4-7]. Although obesity and other metabolic abnormalities have been identified as independent risk factors for cardiovascular disease (CVD), the incidence and mortality of diseases including CVD may differ depending on their combination [8, 9]. For example, a previous study showed that Metabolically Unhealthy Normal Weight (MUNW) and Metabolically Unhealthy Obese (MUHO), but not Metabolically Healthy Obese (MHO) subjects had a higher risk of CVD and all-cause mortality than Metabolically Healthy Normal Weight (MHNW) subjects [8]. Furthermore, the risk of diseases, such as atherosclerotic CVD, was found to be higher in MUNW, MUHO, and MHO subjects than in MHNW subjects [9]. The categorization of subjects based on obesity and the metabolic health status is called the metabolic phenotype and has attracted attention [1, 10-12]. The pathogenesis of metabolic abnormalities has also been suggested to differ between obese and normal weight subjects, such as the underlying genetic background [13]. Therefore, assessments of differences in the risk of various diseases based on metabolic phenotypes, not simple obesity or MetS, may contribute to the prevention of diseases according to patient characteristics.

Similar to CVD, the relationship between obesity, MetS, and cancer has been well-documented. For example, an umbrella review of systematic reviews and meta-analyses showed

112 that the relationship between adiposity and 11 cancers, including colon, breast, and pancreatic
113 cancers, was supported by strong evidence [14]. The relationship between MetS and site-specific
114 cancers has been extensively investigated [15]. A meta-analysis of 43 studies revealed that MetS was
115 significantly associated with various cancers, including liver, colorectal, and breast cancers [15]. On
116 the other hand, evidence for the relationship between metabolic phenotypes and cancer is limited. A
117 prospective cohort study in Sweden showed that obese subjects regardless of metabolic health had a
118 higher risk of total cancer than MHNW subjects [16]. In a prospective cohort study conducted in
119 Taiwan, metabolically unhealthy overweight, but not obese subjects had a significantly higher total
120 cancer risk than MHNW subjects [17]. Recent studies performed in Europe reported a relationship
121 between metabolic phenotypes and obesity-related site-specific cancer [18, 19]. In Japan, MUHO
122 was associated with total cancer mortality [20]. Although data from anthropometric and blood
123 examinations are necessary to estimate metabolic phenotypes, they are costly and time consuming;
124 therefore, criteria by which metabolic phenotypes may be classified based simply on information
125 from questionnaires may be useful for future epidemiological studies.

126 The present study investigated the relationships between metabolic phenotypes and total and
127 site-specific cancer incidence using both examination- and questionnaire-based analyses of a large
128 Japanese population.

129

Materials and Methods

Study design and subjects

A prospective cohort analysis was conducted using data from the Japan Multi-Institutional Collaborative Cohort (J-MICC) Study. Details on the J-MICC study have previously been reported [21-23]. Briefly, the J-MICC Study was launched in April 2005 and recruited subjects aged 35 to 69 years from 14 research areas in Japan. The main purpose of the J-MICC study was to confirm the interactions of lifestyle and genetic factors with the risk of chronic diseases. The study protocol was approved by the Ethics Committee of the Aichi Cancer Center Research Institute (No. H2210001A), Tokushima University Hospital (No. 466-15), and all other institutions participating in the J-MICC Study. Written informed consent was obtained from all subjects.

We selected study subjects from the participants of the J-MICC Study for examination- and questionnaire-based analyses. Examination- and questionnaire-based analyses were different in the definition of metabolic phenotypes. Metabolic phenotypes in examination-based analyses were classified according to anthropometric and biological data and those in questionnaire-based analyses were classified according to the self-reported medical history from questionnaire. These definitions are described in detail below “Definitions of MetS and metabolic phenotypes” section. Dataset version 20210901 was used. In examination-based analyses, 37,915 individuals (17,561 men, 20,354 women) from 7 sites that used the same questionnaire and conducted the blood examination needed to diagnose MetS (Okazaki, Shizuoka, Takashima, Kyoto, Kagoshima, Tokushima, and

Shizuoka-Sakuragaoka) were initially included. We excluded subjects with a history of cancer, myocardial infarction, or stroke or missing information on these diseases (n=4,018), with missing data on the follow-up period (n = 2), with missing data on smoking and drinking habits or physical activity or whose total energy intake was extremely high or low (>4000 or ≤1000 kcal, n=2316), or with missing data on the body mass index (BMI), systolic blood pressure (SBP), diastolic blood pressure (DBP), triglycerides, HDL-cholesterol, or fasting blood glucose (n=6,222). Therefore, 25,357 subjects (12,469 men, 12,888 women) were ultimately included. In questionnaire-based analyses, 67,178 individuals (29,852 men, 37,326 women) from 11 sites that used the same questionnaire (Chiba, Aichi Cancer Center, Okazaki, Shizuoka, Daiko, Takashima, Kyoto, Saga, Kagoshima, Tokushima, and Shizuoka-Sakuragaoka) were initially included. We excluded subjects with a history of cancer, myocardial infarction, or stroke or missing information on these diseases (n=10,364), with missing data on the follow-up period (n = 41), with missing data on smoking and drinking habits or physical activity or whose total energy intake was extremely high or low (n=3,092), or with missing data on the self-reported history of hypertension, dyslipidemia, and diabetes (n=639). Therefore, 53,042 subjects (23,244 men, 29,798 women) were ultimately included. Both selections of study subjects are shown in Figure 1.

Questionnaire

Data collection was performed based on a structured self-administered questionnaire, which subjects completed, and the data obtained were checked by trained staff at the survey. The questionnaire

consisted of a series of questions regarding subjects' sociodemographic characteristics, lifestyle, medical history, and medications. Dietary intakes of green and yellow vegetables, light-colored vegetables, fruit, and miso soup were assessed using a validated short food frequency questionnaire [24, 25]. Total energy and 26 nutrients including calcium intake was assessed with the program developed and validated at the Department of Public Health, Nagoya City University School of Medicine [26] . Dietary intakes of green and yellow vegetables, light-colored vegetables, fruit, miso soup and calcium intake were log-transformed and energy-adjusted using the residual method. Dietary vegetable intake was calculated by adding the intake of green and yellow vegetables and light-colored vegetables.

Educational levels were classified into four categories (≤9 years, 10–15 years, ≥16 years, and unknown). Smoking habits were classified into three categories (current, ex, and non), and the average number of cigarettes per day and age at the initiation of habitual smoking were noted. Pack-years were calculated by multiplying the average number of cigarettes per day by the number of years smoked and divided by 20 (one pack). Drinking habits were classified into three categories (current, ex, and non), and the frequency and amount consumed each time for the following six alcoholic drinks were noted: Japanese sake, shochu, shochu-based cocktails, beer, whiskey, and wine. Ethanol intake (g/day) by current drinkers was calculated based on the amount of ethanol present in each alcoholic drink. Total physical activity during leisure time was estimated using a questionnaire. The frequency (5 categories from never to ≥5 times/week) and average duration (6 categories from

≤30 minutes to ≥4 hours) of the following three groups was reported by subjects: light intensity exercise (e.g., walking and golf) at 3.4 metabolic equivalent of tasks (METs), moderate intensity exercise (e.g., jogging and swimming) at 7.0 METs, and vigorous intensity exercise (e.g., marathon running) at 10.0 METs. The three levels of leisure-time physical activity were calculated as MET hours/week (MET level × hours of activity × events per week), and these values were summed and used as the value for total physical activity in the present study.

Anthropometric and biochemical measurements

Height (cm), weight (kg), SBP and DBP, serum triglycerides, HDL cholesterol, and blood glucose were measured at each research site according to standardized protocols. BMI (kg/m^2) was calculated as weight (kg) divided by the square of height (m^2).

Definitions of MetS and metabolic phenotypes

The definitions of MetS and metabolic phenotypes were described in a previous study [27]. Briefly, we defined MetS based on the Joint Interim Statement Criteria [28]. BMI (≥25 kg/m^2) was used instead of waist circumference (WC for Asians, including Japanese: ≥90 for men and ≥80 for women) because WC was not measured in all subjects [28, 29]. MetS was defined as the combined presence of at least three of the following five criteria: (i) obesity: BMI ≥25 kg/m^2; (ii) elevated blood pressure: SBP ≥130 mmHg and/or DBP ≥85 mmHg, and/or the self-reported use of antihypertensive drugs; (iii) serum triglyceride level ≥150 mg/dL; (iv) serum HDL-cholesterol level <40 mg/dL for

men and <50 mg/dL for women; and (v) blood glucose level ≥100 mg/dL and/or the self-reported use of antidiabetic drugs.

In the classification of metabolic phenotypes, subjects were categorized into four groups based on BMI (normal weight or obesity) and the metabolic health status (healthy or unhealthy). Examination-based metabolic phenotypes were defined using data from anthropometric and blood examinations. Subjects with a normal weight (BMI <25 kg/m^2) were divided into two phenotypes: MUNW and MHNW (≥1 or no components of MetS, respectively). Subjects with obesity (BMI ≥25 kg/m^2) were classified as MUHO and MHO (≥1 or no components of MetS other than BMI, respectively). Questionnaire-based metabolic phenotypes were defined using BMI calculated from self-reported height and weight, a history of hypertension, dyslipidemia, or diabetes, and a medication history for these morbidities. Subjects stratified by obesity with ≥1 disease from the self-reported history or medication for hypertension, dyslipidemia, or diabetes were categorized as metabolically unhealthy. Sensitivity analyses changing the cut-off were also conducted in both examination- and questionnaire-based metabolic phenotypes.

Follow-up and cancer ascertainment

Information on cancer incidence was collected through national cancer registries, regional cancer registries, patient notifications from hospitals, and reports from subjects confirmed by medical records. Data from the national cancer registries provided to us according to the Cancer Registry Promotion Act were processed and analyzed independently for this study. All cancer cases were

224 classified according to the International Classification of Diseases, 10th revision (ICD-10). The
225 outcome of the present study was the incidence of total cancer (C001-809), stomach cancer (C16),
226 colon and rectum cancer (C18-21), liver cancer (C22), pancreatic cancer (C25), and lung and
227 bronchus cancer (C34) in all subjects, breast cancer (C50) and corpus uteri cancer (C54) in women,
228 and prostate cancer in men (C61). Moreover, colorectum cancer was separated out into proximal
229 colon cancer (C18.0-18.4), distal colon cancer (C18.5-18.7), and rectum cancer (C19-C20). In
230 analyses of cancer incidence, person-years of follow-up were calculated using the time from the date
231 of the baseline survey until the occurrence of cancer, death, moving, or the end of the follow-up
232 period (December 31, 2021). Cancer incidence was calculated using the number of incidences
233 divided by the person-years of follow-up. During a median (25%, 75%) follow up of 8.0 (5.5, 10.2)
234 years, 1,584 (951 men, and 633 women) cancer cases were identified in subjects in
235 examination-based analyses, while there were 4,467 (2,423 men and 2,044 women) cancer cases in
236 subjects in questionnaire-based analyses during a median (25%, 75%) follow-up of 9.1 (5.9, 10.5)
237 years.

238 **Statistical analysis**

239 Regarding the baseline characteristics of subjects according to the obesity status, the chi-square test
240 for categorical variables and the Wilcoxon rank sum test for continuous variables were applied.
241 Multivariable Cox proportional hazards regression analyses were conducted to assess the
242 relationships between MetS, the number of components, each individual component, and the

incidence of cancer. The relationship between metabolic phenotypes and cancer incidence was also examined using MHNW subjects as a reference. Model 1 was adjusted for age (continuous), sex, research sites (seven categories in examination-based analyses and 11 categories in questionnaire-based analyses), and educational background (four categories: (≤9 years, 10–15 years, ≥16 years, and unknown); Model 2 was additionally adjusted for pack-years (four categories: 0, >0 and <20, ≤20, unknown), the drinking status (four categories: never, ex, >0 and <20 g/day, ≥20 g/day), and physical activity levels (quartiles). Model 3 was adjusted for energy-adjusted vegetable, fruit, and miso soup intakes (quartiles). Model 4 was additionally adjusted for hormone replacement therapy, age of menarche (four categories: <11, ≥11 and <15, ≥15, unknown), menopausal status and age of menopause (four categories: pre-menopause, <55, ≥55, unknown) in the analyses of breast cancer. Moreover, in addition to model 4 in breast cancer analyses, it was adjusted for history of ovarian disease (three categories: non, current, past) in the model 4 of the analyses of corpus uteri cancer. Antipyretic use (two categories: yes, no), calcium intake (quartiles), and red and processed meat intake (quartiles) were additionally adjusted in the model 4 of the analyses of colorectum cancer. History of hepatitis B and C (two categories: yes or no) were adjusted in the model 4 of the analyses of liver cancer. We conducted sensitivity analyses by handling subjects who had cancer within one year as censored. We additionally conducted analyses by handling subjects who had cancer within two years as censored in the analyses of total and site-specific cancers with the exception of cancers which were fewer than 10 cases in some groups of metabolic phenotypes. The test

for trends in the relationship between the number of components of MetS or metabolic phenotypes and cancer incidence was performed using a likelihood ratio test. Proportional hazards assumptions were checked for each variable using the Schoenfeld residual method. The results obtained indicated that these assumptions were not violated over time.

All statistical analyses were performed using SAS statistical software (Version 9.4 for Windows; SAS Institute Inc., Cary, NC, USA, RRID:SCR_008567). Statistical tests were based on two-sided probabilities, and *P*-values <0.05 were considered to be significant. Forest plot was made using the forestploter package of R (version 4.3.1, RRID:SCR_001905)

Data availability statement

The anonymized minimum data needed to replicate the results of the present study are available upon reasonable request to the corresponding author and after approval by all the participating institutions, the Ministry of Health, Labour and Welfare, and the National Cancer Registry, Japan.

Results

The baseline characteristics of subjects according to obesity for examination- and questionnaire-based analyses are shown in Table 1. Among 25,357 subjects in examination-based analyses, 6,309 (24.9%) were obese (3,812 men, 2,497 women). Among 53,037 subjects in questionnaire-based analyses, 11,559 (21.8%) were obese (6,727 men, 4,832 women). Among subjects in examination-based analyses, obese subjects were more likely to be men and less physically active. Furthermore, obese subjects had a shorter duration of education, were more likely to be current smokers, smoke more cigarettes, be current drinkers, drink more alcohol. Obese subjects also had significantly more self-reported medical histories of colorectal polyps, fatty liver, high blood pressure, diabetes, and dyslipidemia, but a lower medical history of chronic gastritis. In addition, obese subjects were taking more medications for hypertension, diabetes, and high blood cholesterol, but less for constipation. Overall results were similar between subjects in examination-based and questionnaire-based analyses; however, in questionnaire-based analyses, obese subjects were slightly older and had a higher self-reported medical history of hepatitis B. Sex-stratified analyses were shown in Supplementary Table 1. Obese female subjects were more likely to be postmenopausal women. Although overall results were similar between male and female subjects, the significant difference in duration of education, antipyretic medication between normal weight and obesity subjects were only observed in female subjects, and significant difference of medical history of hepatitis B was only observed in male subjects (Supplementary Table 1).

Supplementary Table 2 shows the HR (95% CI) for the risk of cancer according to MetS, the number of components, or each component. Subjects with MetS had a higher risk of cancer than those without MetS in all models. The number of MetS components were associated with cancer incidence. Among MetS components, marginally significant association of obesity, hypertension and elevated blood glucose with a higher risk of cancer were observed. We obtained similar results in examination- and questionnaire-based analyses. Among the components examined, i.e., obesity, hypertension, dyslipidemia, and diabetes, in the self-administered questionnaire, obesity, hypertension, and diabetes were associated with a higher risk of cancer. The results obtained on the relationship between the number of components and cancer incidence in subjects stratified by obesity are shown in Supplementary Table 3. In examination- and questionnaire-based criteria, the number of components was associated with cancer incidence in obese subjects only [Examination-based analyses, model 3, *P*-trend =0.009, Questionnaire-based analyses, model 3, *P*-trend =0.041]. Sex-stratified analyses were showed in Supplementary Table 4. The association between the number of components and cancer incidence in obese subjects were only observed in male subjects both in examination- and questionnaire-based criteria (Supplementary Table 4). Supplementary Table 5 shows the relationships between individual components and cancer incidence in subjects stratified by obesity. In examination-based analyses, an elevated blood glucose level was associated with cancer in obese subjects only [model 3, HR (95% CI): 1.30 (1.07, 1.58)]. In questionnaire-based analyses, high blood pressure and diabetes were associated with cancer incidence in both normal and obese

subjects; however, point estimates were higher in obese subjects. Sex-stratified analyses were also conducted (Supplementary Table 6). Hypertension was significantly associated with cancer incidence in male obese subjects in the questionnaire-based analyses and in female normal weight subjects in both analyses (Supplementary Table 6). The same analyses as those shown in Supplementary Table 3 and 5 by handling subjects with cancer within one year or two years as censored were conducted, and similar results were obtained (Supplementary Table 7 and 8).

Figure 2, 3 and Supplementary Table 9 show the relationship between metabolic phenotypes and cancer incidence in questionnaire-based analyses. MUHO was associated with total cancer in both examination-based analyses [model 3, HR (95% CI): 1.17 (1.01, 1.36)] and questionnaire-based analyses [model 3, HR (95% CI): 1.15 (1.04, 1.26)] (Supplementary Table 9). Analyses of site-specific cancer and sex-stratified analyses were also conducted using questionnaire-based criteria. MHO and MUHO were associated with colorectal cancer and liver cancer in all subjects (Figure 2, Supplementary Table 9). MHO and MUHO were also associated with total cancer and breast cancer in female subjects (Figure 3, Supplementary Table 9). Among female subjects, MUHO subjects had a higher risk of corpus uteri cancer (Figure 3, Supplementary Table 9). Among all subjects, MUNW was associated with pancreatic cancer (Figure 2, Supplementary Table 9). The number of components was significantly associated with pancreatic cancer in normal weight subjects and among components, diabetes was associated with pancreatic cancer in normal weight subjects (Supplementary Table 10). In sensitivity analyses handling subjects with cancer within one year as

censored, a significant association was not observed between MHO and colorectal cancer (Figure 4 and Supplementary Table 11). On the other hand, MUHO was associated with pancreatic cancer (Figure 4 and Supplementary Table 11). MUHO was associated with total cancer incidence in male subjects (Figure 5 and Supplementary Table 11). Moreover, MUHO had tendency of higher risk of total cancer in examination-based analyses although it was not significant (Supplementary Table 11). The analyses were conducted handling subjects with cancer within two years as censored the results were not so altered (Figure 4, 5 and Supplementary Table 11). Regarding breast cancer, age-stratified analyses were also conducted (Supplementary Table 12). MUHO in subjects who was 54 years or younger and MHO and MUHO in subjects who was older than 54 were associated with higher risk of breast cancer (Supplementary Table 12). Moreover, regarding colorectum cancer, the analyses by separating out proximal and distal colon cancer and rectum cancer were also conducted (Supplementary Table 13). MHO was significantly associated with distal colon cancer. The breakdown of site-specific cancer incidence is shown in Supplementary Table 14. It was similar between the subjects of examination-based and those of questionnaire-based analyses (Supplementary Table 14).

Discussion

This prospective cohort study assessed the relationships between metabolic phenotypes and cancer incidence both in examination- and questionnaire-based analyses. Results obtained from both

353 analyses were similar in the characteristics of participants (Table 1), the association between number
354 of components and cancer incidence (Supplementary Table 3), the association between each
355 component and cancer incidence (Supplementary Table 5), and the association between metabolic
356 phenotypes and total cancer incidence (Supplementary Table 9). The results from both analyses were
357 also similar in sex-stratified analyses and sensitivity analyses handling subjects who had cancer
358 within one or two years as censored (Supplementary Table 1, 4, 6, 7, 8, 9, and 11). Moreover,
359 associations were examined between metabolic phenotypes and various site-specific cancers;
360 however, results were only obtained from questionnaire-based analyses (Figure 2 and 3,
361 Supplementary Table 9).

362 To date, few studies have reported a relationship between metabolic phenotypes and various
363 site-specific cancers. A previous study using data from UK Biobank showed that obesity was
364 associated with some cancers, such as endometrial cancer, regardless of the metabolic health status,
365 while other cancers, including colorectal cancer, were associated with MUHO [18]. Moreover, a
366 pooled study conducted in Europe reported a relationship between metabolic phenotypes and
367 obesity-related cancers [19]. To the best of our knowledge, the present study is the first to examine
368 the relationships between metabolic phenotypes and total and site-specific cancers in Asia, where
369 even though the prevalence of obesity is lower, its impact on health is likely to be greater than in
370 Europe [30, 31].

Although most of the present results were consistent with the findings of previous studies performed in Europe, there were some differences. For example, the inverse relationship between MUHO and prostate cancer reported in a previous study using data from UK Biobank was not observed in the present study [18] (Figure 3, Supplementary Table 9). Some studies indicated that MetS and obesity reduced prostate-specific antigen concentrations, which delayed the diagnosis of low-grade prostate cancer [32, 33]. This may be one of the reasons for the inverse relationships observed between MUHO and prostate cancer in the previous study [18]. On the other hand, severe obesity is less common in Japan, which may have contributed to the lack of relationship between MUHO and prostate cancer in the present study [34] (Figure 3, Supplementary Table 9). Moreover, MUHO subjects had a higher risk of corpus uteri cancer in the present study (Figure 3 and Supplementary Table 9). In the previous studies, MHO and MUHO were associated with endometrial cancer, which is the same classification of ICD10 as corpus uteri cancer (C54) in the present study[17, 18]. The reasons for this discrepancy remain unknown; however, differences in the criteria of obesity between the present study (BMI ≥25) and studies conducted in Europe (BMI ≥30) may play a role.

MHO and MUHO were associated with colorectal and liver cancers in all subjects and breast cancer in female subjects; however, an association was not observed between MHO and colorectal cancer in sensitivity analyses handling subjects who had cancer within one year or two years as censored (Figure 2-5, Supplementary Table 9 and 11). Previous studies showed that subjects

with obesity or MetS had a higher risk of colorectal cancer [35, 36]. Regarding liver and breast cancers, a study conducted in Japan showed that MetS was associated with liver cancer in all subjects [37] and female subjects with MetS or a high BMI had a higher risk of liver and breast cancers [37]. Obesity is closely related to the prevalence and severity of nonalcoholic fatty liver disease (NAFLD), which is emerging as one of the major causes of hepatocellular carcinoma, the most common type of liver cancer [38, 39]. Insulin resistance and hyperinsulinemia accompanied by NAFLD may be involved in liver tumorigenesis by activating intracellular signaling pathways, such as the phosphoinositide 3-kinase/Akt/mammalian target of rapamycin pathway [39]. Moreover, NAFLD may affect other gastrointestinal cancers, such as colorectal cancer [40]. Adipokines, proinflammatory cytokines, insulin, and Insulin like growth factor secreted by adipose tissue have been implicated in the development of colorectal cancer [41]. Regarding breast cancer especially post-menopausal breast cancer, increased estrogen production by adipose tissue and the promotion of estrogen receptor expression and transactivation have been suggested to promote its progression [42]. Epidemiological studies also suggested that obesity may be more critical factor for post-menopausal breast cancer than pre-menopausal breast cancer [43] . In our study, obesity was associated with breast cancer regardless of metabolic health in subjects who were older than 54 at baseline and almost all the onset of breast cancer in these subjects may be at post-menopause, while only MUHO was associated with breast cancer in subjects who were 54 years or younger (Supplementary Table 12). Based on the present results, previous findings, and plausible mechanisms, obesity itself and/or

409 other metabolic abnormalities accompanied by obesity may play important roles in the pathogenesis
410 of these cancers.

411 MUNW, but not MHO nor MUHO, was associated with pancreatic cancer, although MUHO
412 was also associated with pancreatic cancer in sensitivity analyses handling subjects who had cancer
413 within one year as censored (Figure 2, 4 and Supplementary Table 9 and 11). Among normal weight
414 subjects, the number of components were significantly associated with pancreatic cancer and
415 diabetes may be the most important factor (Supplementary Table 10). Excess body weight is a
416 well-established risk factor for pancreatic cancer; however, in cohort studies, the association is often
417 underestimated because of the weight loss accompanied by diabetes, subjects with prediagnostic
418 pancreatic cancer often experience [44, 45]. This may be a reason why the association between
419 MUHO and pancreatic cancer was not observed in the main analysis and was unmasked in the
420 sensitivity analysis handling subjects who had cancer within one year as censored in the present
421 study (Figure 2, 4 and Supplementary Table 9 and 11). In the sensitivity analysis, there was still a
422 significant association between MUNW and pancreatic cancer (Figure 4 and Supplementary Table
423 11). Pancreatitis, which is induced by risk factors such as alcohol and smoking may causes diabetes
424 characterized by reduced or normal range of BMI [46, 47]. This pancreatogenic diabetes (Type 3c
425 DM) may play a role in the association between MUNW and pancreatic cancer in the present study.

426 The large number of study subjects is a major strength of the present study. The large
427 sample size made it possible to adjust for various potential confounders in the analyses. Moreover,

428 data from the relatively new cohort may reflect the current condition of MetS, metabolic phenotypes,
429 and cancer in Japan. In contrast, there are several limitations that need to be addressed. Due to the
430 lack of data on WC, we used BMI to assess obesity in examination-based analyses. However, a
431 strong correlation between WC and BMI was previously reported in a study with various ethnic
432 groups, including Japanese (Pearson's correlation coefficients 0.921 for Japanese men and 0.922 for
433 Japanese women) [29, 48, 49]. Furthermore, the assessment of metabolic phenotypes used baseline
434 data, and a status change was not monitored. Moreover, information on the lifestyle and background
435 characteristics of subjects and the components of metabolic phenotypes in questionnaire-based
436 analyses were based on a self-reported questionnaire; therefore, misclassifications may be inevitable.
437 Since number of subjects was limited, it was not possible to conduct the examination-based analyses
438 of site-specific cancer. Another limitation is the difficulties associated with applying the present
439 results directly to populations in other countries because this study was conducted solely on a
440 Japanese population.

441 In conclusion, the present study suggests that the number of metabolic abnormalities is
442 associated with the risk of cancer in obese Japanese adults. Moreover, hypertension and diabetes, but
443 not dyslipidemia, may be key metabolic abnormalities contributing to the risk of cancer. The risk of
444 each site-specific cancer may differ according to metabolic phenotypes. Further studies are
445 warranted on the underlying mechanisms as well as the causal relationship between metabolic
446 phenotypes and each site-specific cancer.

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Author contributions

TVN and TW wrote the first version of the manuscript. KA and other authors critically revised the manuscript. Statistical analyses were independently conducted by TW and SK, who confirmed that the results obtained were consistent. All authors contributed to the study design and data collection and approved the final version of the manuscript.

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Table 1. Background characteristics of participants according to obesity classification.

Characteristics[a]	Normal weight (*n* = 19048)	Obesity (*n* = 6309)	*P*-value[b]
Subjects for the analysis of Examination-based Metabolic phenotypes			
Age (years)	56 (46, 63)	56 (47, 63)	0.136
Exercise during leisure time (MET-hours/week)	6.0 (0.4, 17.9)	5.1 (0, 17.9)	<0.0001
Sex			
Men	8657 (45.4)	3812 (60.4)	<0.0001
Women	10391 (54.6)	2497 (39.6)	
Educational background (years)			
≤9	2240 (11.8)	1002 (15.9)	<0.0001
10–15	12211 (64.1)	3762 (59.6)	
≥16	4479 (23.5)	1505 (23.9)	
Unknown	118 (0.6)	40 (0.6)	
Smoking habit			
Current	3024 (15.9)	1125 (17.8)	<0.0001
Past	4227 (22.2)	1759 (27.9)	
Never	11797 (61.9)	3425 (54.3)	
Pack-years			
0	11797 (61.9)	3425 (54.3)	<0.0001
>0 and <20	3176 (16.7)	989 (15.7)	
≥20	3693 (19.4)	1744 (27.6)	
Unknown	382 (2.0)	151 (2.4)	
Alcohol drinking			
Never	7940 (41.7)	2433 (38.6)	<0.0001
Past	308 (1.6)	106 (1.7)	
>0 and <20 g/day	6585 (34.6)	1969 (31.2)	
≥20 g/day	4215 (22.1)	1801 (28.6)	
Medical history			
Gastric ulcer	2313 (12.1)	694 (11.0)	0.015
Chronic gastritis	2247 (11.8)	532 (8.4)	<0.0001
Colorectal polyps	1648 (8.7)	623 (9.9)	0.003
Hepatitis B	230 (1.2)	92 (1.5)	0.123
Hepatitis C	156 (0.8)	53 (0.8)	0.872
Fatty liver	1159 (6.1)	1172 (18.6)	<0.0001
Asthma	1156 (6.1)	398 (6.3)	0.493
High blood pressure	2916 (15.3)	1908 (30.2)	<0.0001
Diabetes	835 (4.4)	544 (8.6)	<0.0001
Dyslipidemia	2621 (13.8)	1229 (19.5)	<0.0001
Medication			
High blood pressure	2389 (12.5)	1683 (26.7)	<0.0001
Diabetes	504 (2.7)	393 (6.2)	<0.0001
High blood cholesterol	1527 (8.0)	793 (12.6)	<0.0001
Sleeping pills	661 (3.5)	221 (3.5)	0.902
Antipyretic	548 (2.9)	197 (3.1)	0.317
Laxative	766 (4.0)	193 (3.1)	0.0005

Characteristics[a]	Normal weight (*n* = 41483)	Obesity (*n* = 11559)	*P*-value[b]
Subjects for the analysis of Questionnaire-based Metabolic phenotypes			
Age (years)	55 (46, 62)	55 (47, 62)	<0.0001
Exercise during leisure time	6.0 (0.4, 17.9)	5.1 (0.4, 16.2)	<0.0001
Sex			
Men	16517 (39.8)	6727 (58.2)	<0.0001
Women	24966 (60.2)	4832 (41.8)	
Educational background (years)			
≤9	3344 (8.1)	1382 (12.0)	<0.0001
10–15	27355 (65.9)	6992 (60.5)	
≥16	10582 (25.5)	3126 (27.0)	
Unknown	202 (0.5)	59 (0.5)	
Smoking habit			
Current	6795 (16.4)	2306 (20.0)	<0.0001
Past	8527 (20.6)	3147 (27.2)	
Never	26161 (63.1)	6106 (52.8)	
Pack-years			
0	26161 (63.1)	6106 (52.8)	<0.0001
>0 and <20	6694 (16.1)	1825 (15.8)	
≥20	7963 (19.2)	3388 (29.3)	
Unknown	665 (1.6)	240 (2.1)	
Alcohol drinking			
Never	17261 (41.6)	4507 (39.0)	<0.0001
Past	848 (2.0)	248 (2.2)	
>0 and <20 g/day	14683 (35.4)	3600 (31.1)	
≥20 g/day	8691 (21.0)	3204 (27.7)	
Medical history			
Gastric ulcer	5534 (13.3)	1485 (12.9)	0.166
Chronic gastritis	5301 (12.8)	1179 (10.2)	<0.0001
Colorectal polyps	3340 (8.1)	1135 (9.8)	<0.0001
Hepatitis B	496 (1.2)	178 (1.5)	0.004
Hepatitis C	442 (1.1)	143 (1.2)	0.118
Fatty liver	2539 (6.1)	2309 (20.0)	<0.0001
Asthma	2600 (6.3)	772 (6.7)	0.109
High blood pressure	5680 (14.1)	3457 (29.9)	<0.0001
Diabetes	1760 (4.2)	970 (8.4)	<0.0001
Dyslipidemia	5919 (14.3)	2443 (21.1)	<0.0001
Medication			
High blood pressure	4681 (11.3)	2974 (25.7)	<0.0001
Diabetes	1071 (2.6)	713 (6.2)	<0.0001
High blood cholesterol	3115 (7.5)	1458 (12.6)	<0.0001
Sleeping pills	1696 (4.1)	431 (3.7)	0.081
Antipyretic	1282 (3.1)	395 (3.4)	0.076
Laxative	1924 (4.6)	377 (3.3)	<0.0001

MET, metabolic equivalent.

[a] Median (25%, 75%) or number of subjects (%).

[b] Wilcoxon's rank sum test or Chi-square test.

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Figure legends

Figure 1. Flowcharts of the selection of study participants.

(A) Study participants for analyses of examination-based metabolic phenotypes.

(B) Study participants for analyses of questionnaire-based metabolic phenotypes.

Figure 2. Relationships between questionnaire-based metabolic phenotypes and site-specific cancers.

HRs and 95 % CIs are shown as points and error bars.

Cox proportional hazard models to estimate association between metabolic phenotypes and site-specific cancers after adjusting for age, sex, research sites, educational background, pack-years, drinking habit, physical activity level, and miso soup, fruits and vegetables consumption.

HR, hazard ratio; CI, confidence interval; MHNW, Metabolically healthy normal weight; MUNW, Metabolically unhealthy normal weight; MHO, Metabolically healthy obesity; MUHO, Metabolically unhealthy obesity.

Figure 3. Sex-stratified analyses of relationships between questionnaire-based metabolic phenotypes and site-specific cancers.

HRs and 95 % CIs are shown as points and error bars.

Sex-stratified Cox proportional hazard models to estimate association between metabolic phenotypes and site-specific cancers after adjusting for age, research sites, educational background, pack-years, drinking habit, physical activity level, and miso soup, fruits and vegetables consumption.
HR, hazard ratio; CI, confidence interval; MHNW, Metabolically healthy normal weight; MUNW, Metabolically unhealthy normal weight; MHO, Metabolically healthy obesity; MUHO, Metabolically unhealthy obesity.

Figure 4. Relationships between questionnaire-based metabolic phenotypes and site-specific cancers handling subjects who had cancer within one year or two years as censored.

HRs and 95 % CIs are shown as points and error bars.
Cox proportional hazard models to estimate association between metabolic phenotypes and site-specific cancers after adjusting for age, sex, research sites, educational background, pack-years, drinking habit, physical activity level, and miso soup, fruits and vegetables consumption.
HR, hazard ratio; CI, confidence interval; MHNW, Metabolically healthy normal weight; MUNW, Metabolically unhealthy normal weight; MHO, Metabolically healthy obesity; MUHO, Metabolically unhealthy obesity.

Figure 5. Sex-stratified analyses of relationships between questionnaire-based metabolic phenotypes and site-specific cancers handling subjects who had cancer within one year or two years as censored.

HRs and 95 % CIs are shown as points and error bars.

Sex-stratified Cox proportional hazard models to estimate association between metabolic phenotypes and site-specific cancers after adjusting for age, research sites, educational background, pack-years, drinking habit, physical activity level, and miso soup, fruits and vegetables consumption.

HR, hazard ratio; CI, confidence interval; MHNW, Metabolically healthy normal weight; MUNW, Metabolically unhealthy normal weight; MHO, Metabolically healthy obesity; MUHO, Metabolically unhealthy obesity.

Figure 1

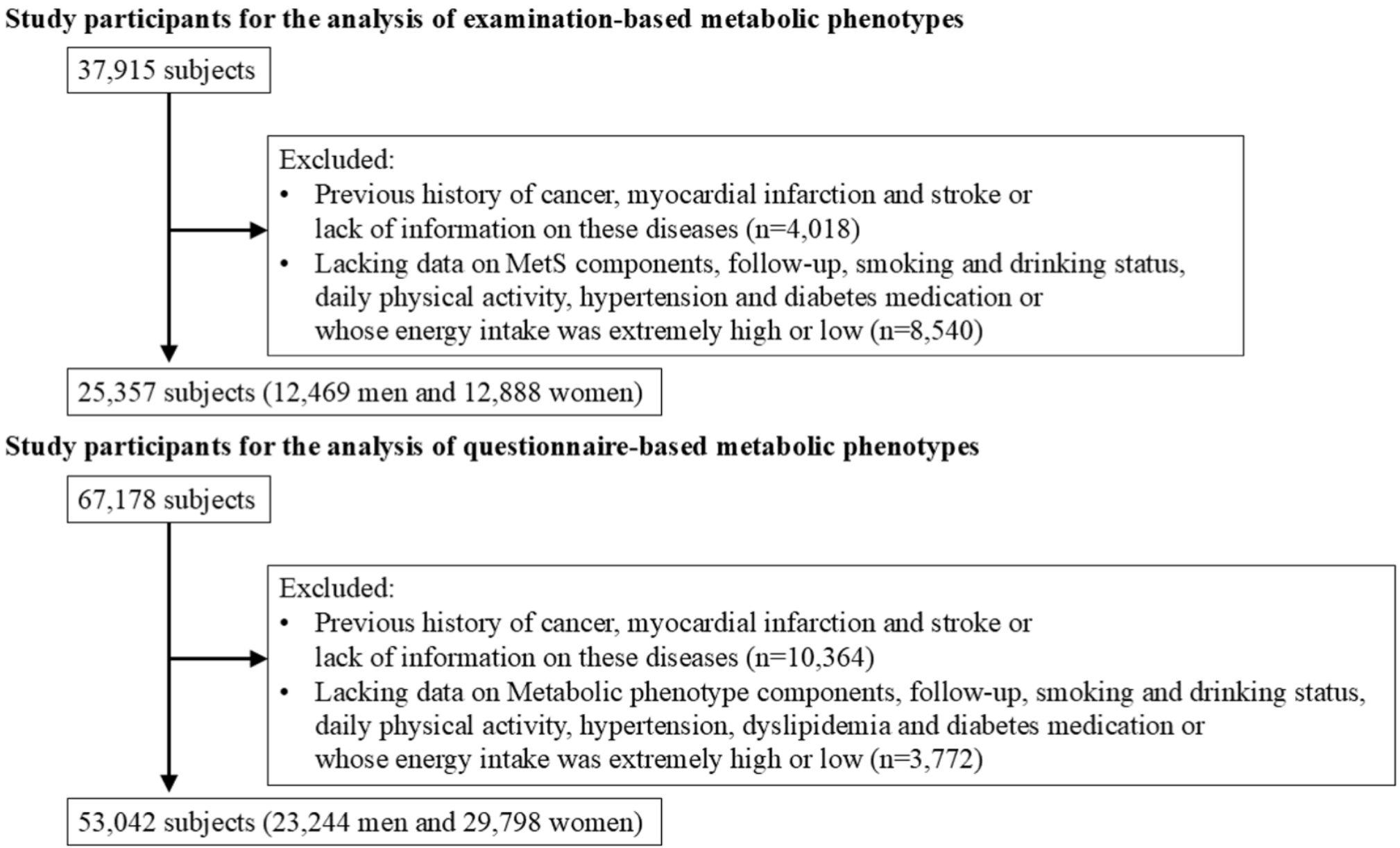

Figure 2

Subgroup	Participants	Person-years	No. of cases	HR(95% CI)
Total cancer				
MHNW	30099	246204.1	2183	1.00 (1.00 to 1.00)
MHO	6377	53399.4	497	1.06 (0.96 to 1.17)
MUNW	11384	91532.3	1211	1.05 (0.97 to 1.12)
MUHO	5182	42344	576	1.15 (1.04 to 1.26)
Stomach				
MHNW	30099	246204.1	253	1.00 (1.00 to 1.00)
MHO	6377	53399.4	47	0.76 (0.56 to 1.04)
MUNW	11384	91532.3	178	1.13 (0.92 to 1.37)
MUHO	5182	42344	67	0.93 (0.71 to 1.22)
Colon and rectum				
MHNW	30099	246204.1	258	1.00 (1.00 to 1.00)
MHO	6377	53399.4	79	1.41 (1.09 to 1.82)
MUNW	11384	91532.3	159	1.09 (0.89 to 1.34)
MUHO	5182	42344	91	1.45 (1.13 to 1.85)
Liver				
MHNW	30099	246204.1	38	1.00 (1.00 to 1.00)
MHO	6377	53399.4	23	2.39 (1.41 to 4.03)
MUNW	11384	91532.3	36	1.54 (0.97 to 2.46)
MUHO	5182	42344	27	2.36 (1.43 to 3.92)
Pancreas				
MHNW	30099	246204.1	64	1.00 (1.00 to 1.00)
MHO	6377	53399.4	14	1.06 (0.59 to 1.89)
MUNW	11384	91532.3	63	1.60 (1.12 to 2.29)
MUHO	5182	42344	24	1.51 (0.94 to 2.44)
Lung and Bronchus				
MHNW	30099	246204.1	234	1.00 (1.00 to 1.00)
MHO	6377	53399.4	59	1.09 (0.82 to 1.46)
MUNW	11384	91532.3	137	0.94 (0.75 to 1.16)
MUHO	5182	42344	56	0.86 (0.64 to 1.16)

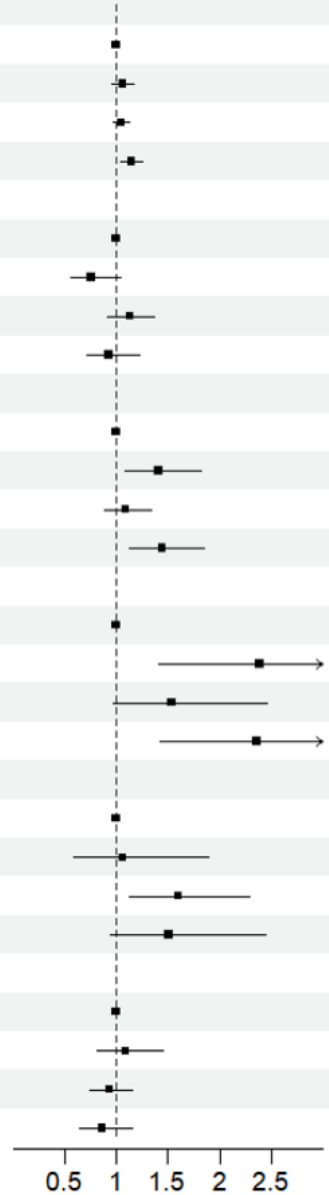

Figure 3

Subgroup	Participants	Person-years	No. of cases	HR(95% CI)
Male				
Total cancer				
MHNW	11083	89738.8	1018	1.00 (1.00 to 1.00)
MHO	3597	29773.1	276	0.95 (0.83 to 1.09)
MUNW	5434	42650.9	739	1.05 (0.95 to 1.15)
MUHO	3130	25117.7	390	1.11 (0.99 to 1.25)
Prostate				
MHNW	11083	89738.8	214	1.00 (1.00 to 1.00)
MHO	3597	29773.1	41	0.75 (0.54 to 1.05)
MUNW	5434	42650.9	145	0.91 (0.74 to 1.13)
MUHO	3130	25117.7	88	1.22 (0.95 to 1.57)
Female				
Total cancer				
MHNW	19016	156465.3	1165	1.00 (1.00 to 1.00)
MHO	2780	23626.2	221	1.37 (1.19 to 1.59)
MUNW	5950	48881.4	472	1.10 (0.98 to 1.23)
MUHO	2052	17226.3	186	1.32 (1.12 to 1.55)
Breast				
MHNW	19016	156465.3	370	1.00 (1.00 to 1.00)
MHO	2780	23626.2	71	1.45 (1.12 to 1.88)
MUNW	5950	48881.4	121	1.10 (0.89 to 1.38)
MUHO	2052	17226.3	59	1.63 (1.22 to 2.17)
Corpus uteri				
MHNW	19016	156465.3	65	1.00 (1.00 to 1.00)
MHO	2780	23626.2	11	1.36 (0.71 to 2.59)
MUNW	5950	48881.4	17	0.75 (0.43 to 1.31)
MUHO	2052	17226.3	13	1.95 (1.04 to 3.63)

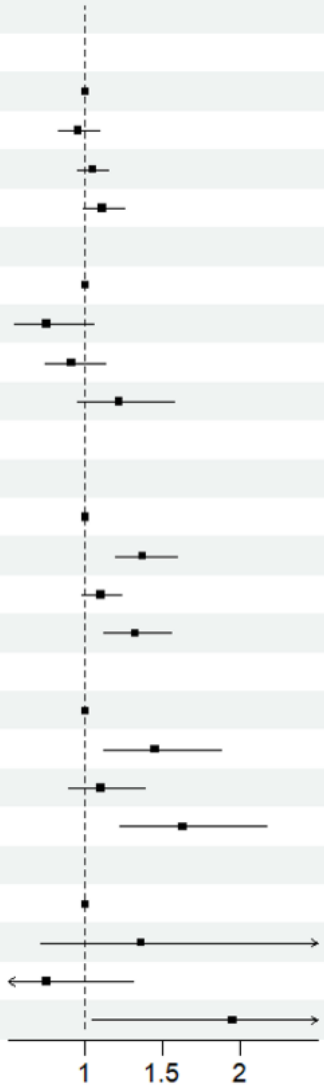

Figure 4

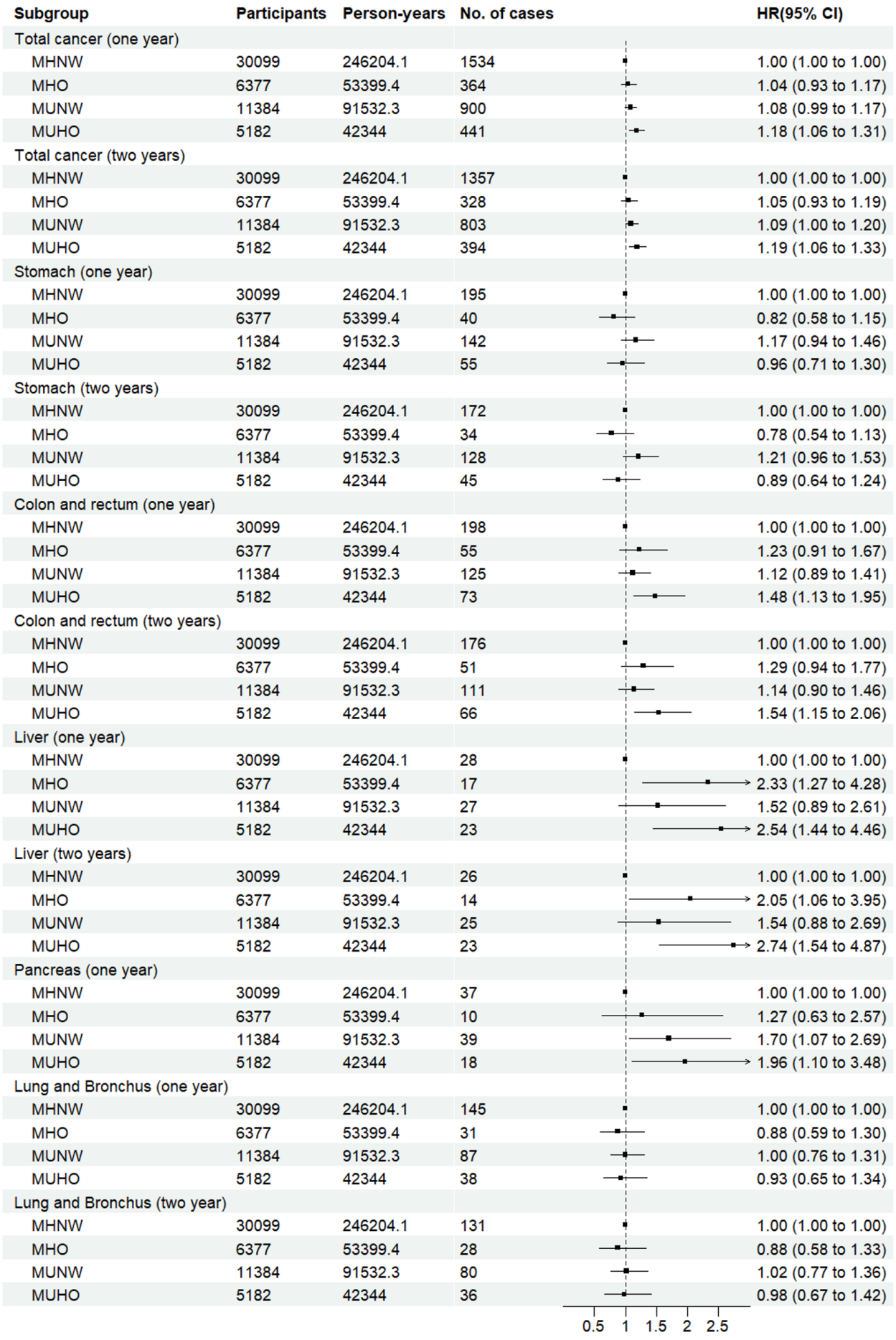

Figure 5