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ORIGINAL ARTICLE

Metabolic syndrome is linked to most cancers incidence

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Abstract

Since many people die of either cancers or cardiovascular diseases worldwide, it is important to find the clinical pitfall that provokes cardiovascular diseases and cancer overall. Since metabolic syndrome (MetS) is largely linked to cardiovascular diseases, we have come to consider that MetS, even in its early state, may prime the occurrence of cancers overall. Indeed, the importance of MetS in causing pancreatic cancer has been proved using our large medical database. We analyzed Japanese healthcare and clinical data in 2005, who were followed up until 2020 and we examined the incidence of major cancers. At the enrollment, we examined the presence or absence of MetS judged by either Japanese criteria or NCEP/ATPIII. Of 2.7 million subjects without missing data, 102,930; 200,231; 237,420; 63,435; 76,172; and 2,422 subjects suffered lung, stomach, colon, liver and prostate cancer, respectively, and myelogenous leukemia during follow-up. MetS, defined by Japanese criteria, increased ($p < 0.005$ each) the incidence of cancer with a hazard ratio (HR) of 1.03–1.47 for lung, stomach, colon, liver, prostate cancers, and myelogenous leukemia. According to Japanese criteria, cancer incidence in the pre-stage MetS group was comparable to the MetS group. The results were almost identical when we defined MetS using NCEP ATP III. Taken together, we conclude that MetS is linked to majority of cancers.

Keywords Most cancers · Metabolic syndrome · Big data · Early stage of metabolic syndrome

Introduction

Cancers and cardiovascular diseases place a significant burden on patients and national economies worldwide [1, 2]. The major cancers with high incidence and mortality are lung, stomach, colon, liver, prostate and pancreas cancers. Early detection, prompt diagnosis, and innovative medical and surgical treatments have gradually conquered these cancers. However, the mortality due to cancers has been high in developed countries. Cancers are reportedly primed by family history [3], genetic background [4], smoking [5–7], and type II diabetes mellitus (T2D) [8]. We and several investigators have reported that metabolic syndrome (MetS) increases the risk of pancreatic cancer [9, 10] as well as cardiovascular diseases [11, 12]. The molecular mechanisms of MetS, such as (1) insulin, (2) adipokines, (3) estrogen, and (4) reactive oxygen species (ROS) [13], may affect the incidence of cardiovascular diseases but also pancreatic cancer or even cancers overall. Indeed, this fact has been shown in a meta-analysis using small sampling data [14]. This research showed that MetS increases the probability of cancers overall; however, no large single cohort data of

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several million individuals from the general population has determined whether MetS or even early phases of MetS is linked to the occurrence of most cancers.

Since we formed a cohort of several million individuals from the general population and followed them for more than 10 years, we decided to investigate the relationship between MetS or the early phase of MetS and the incidence of major cancers and myelogenous leukemia. We investigated whether the incidence of lung, stomach, colon, liver and prostate cancers changed in subjects with MetS compared to those without MetS over 10 years in a Japanese cohort. We also examined the correlation between MetS and myelogenous leukemia as a reference, as we did not anticipate such an association.

Materials and methods

Study design

This retrospective observational study adhered to the principles of the Declaration of Helsinki and the Japanese Ethical Guidelines for Clinical Research.

Participants

Our analyses were based on data from healthcare insurance claims provided by JMDC, Inc. in Tokyo, Japan. The database contained standardized eligibility and claims data provided by health insurance societies for about 4.6 million insured individuals between 2005 and 2020. It included the data of general corporation employees, their family members, and all medical treatments received by insured individuals at treatment facilities. It also included a comprehensive record of all treatments administered to a patient. For this study, we disposed of the decoding indexes kept in JMDC, Inc. and analyzed the personal data using unlinkable anonymization.

Ethics

The external Ethics Committee of the Kinshukai Medical Group approved this retrospective observational study (the approval number: 2024-3). The Study Committee decided that based on the Japanese Clinical Research Guidelines, it was not essential to obtain informed consent from patients selected for inclusion in this study because the study was a retrospective observational study. Instead, we made a public announcement in accordance with the Ethics Committee's request and the Japanese Clinical Research Guidelines.

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Definition of mets

The Japanese MetS criteria require abdominal central obesity with an abdominal circumference at the umbilical level of men: ≥ 85 cm, women: ≥ 90 cm with ≥ 2 factors, (1) elevated triglycerides and/or reduced high-density lipoprotein, (2) elevated blood pressure, and (3) elevated fasting glucose levels [15]. The presence of abdominal central obesity combined with one factor is pre-metabolic syndrome (preMetS). We also defined the non-MetS group as subjects not classified as having either MetS or preMetS.

MetS was also defined according to the modified National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) criteria [16].

The study protocol

We initially excluded 42,885 subjects (men: 19,439, women: 23,446) and 1,825,660 subjects (men: 1,146,691, women: 678,969) from our cohort of 4,600,443 who had no observation period and missing data, respectively. After identifying 2,731,898 subjects (men: 1,587,107, women: 1,144,791) and excluding those who had experienced each cancer, we tested the occurrence of lung, stomach, colon, liver, prostate, breast, or cervical cancer and myelogenous leukemia in 2,703,825; 2,668,954; 2,667,654; 2,712,393; 1,561,789; 1,112,016; 1,122,100; and 2,730.532 subjects, respectively, according to the International Classification of Diseases 10th Revision (ICD-10, coded as I10–I15). We found 102,930, 200,231, 237,420, 63,435, 76,172, and 2,422 subjects suffered lung, stomach, colon, liver, and prostate cancer and myelogenous leukemia, respectively, during follow-up. After acquiring each data set, we used Kaplan–Meier analysis to compare the occurrence of each cancer or myelogenous leukemia in the cohorts with and without MetS or preMetS. We also calculated hazard ratios (HRs) using Cox proportional hazard models between three or two groups.

Statistics

Time-to-event data were evaluated using Kaplan–Meier estimates and compared using the log-rank test for the primary analyses. The entry time, i.e., time = 0 for the Kaplan–Meier plots, varied. Censoring occurred when the patient died or was lost to follow-up. We employed complete case analysis (Listwise Deletion) for the missing data, and a sensitivity analysis was not performed.

Cox proportional hazard models were used to estimate HRs with MetS or preMetS group assignment or combinations of the components with the MetS, preMetS, and

non-MetS groups to calculate the *p*-values regarding the hypothesis testing between the groups. The models were adjusted for smoking, age, and sex since the incidence of cancers is known to be affected by these factors.

After checking the interactions between the variables age, sex, and smoking through likelihood ratio tests on regression coefficients of interaction terms, the interaction between sex and age was found significant. Therefore, we used the model that included the sex-age interaction term.

All statistical analyses were performed using Python v3.10 and packages such as lifelines v0.27.8 (https://github.com/nkimoto/PKMetS).

Results

The patients' clinical characteristics

The clinical characteristics of patients with and without preMetS or MetS are listed in Table 1.

In the left to right columns, all data, the Non-MetS, PreMetS, and MetS groups judged by the Japanese criteria of MetS, and Non-MetS and MetS groups judged by NCEP/ATPI criteria of MetS. There are differences of the clinical parameters between each group because of absence and presence of MetS, however, there are not differences between the Non-MetS and MetS groups judged by the Japanese criterial of MetS and NCEP/ATPI criteria of MetS.

Kaplan–meier analyses for the incidence of cancers among the subjects with and without mets judged by the japanese criterial of mets

Figures 1, 2 and 3 depict the results of the Kaplan–Meier analysis of the subjects with and without MetS for the incidence of lung (A-1), stomach (B-1), colon (C-1), liver (D-1) and prostate (E-1) cancer: Both preMetS and MetS increased the incidence of lung (hazard ratio [HR], 1.05; 95% confidence interval [CI], 1.03–1.07; $p < 0.005$: HR, 1.04; 95% CI 1.02–1.06; $p < 0.005$), stomach (HR, 1.05; 95% CI 1.04–1.07; $p < 0.005$: HR, 1.03; 95% CI 1.02–1.04; $p < 0.005$), colon (HR, 1.07; 95% CI 1.06–1.09; $p < 0.005$: HR, 1.07; 95% CI 1.06–1.08; $p < 0.005$), liver (HR, 1.26; 95% CI 1.22–1.29; $p < 0.005$: HR, 1.42; 95% CI 1.39–1.45; $p < 0.005$), and prostate cancer HR, 1.14; 95% CI 1.12–1.16; $p < 0.005$: HR, 1.14; 95% CI 1.12–1.16; $p < 0.005$). Both

Table 1 Characteristics of 2,731,898 subjects with complete data for identifying MetS and important risk factors

The parameters for the diagnosis of MetS and important risk factors	All data (N = 2,731,898)	Japanese criteria of MetS			NCEP/ATPI criteria of MetS	
		Non-MetS (N = 2,061,441)	PreMetS (N = 285,678)	MetS (N = 384,779)	Non-MetS (N = 2,396,505)	MetS (N = 335,393)
Women, n (%)	1,144,791 (41·9%)	1,018,216 (50·6%)	47,332 (16·6%)	54,234 (14·1%)	1,049,142 (43·8%)	95,649 (28·5%)
Age, median age	53 (46–61)	58 (50–65)	55 (48–62)	52 (45–60)	52 (45–60)	58 (51–65)
Smoker, n (%)	679,796 (24·9%)	461,614 (22·4%)	87,586 (30·7%)	130,596 (33·9%)	574,185 (24·0%)	105,611 (31·5%)
BMI, median BMI	22.5 (20·3–25·0)	21·4 (19·7–23·2)	26·0 (24·5–28·0)	27·0 (25·1–29·5)	22·0 (20·0–24·2)	27·0 (24·8–29·5)
Abd circumference, median cm	80·5 (74·0–87·2)	77·5 (72·0–82·0)	91·0 (87·6–95·4)	93·0 (89·0–98·5)	79·0 (73·0–85·0)	93·0 (88·0–98·5)
sBP, median mmHg	118 (108–129)	115 (105–125)	122 (114–128)	133 (125–142)	116 (106–126)	134 (126–143)
dBP, median mmHg	73 (65–82)	71 (64–79)	76 (70–82)	85 (78–91)	72 (64–80)	85 (78–91)
HbA1c, median %	5·4 (5·2–5·7)	5·4 (5·2–5·6)	5·5 (5·3–5·8)	5·7 (5·5–6·1)	5·4 (5·2–5·6)	5·8 (5·5–6·2)
Fasting glucose, medain mg/dl	92 (86–99)	90 (85–97)	95 (89–102)	101 (93–113)	91 (85–97)	105 (99–117)
HDL-cholesterol, median mg/dl	62 (51–74)	65 (55–77)	54 (47–63)	49 (42–58)	63 (53–75)	48 (41–57)
LDL-cholesterol, median mg/dl	119 (99–140)	115 (96–136)	128 (108–148)	132 (111–153)	117 (98–138)	131 (110–153)
TG, median mg/dl	83 (58–124)	73 (53–103)	104 (78–135)	162 (111–218)	77 (55–110)	173 (125–233)

Values are median (interquartile ranges), and only values of "women" and "smoker" are number (percent)

Please note that since the entry time in each subject varied, we could not show the exact year for the entry. Because our database is consisted with the annual data from 2005 to 2020. If the entry criteria are matched to the characteristics of the subjects, we enrolled such subjects irrespective of the entry year

BMI body mass index, *Abd* abdominal, *sBP* systolic blood pressure, *dBP* diastolic blood pressure, *Hb* hemoglobin, *HbA1c* hemoglobin A1c, *HDL* high density lipoprotein, *LDL* low density lipoprotein, *TG* triglyceride

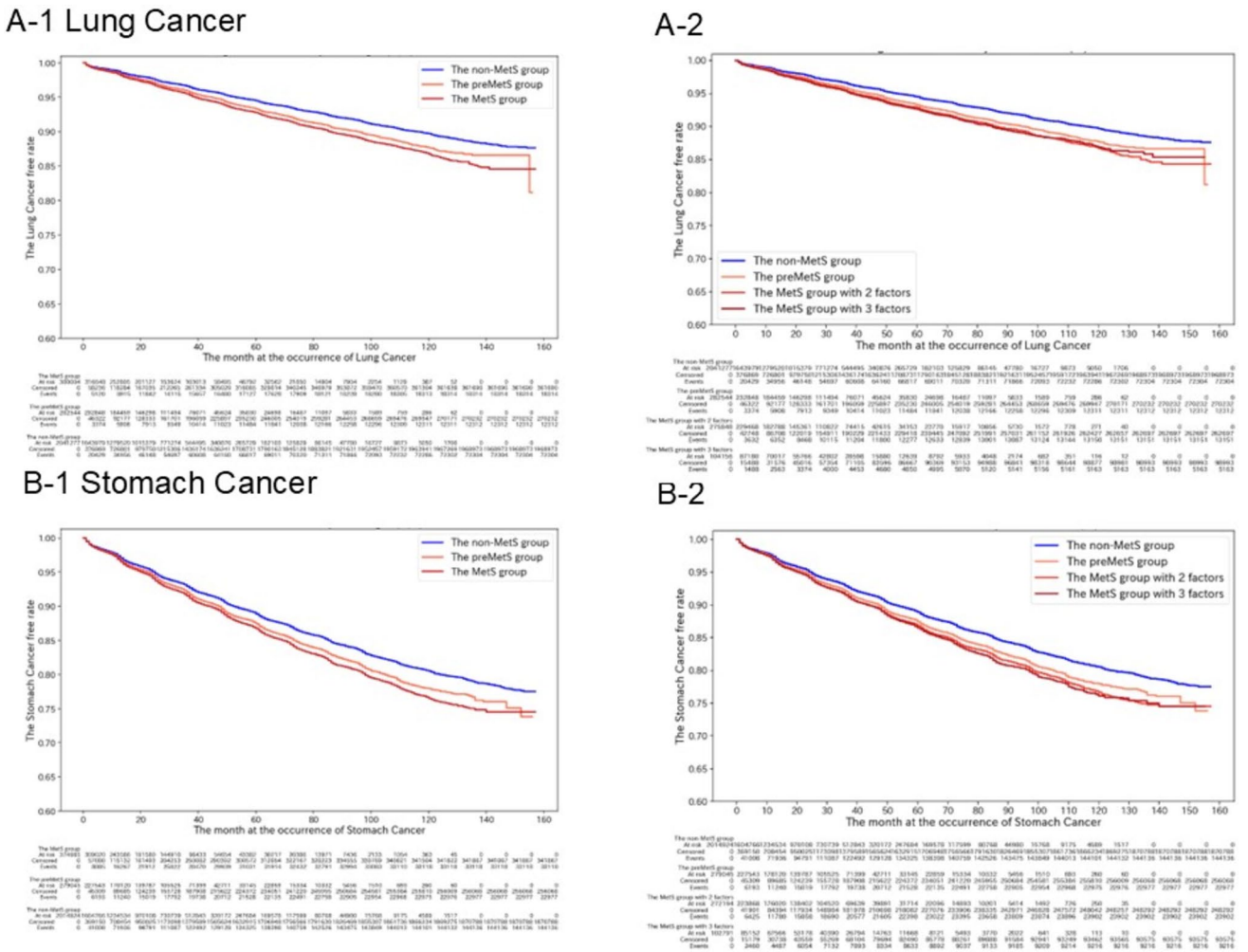

Fig. 1 Kaplan–Meier curves of lung (**A-1**) or stomach (**B-1**) cancer incidence in preMetS or MetS, and Kaplan–Meier curves of lung (**A-2**) or stomach (**B-2**) cancer incidence in the MetS groups with 2 and 3 factors based on Japanese MetS criteria. In **A-2,** HRs of MetS with 2 and 3 factors are 1.04 (95% CI 1.02–1.06; $p < 0.005$), and 1.05 (95% CI 1.02–1.08; $p < 0.005$), respectively. In **B-2**, HRs of MetS with 2 and 3 factors are 1.03 (95% CI 1.01–1.04; $p < 0.005$), and 1.03 (95% CI 1.01–1.05; $p < 0.01$), respectively

preMetS and MetS increased the incidence of myelogenous leukemia (Fig. 4-F-1 HR, 1.16; 95% CI 1.02–1.32; $p = 0.02$: HR, 1.47; 95% CI 1.32–1.63; $p < 0.005$). When MetS factors increased, the probability of developing lung, stomach, colon, liver, and prostatic cancer and myelogenous leukemia increased (A-2 to F-2 in Figs. 1, 2, 3).

Kaplan–meier analyses for the incidence of cancers among the subjects with and without mets judged by NCEP/ATP III criteria of mets

The results of the Kaplan–Meier analysis of subjects with or without MetS defined by NCEP/ATP III criteria of MetS for the incidence of cancers and myelogenous leukemia (Figs. 4, 5, 6) are almost identical to the results shown in Figs. 1, 2 and 3.

In A-1 and B-1in Fig. 4, MetS increased the incidence of lung or stomach cancer (HR, 1.04; 95% confidence interval [CI], 1.02–1.04; $p < 0.005$: HR, 1.02; 95% CI 1.00–1.03; $p < 0.05$). In A-2, when factors of MetS increase from 1 to 5, HR for lung cancer increased to 0.98 (95% CI 0.96–0.99; $p < 0.005$), 0.99 (95% CI 0.97–1.01, $p = 0.20$), 1.01 (95% CI 0.99–1.03, $p = 0.28$), 1.06 (95% CI 1.03–1.10, $p < 0.005$), and 1.08 (95% CI 1.00–1.16, $p < 0.05$), respectively. In B-2, when factors of MetS increase from 1 to 5, HR for stomach cancer increased to1.01 (95% CI 1.00–1.03; $p < 0.05$), 1.02 (95% CI 1.00–1.03; $p < 0.05$), 1.02 (95% CI 1.00–1.03; $p < 0.05$), 1.06 (95% CI 1.03–1.08, $p < 0.005$), and 1.02 (95% CI 0.96–1.08, $p = 0.56$), respectively.

In C-1 and D-1 in Fig. 5, MetS increased the incidence of colon or liver cancer (HR, 1.07; 95% CI 1.05–1.08; $p < 0.005$: HR, 1.44; 95% CI 1.42–1.47; $p < 0.005$). In C-2, when factors of MetS increase from 1–5, HR for

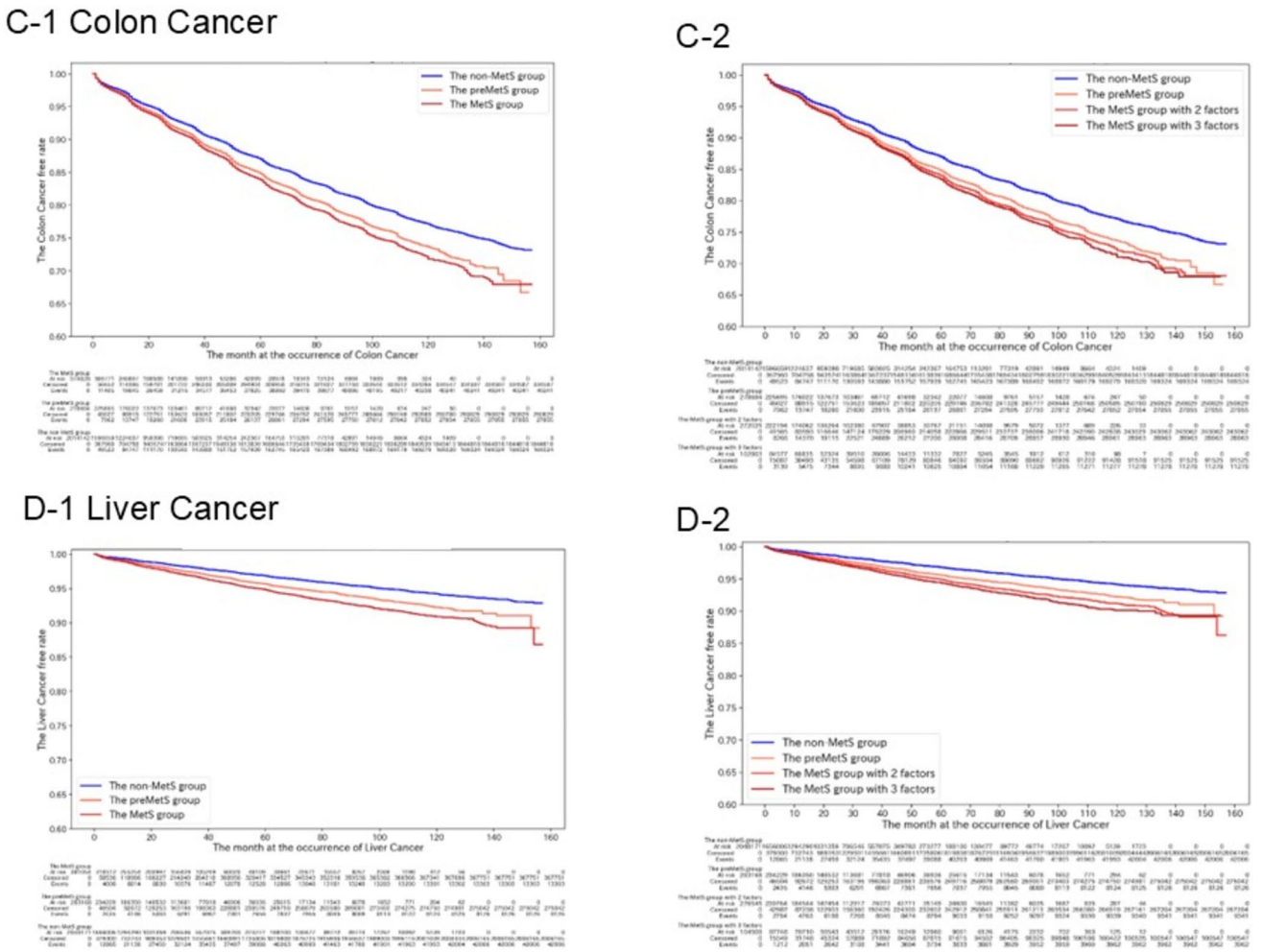

Fig. 2 Kaplan–Meier curves of colon (**C-1**) or liver (**D-1**) cancer incidence in preMetS or MetS, and Kaplan–Meier curves of colon (**C-2**) or liver (**D-2**) cancer incidence in the MetS groups with 2 and 3 factors based on Japanese MetS criteria. In **C-2**, HRs of MetS with 2 and 3 factors are 1.06 (95% CI 1.05–1.07; $p < 0.005$), and 1.07 (95% CI 1.05–1.09; $p < 0.005$), respectively. In **D-2**, HRs of MetS with 2 and 3 factors are 1.38 (95% CI 1.35–1.42; $p < 0.005$), and 1.53 (95% CI 1.48–1.58; $p < 0.005$), respectively

colon cancer increased to 1.01 (95% CI 1.00–1.02; $p < 0.05$), 1.03 (95% CI 1.02–1.04, $p < 0.005$), 1.07 (95% CI 1.06–1.09, $p < 0.005$), 1.12 (95% CI 1.09–1.14, $p < 0.005$), and 1.09 (95% CI 1.03–1.15, $p < 0.005$), respectively.

In E-1 and F-1 in Fig. 6, MetS increased the incidence of prostate cancer or myelogenous leukemia (HR, 1.10; 95% CI 1.08–1.12; $p < 0.005$: HR, 1.57; 95% CI 1.41–1.74; $p < 0.005$). In E-2, when factors of MetS increase from 1 to 5, HR for prostate cancer increased to 1.10 (95% CI 1.08–1.12; $p < 0.005$), 1.11 (95% CI 1.09–1.14, $p < 0.005$), 1.17 (95% CI 1.15–1.20, $p < 0.005$), 1.18 (95% CI 1.14–1.22, $p < 0.005$), and 1.22 (95% CI 1.12–1.32, $p < 0.005$), respectively. In F-2, when factors of MetS increase from 1 to 5, HR for myelogenous leukemia increased to1.18 (95% CI 1.06–1.31; $p < 0.005$), 1.40 (95% CI 1.25–1.57; $p < 0.005$), 1.65 (95% CI 1.44–1.89; $p < 0.005$), 2.25 (95% CI 1.88–2.71, $p < 0.005$), and 2.46 (95% CI 1.67–3.61, $p < 0.005$), respectively.

Discussion

MetS primes or causes most cancers and myelogenous leukemia, even at early- or pre-stage MetS.

First of all, we need to consider the rationale and advantages of this investigation. One method to understand the comprehensive relationship between MetS and most cancers is to investigate the meta-analysis of many publications about MetS and cancers using clinical studies with small or moderate sample sizes [14]. Of course, meta-analysis provides a powerful conclusion based on the hypothesis; however, the definition of the obtained data varies in the literature. Thus, there may be a risk of the conclusion being

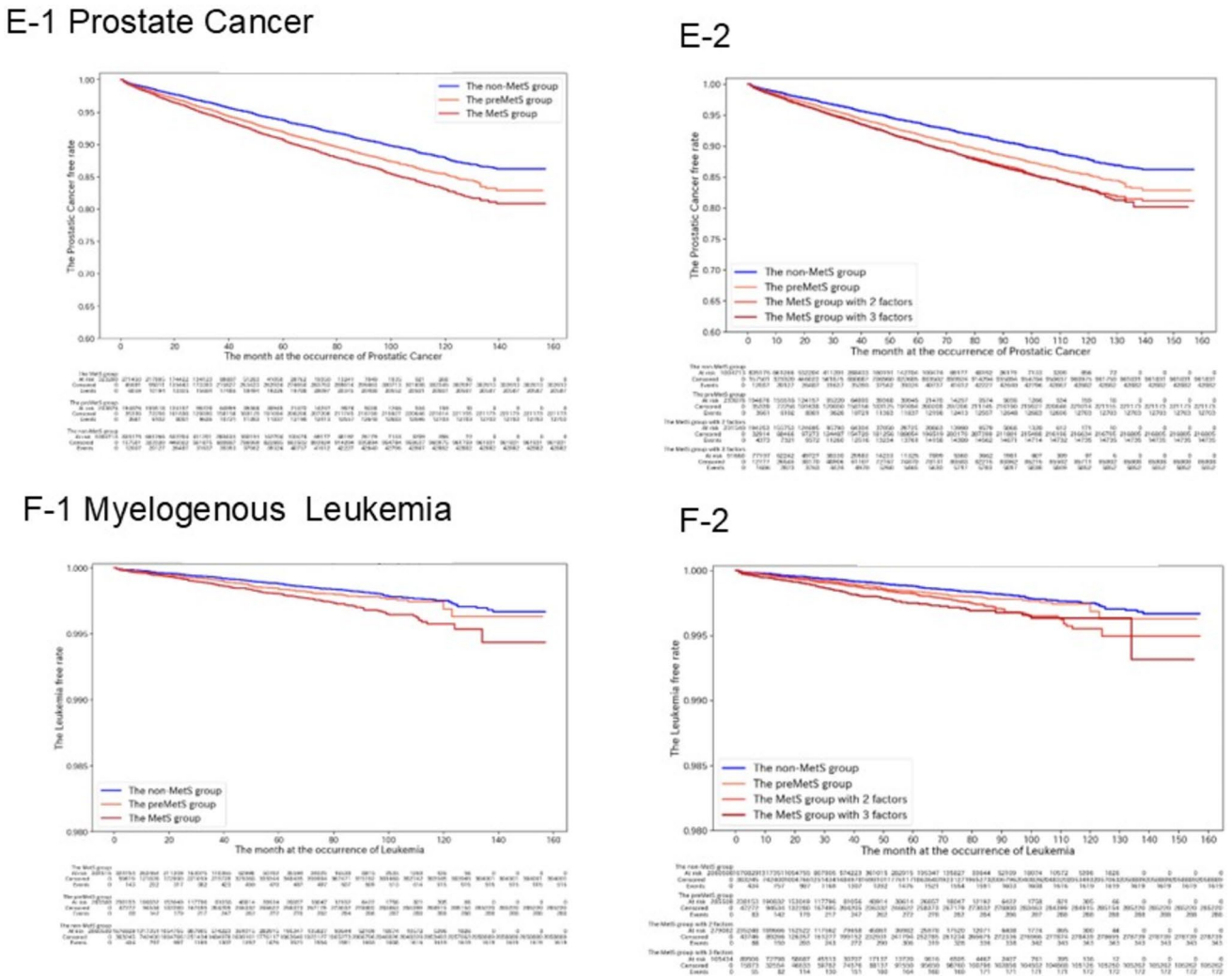

Fig. 3 Kaplan–Meier curves of prostate cancer (**E-1**) or myelogenous leukemia (**F-1**) incidence with preMetS or MetS groups, and Kaplan–Meier curves of prostate cancer (**E-2**) or myelogenous leukemia (**F-2**) incidence in the MetS groups with 2 and 3 factors based on Japanese MetS criteria. Note that the Y-axis scale for myelogenous leukemia is enlarged compared to the other figures. In **E-2**, HRs of MetS with 2 and 3 factors are 1.14 (95% CI 1.12–1.16; $p < 0.005$), and 1.12 (95% CI 1.09–1.15; $p < 0.005$), respectively. In **F-2**, HRs of MetS with 2 and 3 factors are 1.34 (95% CI 1.19–1.51; $p < 0.005$), and 1.72 (95% CI 1.46–2.02; $p < 0.005$), respectively

misconstrued or the precise conclusion being obscured within the margin of error [17]. Furthermore, the dataset for each investigational cohort is constrained by a limited and different number of parameters and subjects, with observed cancers within each cohort restricted to single or a few types of cancers. Another method is to employ single uniform big data that has collected much clinical data to define MetS and the evidence of the occurrence of cancers. This study adhered to a scenario that had not been executed previously; however, several difficulties were encountered. First, to define MetS using different criteria, such as NCEP ATP III and the Japanese criteria, we need to obtain the raw clinical data of each subject. We analyzed the data using these two criteria. The merit in using the Japanese criteria is that (1) we used the Japanese population, and (2) the Japanese criteria provide the preMetS, an early phase before the onset of MetS.

On the other hand, to extend our results to the international understanding of the link between MetS and cancers, we must employ the Western guideline of MetS, i.e., NCEP ATP III. Second, collecting complete clinical data and the definite occurrence of cancers is necessary, which seems impossible. We were fortunate to obtain the accurate diagnosis of cancers for Japanese populations since Japanese clinicians have to report the occurrence of cancers diagnosed in hospitals to the government by law in Japan [18]. We were ready to employ the second method to investigate the relationship between MetS and cancers overall for the first time.

Secondly, we need to consider the role of MetS as a potential risk for most cancers. We found that liver and

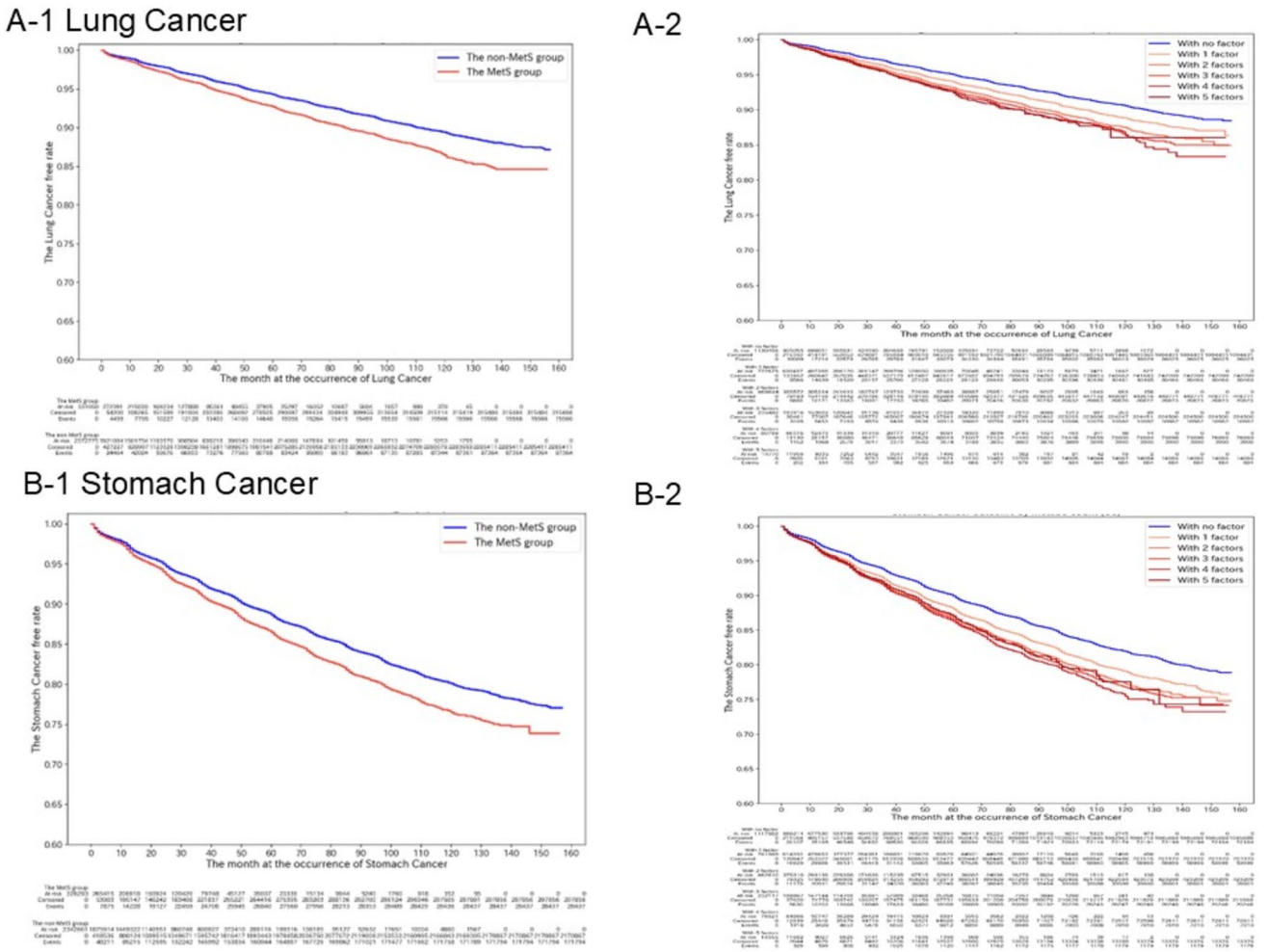

Fig. 4 Kaplan–Meier curves for the incidence of lung (**A-1**) or stomach (**B-1**) cancer with MetS, and Kaplan–Meier curves of the incidence of lung (**A-2**) or stomach (**B-2**) cancer among the six groups with 0–5 components of MetS based on the modified criteria of NCEP/ATPIII

pancreatic cancer [9, 19] are most affected by MetS, as has been reported by other researchers [20]. This evidence is understandable because MetS causes nonalcoholic steatohepatitis (NASH) and nonalcoholic fatty liver disease (NAFLD) via the common cause of insulin resistance [21], and NASH or NAFLD may prime liver cancer [22]. MetS also burdens pancreatic cells and may prime pancreatic cancer [19, 23]. Importantly, this study revealed that early-phase or even pre-phase MetS causes liver cancer like MetS. Furthermore, the MetS factors, such as hypertension unrelated to obesity, contribute to liver carcinogenesis [24, 25].

We unexpectedly discovered a strong correlation between MetS and hematologic malignancies such as myelogenous leukemia. Previous data show that obesity is linked to blood cancer risk [26]; however, there is no clear data that myelogenous leukemia is involved in the pathophysiology of MetS. Thinking about how MetS causes myelogenous leukemia is to consider molecular aspects of MetS, which culminate in (1) insulin, (2) adipokines, (3) ROS, and (4) estrogen [13]. Insulin is a major anabolic hormone that can stimulate cell proliferation. The effects of insulin on cancer cell proliferation in vivo may be mediated by an indirect mechanism, such as insulin-like growth factor (IGF)-1 stimulation. The activation of the IGF-1 receptor stimulates the p21ras/MAPK pathway for cell proliferation and the PI3K/AKT cell survival pathway [27]. IGF-1 also stimulates angiogenesis by increasing vascular endothelial growth factor (VEGF) production [28]. These lines of evidence may be linked to the incidence of myelogenous leukemia.

Lastly, we need to discuss about the study limitations and features**.** This study revealed that the incidence of stomach, lung, prostate, or colon cancer modestly increased in MetS subjects. However, HRs in these cancers were relatively small compared to liver cancer or myelogenous leukemia. Although there has been no clear probability link between the pathophysiological conditions induced by MetS and the carcinogenesis of these neoplasia, the changes in neurohumoral factors attributable to MetS may prime the incidence

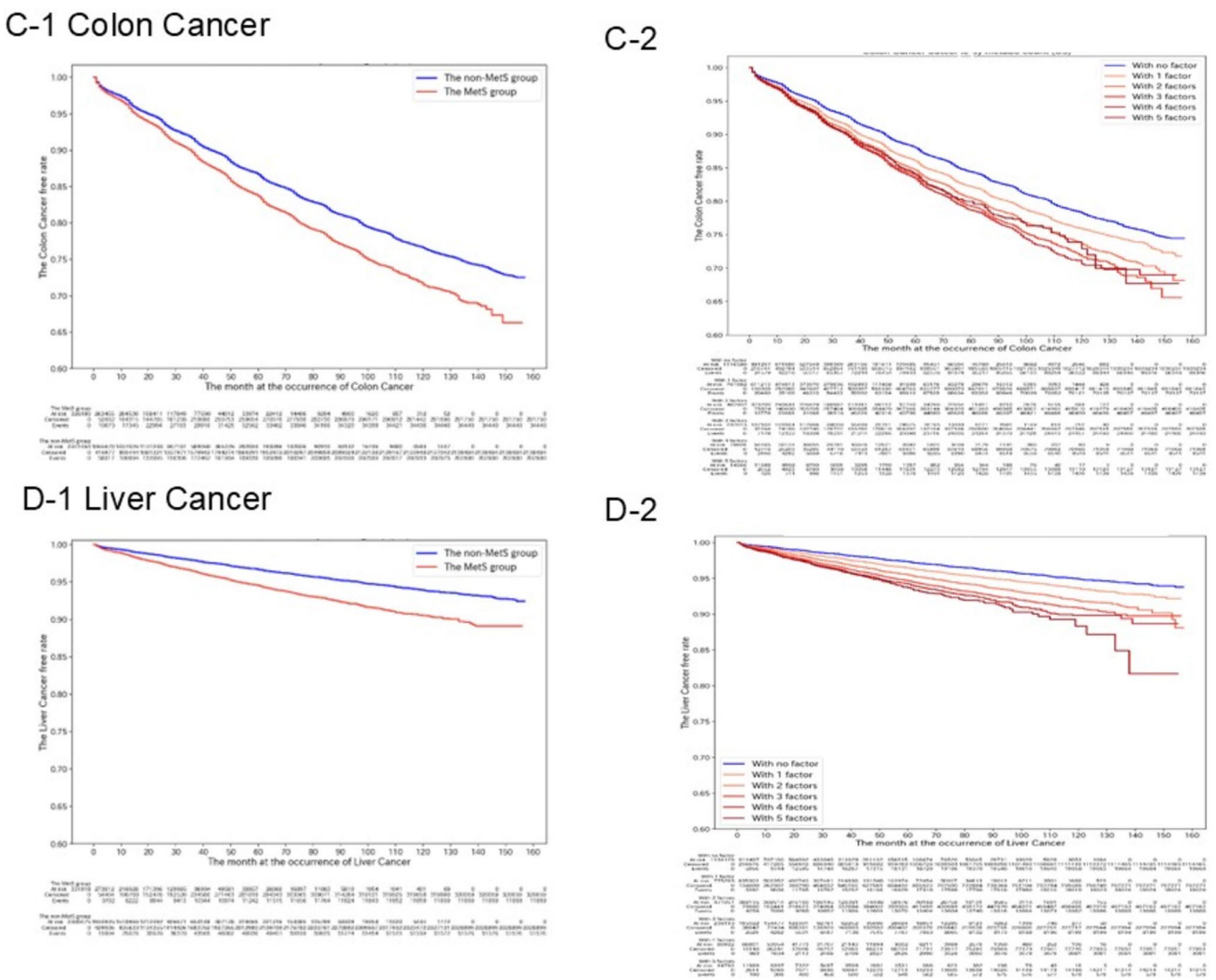

Fig. 5 Kaplan–Meier curves for the incidence of colon (**C-1**) or liver (**D-1**) cancer with MetS, and Kaplan–Meier curves of the incidence of colon (**C-2**) or liver (**D-2**) cancer among the six groups with 0–5 components of MetS based on the modified criteria of NCEP/ATPIII

of these cancers, and we need to pay attention to these cancers in the subjects with MetS.

We need to conclude carefully for MetS and cancers overall. The analyses of big data may reveal subtle changes in the cohort. However, we found that each factor responsible for MetS is independently related to cancers overall (Figs. 4, 5, 6), suggesting that MetS constitutes a factor that increases the probability of cancers stepwise.

There may be racial differences in whether MetS regulates the incidence of cancers. The highest prevalence of cancer is in North America, with 1.5% of the population. Western Europe and Japan are 1.2% and 1.0%, respectively [29]. Since the lifestyle in Japan is recently westernized, cancers with high prevalence are becoming similar in Western countries and Japan, and the population with MetS has increased in Japan. Since we employed a diagnostic method using the NCEP ATP III and Japanese criteria, our study conclusion has not changed, suggesting that the present conclusion can be applicable worldwide.

This study cohort was obtained from employees of general corporations and their family members. The merit of this cohort is that the subjects are from all over Japan; the demerit is that since this cohort lacked the subjects over 80 years old, the average age of the cohort may be younger than the average of Japanese people. In 2020, the average age of the Japanese population was 48.9 years, and the cohort of this study had a similar age with lacks in very older adults over 80 years. Furthermore, as for the generalization of the present results to the Japanese populations, we consider that our data does not solely represent a group with particularly high health awareness, because this cohort primarily consists of data from ordinary employees and their families collected through company health checkups, which are required by Japanese law to be conducted at least once a

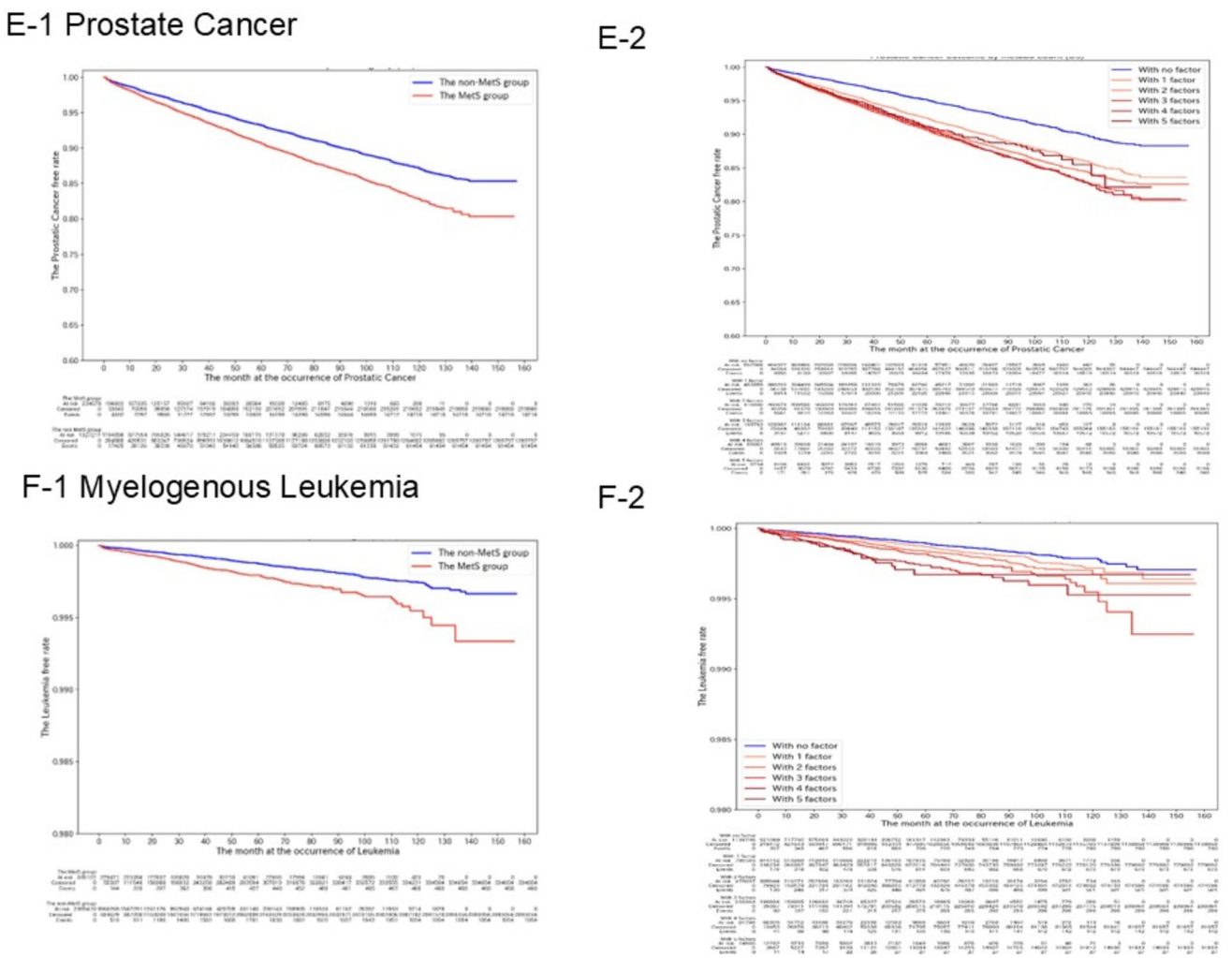

Fig. 6 Kaplan–Meier curves for the incidence of prostate cancer (**E-1**) or myelogenous leukemia (**F-1**) with MetS, and Kaplan–Meier curves of the incidence of prostatic cancer (**E-2**) or myelogenous leukemia (**F-2**) among the six groups with 0–5 components of MetS based on the modified criteria of NCEP/ATPIII. Note that the scale of Y axis for myelogenous leukemia is enlarged compared with the other figures

year. Therefore, the diet situation may not be different from standard Japanese populations, partially shown by BMI levels. Additionally, the smoking rate in our data (from 2005 to 2020) is 24.9%, which is higher than the national statistic for Japan (16.7% in 2019). This discrepancy may be attributable to the fact that our data has been collected since 2005. However, we normalized the HRs of cancer onsets with and without metabolic syndrome by the factor of smoking, so we believe that smoking is not a confounding factor of the present study.

The drugs used in this cohort may be changed because of the drug discovery for the observation period, especially the drugs for diabetes. In the present study, we did not use the data of the administered drugs, and we used the glycemic control values such as the glucose and HbA_1C levels. Therefore, even if the drug use since 2005 has changes, the used parameters such as HbA_1C levels in the cohort have not been changed. Furthermore, the diabetic drugs have not been used in this cohort since this cohort consists with and without MetS and we have excluded the diabetic patients at the entry.

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Data availability The data analyzed in this study are available from the corresponding author upon reasonable request.

Declarations

Conflict of interest Relationships to industry do not exist for N.K, Y.M., Y.Y., T.A., M.Y., T.W., and S.T. Y.S. reports personal fees from AstraZeneca, personal fees from Otsuka Pharmaceutical, personal

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