# Metabolic syndrome is linked to the incidence of pancreatic cancer

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## Summary

**Background** Although previous studies have showed that metabolic syndrome is one of the contributors of pancreatic cancer, there is no clear consensus that early stages of metabolic syndrome are linked to increased incidence of pancreatic cancer. Therefore, we confirmed the linkage between metabolic syndrome and pancreatic cancer, and shown that even early stage of metabolic syndrome is linked to pancreatic cancer in the retrospective observational study.

**Methods** We recruited approximately 4.6 million Japanese in 2005 and followed up these subjects for more than 10 years. At the time of the enrollment, after obtaining clinical data with prescribed drugs and examining the presence or absence of metabolic syndrome (MetS), we followed up on these subjects with and without MetS to examine the incidence of pancreatic cancer. The modified criteria of the National Cholesterol Education Program Adult Treatment Panel III (NCEP/ATPIII) were used to define MetS.

**Findings** During the 40.7-month average follow-up period for 2,707,296 subjects with complete data for identifying MetS and important risk factors without pancreatic cancer before the enrollment, 87,857 suffered from pancreatic cancer. Pancreatic cancers occurred in 16,154 of 331,229 subjects (4.9%) in the MetS group and 71,703 of 2,376,067 patients (3.0%) in the non-MetS group (hazard ratio (HR), 1.37; 95% confidence interval [CI], 1.34–1.39; $p < 0.0001$ after the adjustment with age, smoking and sex). As the number of the constituent factors of MetS increased from one to five, the incidence of pancreatic cancer correspondingly increased (HR: 1.11, 1.23, 1.42, 1.66 and 2.03 using Cox proportional hazard models, $p < 0.0001$ each). When we defined MetS using the Japanese criteria, the results are in accord with the results using NCEP/ATPIII. Especially pre-metabolic syndrome (pre-MetS) in the Japanese criteria was tightly linked to the incidence of pancreatic cancers.

**Interpretation** MetS is confirmed to be linked to pancreatic cancer. Although we cannot conclude causality. We also demonstrated the link between pre-MetS and pancreatic cancer.

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**Keywords:** Big data; Pancreatic cancer; Metabolic syndrome; Prevention of metabolic syndrome; Early stage of metabolic syndrome

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## Research in context

### Evidence before this study

Previous literature has showed that metabolic syndrome is one of the contributors of pancreatic cancer, although there is some controversy about the link. Furthermore, there is no clear consensus that an early stage of metabolic syndrome is linked to increased incidence of pancreatic cancer.

### Added value of this study

The present study has confirmed that metabolic syndrome is linked to increased incidence of pancreatic cancer. In addition, pre-metabolic syndrome defined by the Japanese criteria of metabolic syndrome was also linked to the incidence of pancreatic cancer. This is confirmed by the fact that the incidence of pancreatic cancer correspondingly increased as the number of the constituent factors of metabolic syndrome increased, suggesting that early stages of metabolic syndrome are linked to pancreatic cancer.

### Implications of all the available evidence

The incidence of pancreatic cancer is linked to smoking, type II diabetes mellitus, and chronic pancreatitis. In this study, we have confirmed the link between metabolic syndrome and also early stages of metabolic syndrome and pancreatic cancer. Taken together with all available evidence, we further endorse that the treatment and prevention of metabolic syndrome as preventive strategies to reduce pancreatic cancer incidence.

## Introduction

Cancers and cardiovascular diseases have placed a significant burden on both individual patients and national economies around the world.[1] Cancer has been gradually and eventually conquered because of early detection and prompt diagnosis using novel imaging techniques or biomarkers for diagnosis, as well as rapid progress of regimens for innovative medical and surgical treatments. However, pancreatic cancer has been recognized as the most lethal of all cancers because the incidence and mortality rates are nearly similar, suggesting that the time of prevention and diagnosis may be too late for pancreatic cancer to be treated comprehensively.[2] Every year, more than 40,000 people in Japan are newly diagnosed with pancreatic cancer,[3] and effectively preventing and early diagnosing pancreatic cancer is extremely difficult, resulting in delayed diagnosis and the inoperability and incurability of this cancer. Pancreatic cancer, one of the most common tumors, has now become a leading cause of death among all cancers, with an estimated mortality rate approaching 100%.[2] Indeed, in the United States, pancreatic cancer is the fourth leading cause of cancer death, and it is the fifth leading cause of cancer death in Japan.[3] Pancreatic cancer is reportedly is linked to by smoking,[4] type II diabetes mellitus (T2D),[5] and chronic pancreatitis,[6] all of which may impair pancreatic function, i.e., production of not only digestive enzymes of amylase, lipase, and trypsin but also insulin, glucagon, and somatostatin.[7] The first three factors are related to food digestion, while the latter three are related to glucose metabolism. When the burden on the pancreas is combined, it can cause or be caused by metabolic syndrome. Metabolic syndrome (MetS), which includes the factors such as high blood pressure, high blood sugar, excess body fat around the waist, and abnormal cholesterol or triglyceride levels, is a cluster of conditions that occur together and increase the risk of cardiovascular disease (CVD), stroke, and T2D. While there is evidence that MetS is linked to pancreatic cancer,[8] other studies partially or completely deny such a linkage.[9–11] We further hypothesized that the increases in the number of the factors constituting MetS may increase the incidence of pancreatic cancer, however, there is no clear such consensus.

To confirm the linkage between MetS and pancreatic cancer, we investigated whether the incidence of pancreatic cancer was higher in subjects with MetS than those without MetS over a 10-year period in a Japanese cohort. Furthermore, to show that even early stages of MetS is linked to pancreatic cancer, we investigated the linkage between pre-MetS and pancreatic cancer and the relationship between the number of the factors constituting MetS and the incidence of pancreatic cancer.

## Methods

### Study design

The present study was a retrospective observational study that adhered to the principles of the Declaration of Helsinki and the Japanese Ethical Guidelines for Clinical Research.

### Participants

Our analyses were based on healthcare insurance claims data obtained by JMDC, Japan Medical Data Center, a Japanese leading company to form the Japanese medical data base. The database contained standardized eligibility and claims data provided by health insurance societies for 4.6 million insured individuals between 2005 and 2020, and it included the data of general corporation employees and their family members, as well as all medical treatments received by insured individuals at all treatment facilities and a comprehensive record of all treatments administered to a given patient. We analyzed the personal data using unlinkable anonymization.

### Ethics

The study protocol was approved by the external Ethics Committee of the Evidence Founder Club in Osaka (EU20210515-1). The Committee decided that, based on the Japanese Clinical Research Guidelines, it was not necessary to obtain informed consent from patients selected for inclusion in this study because it was a retrospective observational study. Instead, JMDC issued a public announcement in accordance with the request of the Ethics Committee and the Japanese Clinical Research Guidelines.

### Definition of MetS

MetS was defined by the modified criteria of the National Cholesterol Education Program Adult Treatment Panel III (NCEP/ATPIII),[12] with the presence of ≥3 of the following factors: (1) serum triglycerides (TG) ≥1.69 mmol/L (150 mg/dL); (2) high-density lipoprotein (HDL)-cholesterol <1.03 mmol/L (40 mg/dL) for men and <1.29 mmol/L (50 mg/dL) for women; (3) glucose ≥6.11 mmol/L (110 mg/dL) fasting or ≥7.77 mmol/L (140 mg/dL) non-fasting, or on treatment; (4) blood pressure (BP) ≥130/85 mm Hg or medication use; and (5) body mass index (BMI) ≥25.0 kg/m$^2$. The Japanese criteria of MetS require abdominal central obesity of abdominal circumference length at umbilical level (men: ≥85 cm, women: ≥90 cm) rather than BMI with ≥2 factors of (1) elevated TG and/or reduced HDL, (2) elevated BP, and (3) elevated fasting glucose levels.[13] The presence of abdominal central obesity combined with either one factor is referred to as pre-metabolic syndrome (preMetS). We also defined the non-MetS group as those subjects who were not classified as having MetS or preMetS. The subjects with T2D were excluded.

### The study protocol

To begin with, we excluded 42,885 subjects without no observation period and 1,825,660 subjects with missing data from our cohort of 4,600,443 (Fig. 1). We obtained and recorded clinical data from for all enrolled subjects before examining and identifying those who were diagnosed with pancreatic cancer according to the International Classification of Diseases 10th Revision (ICD-10, coded as I10–I15). We used Kaplan–Meier estimates to compare the occurrence of pancreatic cancer in the cohorts with and without MetS over a period of 40.7 months. In the enrolled subjects, 472,053 and 22,355 were followed up more than 5 and 10 years, respectively. We also calculated hazard ratios (HRs) using Cox proportional hazard models between two groups and among groups with 0–5 factors for the components of MetS. We also used the National Cholesterol Education Program Adult Treatment Panel III definition of MetS.[12]

To investigate the effects of metabolic dynamics on the occurrence of pancreatic cancer, as one of our sub-analyses we enrolled 206,847 subjects whose metabolic states were well followed up in both 2010–2011 and 2012–2013. We classified these enrolled subjects into 4 groups by the presence and absence of MetS at 1) 2010–2011 and at 2) 2012–2013: two groups with MetS at 2010–2011 with and without MetS at 2012–2013, and two groups with non-MetS at 2010–2011 with and without MetS at 2012–2013. When we checked the data during 2010–2013, the participants with MetS at 2010 or 2011 were categorized into MetS-recovered (10,034 subjects) and MetS-persistent (13,595 subjects) groups according to the conditions that MetS is improved/disappeared or persisted, and we followed up these subjects at the end of observation or the onset of pancreatic cancer. The participants with non-MetS at 2010 or 2011 were categorized into MetS-developed (11,248 subjects) and MetS-free (171,970 subjects) groups according to the condition that the MetS is appeared or free, and we followed up these subjects at the end of observation or the onset of pancreatic cancer.

Furthermore, to test the causality of pancreatic cancer, we excluded the subjects with pancreatic cancer that occurred in 3 years after the entry as the sub-analysis.

On the other hand, we used the Japanese criteria for MetS[13] and performed the same analyses using Kaplan–Meier estimates and Cox proportional hazard models between the groups with and without MetS or the pre-MetS group. We further divided the MetS group into two groups: those with 2 factors and those with 3 factors in addition to abdominal central obesity.

### Statistics

For the primary analyses, time-to-event data were evaluated using Kaplan–Meier estimates and compared using log-rank test. 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. For the missing data, we employed complete case analysis (Listwise Deletion) and sensitivity analysis was not performed.

Cox proportional hazard models were used to estimate the HRs with MetS group assignment or combinations of the components with the MetS and non-MetS groups, and 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 pancreatic cancer is known to be affected by these factors.

Age was handled as a continuous variable for Cox proportional hazards models. We have tested the assumption of log-linearity and a score test based on scaled Schoenfeld residuals including a scatter plot with survival time on the horizontal axis, and the scaled Schoenfeld residuals on the vertical axis confirmed that there is no strong evidence indicating the absence of log-linearity in any of the variables.

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

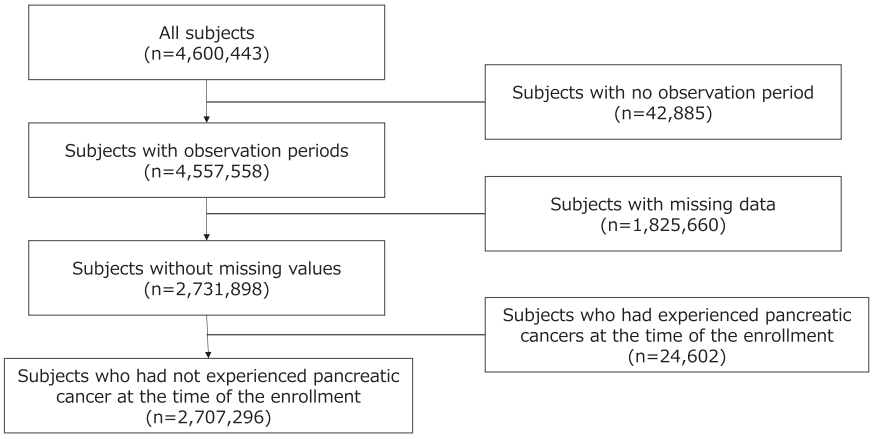



***Fig. 1:*** The consort diagram for the selection of the enrolled subjects.

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

### Role of funding source

Study sponsors did not participate in the study design, the collection, analysis, and interpretation of data, the writing of the manuscript, or in the decision to submit the study for publication.

## Results

The clinical characteristics of the patients are listed in Table 1. Further, the clinical parameters of subjects with and without MetS were compared (Table 1) using NCEP/ATPI or Japanese criteria. In the overall population, pancreatic cancer occurred in 16,154 of 331,229 subjects (4.9%) in the MetS group and 71,703 of 2,376,067 patients (3.0%) in the non-MetS group over a period of 15.2 years (hazard ratio (HR), 1.37; 95% confidence interval [CI], 1.34–1.39; $p < 0.0001$ after the adjustment with age, smoking and sex and interactions between age and sex). Table 2 shows the number and percentages of excluded subjects with missing data for the diagnosis of MetS and important risk factors, and there were small differences of each parameter between the subjects with and without missing data. Fig. 2A depicts the results of the Kaplan–Meier analysis of subjects with and without MetS for the incidence of pancreatic cancer, showing that subjects with MetS are more likely to be linked to pancreatic cancer. We tested the ideas that an increase in the factors constituting MetS in the MetS groups further increases the incidence of pancreatic cancer.

| The parameters for the diagnosis of MetS and important risk factors | All data (N = 2,707,296) | NCEP/ATPI criteria of MetS | | Japanese criteria of MetS | | |
|---|---|---|---|---|---|---|
| | | Non-MetS (N = 2,376,067) | MetS (N = 331,229) | Non-MetS (N = 2,043,791) | PreMetS (N = 283,024) | MetS (N = 380,481) |
| Women, n (%) | 1,132,828 (41.8%) | 1,038,731 (43.7%) | 94,097 (28.4%) | 1,032,728 (50.5%) | 46,696 (16.5%) | 53,404 (14.0%) |
| Age, median age | 53 (46–61) | 52 (45–60) | 58 (51–65) | 57 (50–65) | 55 (48–62) | 52 (45–60) |
| Smoker, n (%) | 674,813 (24.9%) | 570,302 (24.0%) | 104,511 (31.5%) | 458,545 (22.4%) | 86,920 (30.7%) | 129,348 (34.0%) |
| BMI, median BMI | 22.5 (20.3–25.0) | 22.0 (20.1–24.2) | 27.0 (24.8–29.5) | 21.5 (19.7–23.2) | 26.0 (24.5–28.0) | 27.0 (25.1–29.5) |
| Abd circumference, median cm | 80.5 (74.0–87.2) | 79.0 (73.0–85.0) | 93.0 (88.0–98.5) | 77.5 (72.0–82.0) | 91.0 (87.6–95.4) | 93.0 (89.0–98.5) |
| sBP, median mmHg | 118 (108–129) | 116 (106–126) | 134 (126–143) | 115 (105–125) | 122 (114–128) | 133 (125–142) |
| dBP, median mmHg | 73 (65–82) | 72 (64–80) | 85 (78–91) | 71 (64–79) | 76 (70–82) | 85 (78–91) |
| HbA1c, median % | 5.4 (5.2–5.7) | 5.4 (5.2–5.6) | 5.8 (5.5–6.2) | 5.4 (5.2–5.6) | 5.5 (5.3–5.7) | 5.7 (5.5–6.1) |
| Fasting glucose, median mg/dL | 92 (86–99) | 91 (85–97) | 105 (99–117) | 90 (85–96) | 95 (89–102) | 101 (93–113) |
| HDL-cholesterol, median mg/dL | 62 (51–74) | 63 (53–75) | 48 (41–57) | 65 (55–77) | 54 (47–63) | 49 (42–58) |
| LDL-cholesterol, median mg/dL | 119 (99–140) | 117 (98–138) | 131 (110–153) | 115 (96–136) | 128 (108–148) | 132 (111–153) |
| TG, median mg/dL | 83 (58–124) | 77 (55–110) | 173 (125–233) | 73 (53–103) | 104 (78–135) | 162 (111–218) |

Abbreviations: 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. 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.

***Table 1:*** **Characteristics of 2,707,296 subjects with complete data for identifying MetS and important risk factors without pancreatic cancer before the enrollment.**

| The parameters for the diagnosis of MetS and important risk factors | The number of missing data | The percentage of missing data (%) | The values of the subjects with missing data (n = 1,825,660) | The values of the subjects without missing data (n = 2,731,898) |
|---|---|---|---|---|
| Women, n (%) | 0 | 0.0 | 678,969 (37.2%) | 1,144,791 (41.9%) |
| Age, median age | 0 | 0.0 | 45 (35–56) | 53 (46–61) |
| Smoker, n (%) | 3,83,394 | 8.4 | 414,102 (28.7%) | 679,796 (24.9%) |
| BMI, median BMI | 93,394 | 2.0 | 22.0 (20.0–24.6) | 22.5 (20.3–25.0) |
| Abd circumference, median cm | 6,60,953 | 14.5 | 79.8 (73.0–87.0) | 80.5 (74.0–87.2) |
| sBP, median mmHg | 94,065 | 2.1 | 118 (108–128) | 118 (108–129) |
| dBP, median mmHg | 94,065 | 2.1 | 71 (64–79) | 73 (65–82) |
| HbA1c, median % | 9,38,596 | 20.6 | 5.3 (5.1–5.6) | 5.4 (5.2–5.7) |
| FBS(mg/dL) | 9,61,878 | 21.1 | 84 (89–96) | 86 (92–99) |
| HDL-cholesterol, median mg/dL | 2,84,909 | 6.3 | 61 (51–72) | 62 (51–74) |
| LDL-cholesterol, median mg/dL | 3,35,688 | 7.4 | 112 (92–134) | 119 (99–140) |
| TG, median mg/dL | 2,84,666 | 6.2 | 82 (56–126) | 83 (58–124) |

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

***Table 2:*** **Characteristics of 1,825,660 subjects excluded from the study because of missing values for the diagnosis of MetS and important risk factors and the comparison with 2,731,898 subjects without missing data.**

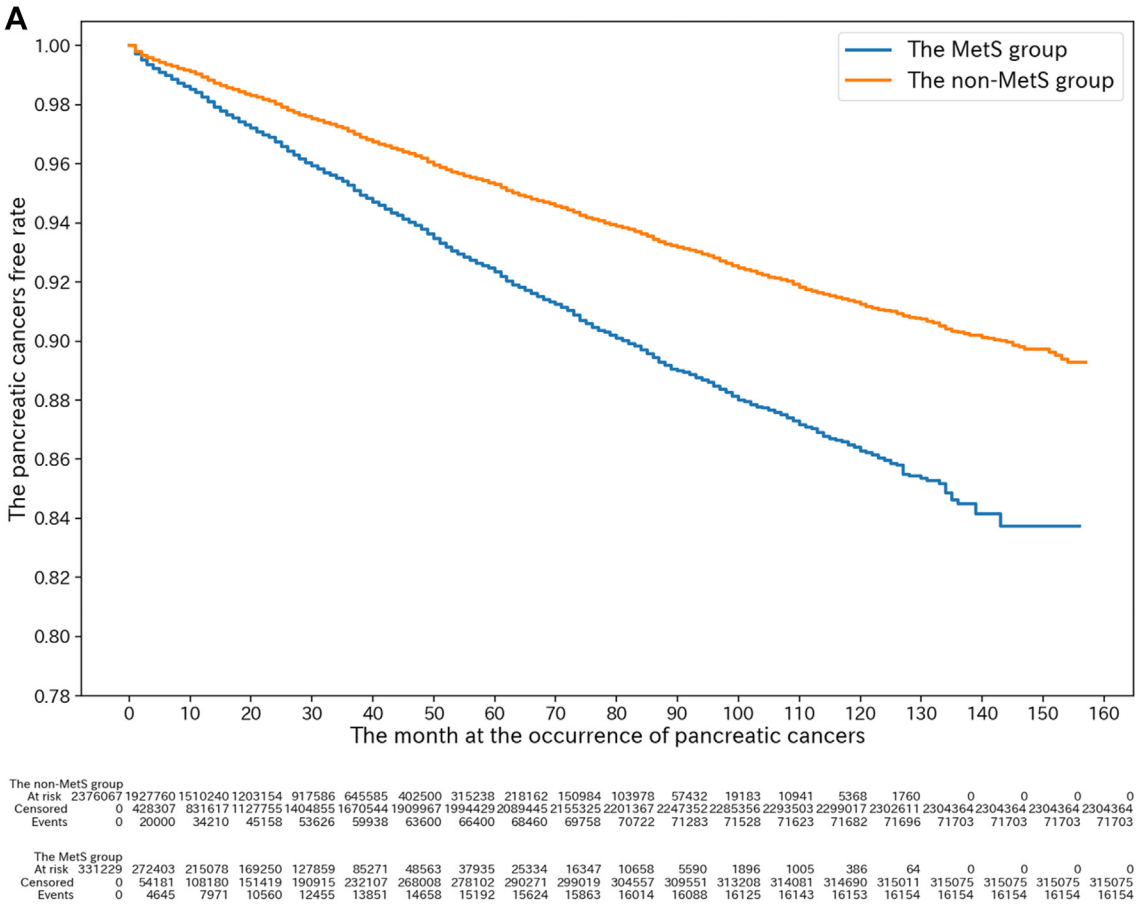
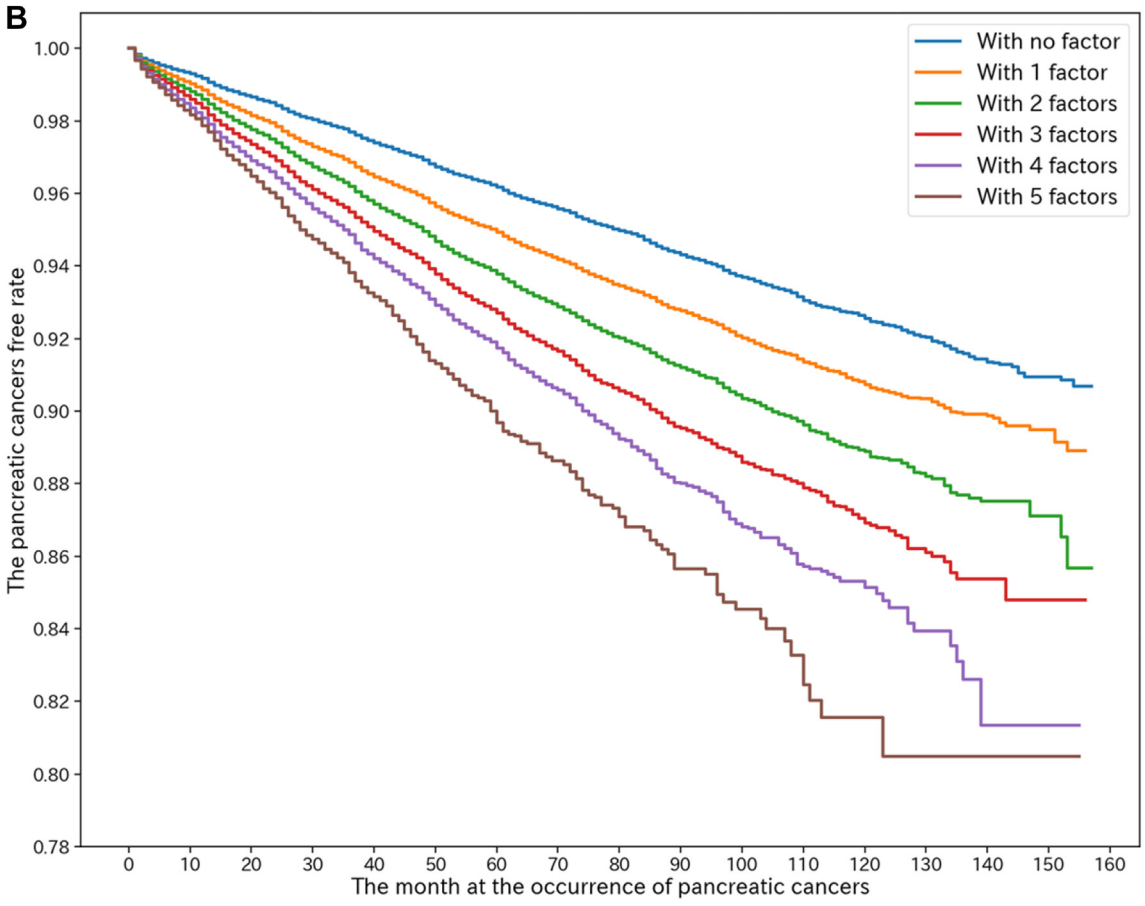



***Fig. 2:*** Kaplan–Meier curves for the incidence of the pancreatic cancer with and without MetS (A) and for the incidence of pancreatic cancer among the six groups with 0–5 components of MetS (B) based on the modified criteria of NCEP/ATPIII.

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|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| With no factor | | | | | | | | | | | | | | | | | | | | |
| At risk | 1132187 | 908621 | 703703 | 561016 | 429577 | 308876 | 199145 | 154738 | 107310 | 75469 | 52247 | 29327 | 9974 | 5787 | 3003 | 1080 | 0 | 0 | 0 | 0 |
| Censored | 0 | 216007 | 415555 | 554232 | 682496 | 800716 | 909002 | 952229 | 998794 | 1030029 | 1052826 | 1075480 | 1094728 | 1098865 | 1101615 | 1103530 | 1104608 | 1104608 | 1104608 | 1104608 |
| Events | 0 | 7559 | 12929 | 16939 | 20114 | 22595 | 24040 | 25220 | 26083 | 26689 | 27114 | 27380 | 27485 | 27535 | 27569 | 27577 | 27579 | 27579 | 27579 | 27579 |
| With 1 factor | | | | | | | | | | | | | | | | | | | | |
| At risk | 773771 | 632629 | 499961 | 399088 | 303991 | 212073 | 129875 | 102426 | 71329 | 49248 | 33952 | 18705 | 6134 | 3481 | 1686 | 526 | 0 | 0 | 0 | 0 |
| Censored | 0 | 133996 | 261568 | 358431 | 450524 | 540268 | 621204 | 647685 | 678074 | 699737 | 714697 | 729758 | 742245 | 744874 | 746654 | 747809 | 748332 | 748332 | 748332 | 748332 |
| Events | 0 | 7146 | 12242 | 16252 | 19256 | 21430 | 22692 | 23660 | 24368 | 24786 | 25122 | 25308 | 25392 | 25416 | 25431 | 25436 | 25439 | 25439 | 25439 | 25439 |
| With 2 factors | | | | | | | | | | | | | | | | | | | | |
| At risk | 470109 | 386510 | 306576 | 243050 | 184018 | 124636 | 73480 | 58074 | 39523 | 26267 | 17779 | 9400 | 3075 | 1673 | 679 | 154 | 0 | 0 | 0 | 0 |
| Censored | 0 | 78304 | 154494 | 215092 | 271835 | 329560 | 379761 | 394515 | 412577 | 425559 | 433844 | 442114 | 448383 | 449764 | 450748 | 451272 | 451424 | 451424 | 451424 | 451424 |
| Events | 0 | 5295 | 9039 | 11967 | 14256 | 15913 | 16868 | 17520 | 18009 | 18283 | 18486 | 18595 | 18651 | 18672 | 18682 | 18683 | 18685 | 18685 | 18685 | 18685 |
| With 3 factors | | | | | | | | | | | | | | | | | | | | |
| At risk | 235679 | 194089 | 153248 | 120845 | 91375 | 61130 | 35049 | 27404 | 18355 | 11903 | 7801 | 4083 | 1344 | 713 | 263 | 46 | 0 | 0 | 0 | 0 |
| Censored | 0 | 38454 | 77057 | 107673 | 135872 | 165163 | 190688 | 197957 | 206716 | 213005 | 217004 | 220676 | 223386 | 224006 | 224451 | 224667 | 224713 | 224713 | 224713 | 224713 |
| Events | 0 | 3136 | 5374 | 7161 | 8432 | 9386 | 9942 | 10318 | 10608 | 10771 | 10874 | 10920 | 10949 | 10960 | 10965 | 10966 | 10966 | 10966 | 10966 | 10966 |
| With 4 factors | | | | | | | | | | | | | | | | | | | | |
| At risk | 80800 | 66427 | 52564 | 41229 | 31116 | 20657 | 11598 | 9055 | 6017 | 3849 | 2482 | 1315 | 474 | 248 | 104 | 15 | 0 | 0 | 0 | 0 |
| Censored | 0 | 13119 | 26081 | 36765 | 46359 | 56465 | 65319 | 67725 | 70644 | 72748 | 74073 | 75218 | 76053 | 76273 | 76412 | 76501 | 76516 | 76516 | 76516 | 76516 |
| Events | 0 | 1254 | 2155 | 2806 | 3325 | 3678 | 3883 | 4020 | 4139 | 4203 | 4245 | 4267 | 4273 | 4279 | 4284 | 4284 | 4284 | 4284 | 4284 | 4284 |
| With 5 factors | | | | | | | | | | | | | | | | | | | | |
| At risk | 14750 | 11887 | 9266 | 7176 | 5368 | 3484 | 1916 | 1476 | 962 | 595 | 375 | 192 | 78 | 44 | 19 | 3 | 0 | 0 | 0 | 0 |
| Censored | 0 | 2608 | 5042 | 6981 | 8684 | 10479 | 12001 | 12420 | 12911 | 13266 | 13480 | 13657 | 13769 | 13802 | 13827 | 13843 | 13846 | 13846 | 13846 | 13846 |
| Events | 0 | 255 | 442 | 593 | 698 | 787 | 833 | 854 | 877 | 889 | 895 | 901 | 903 | 904 | 904 | 904 | 904 | 904 | 904 | 904 |

***Fig. 2:*** (continued)

When the factors constituting MetS increased, the probability of developing pancreatic cancer increased (Fig. 2B). Fig. 3 depicts HRs for the occurrence of pancreatic cancer and MetS; as the number of the constituent factors of MetS increased from one to five, the incidence of pancreatic cancer correspondingly increased (HRs: 1.11, 1.23, 1.42, 1.66, and 2.03, $p < 0.0001$ each).

As for the effects of changes in status of MetS, HRs of MetS-free and MetS-developed groups were HR: 1.00 and HR: 1.38; 95% CI, 1.25–1.53 ($p < 0.0001$), respectively; HRs of MetS-recovered (23% of subjects with MetS group) and MetS-persistent groups were 1.29 (95% CI, 1.14–1.43, $p < 0.001$) and HR, 1.51 (95% CI, 1.38–1.66, $p < 0.0001$), respectively. The results of the Kaplan–Meier analysis of MetS-free and MetS-developed groups, and MetS-recovered and MetS-persistent groups for the incidence of pancreatic cancer are shown in Fig. 4, and they are in accord with the results of HRs.

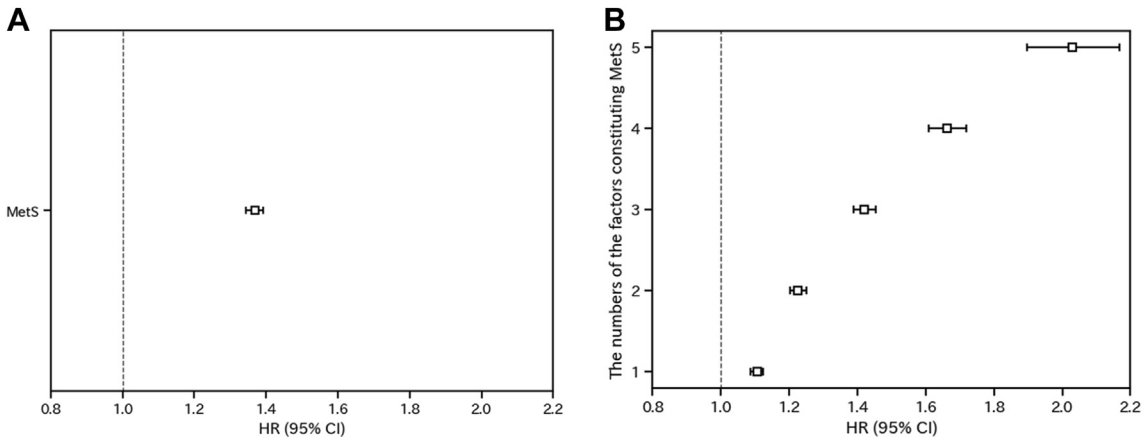
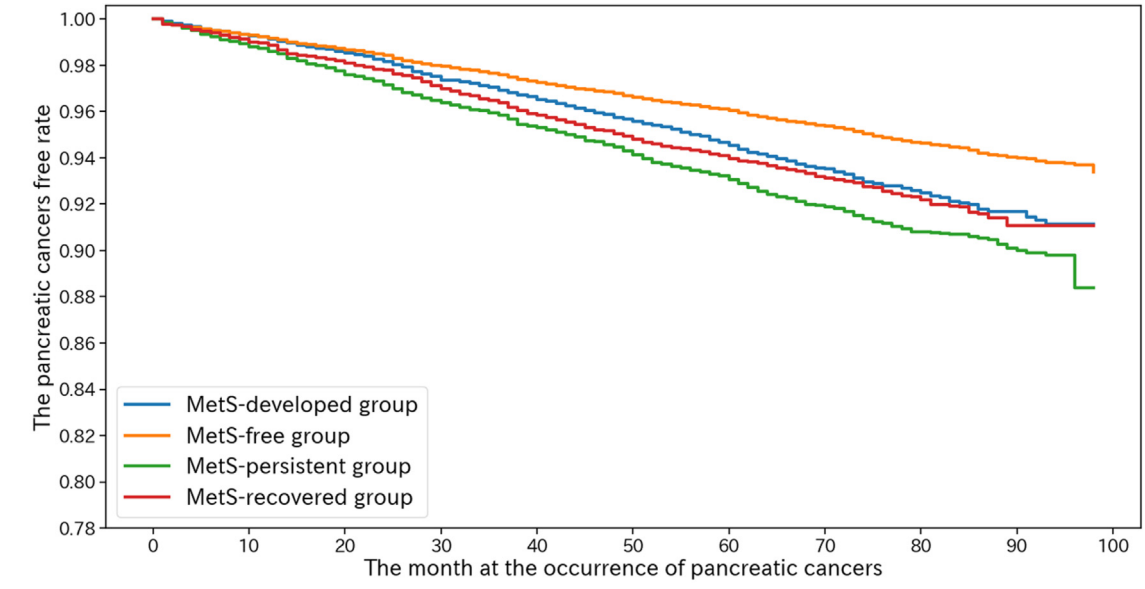



*Fig. 3:* HRs for the incidence of the pancreatic cancer with and without MetS (A) and for the incidence of pancreatic cancer among the six groups with 0–5 components of MetS (B) based on the modified criteria of NCEP/ATPIII. (A) HR is 1.37 (95% CI, 1.34–1.39; p < 0.0001). (B) When factors of MetS increase from 1 to 5, HR increased to 1.11 (95% CI, 1.09–1.12; p < 0.0001), 1.23 (95% CI, 1.20–1.25, p < 0.0001), 1.42 (95% CI, 1.39–1.45, p < 0.0001), 1.66 (95% CI, 1.61–1.72, p < 0.0001), and 2.03 (95% CI, 1.90–2.17, p < 0.0001), respectively.

When we excluded the subjects with pancreatic cancer detected in 3 years after the entry, we obtained HRs 1.38 (95% CI, 1.33–1.42, p < 0.0001 compared with no-MetS group). The results of the Kaplan–Meier analysis without the subjects with pancreatic cancer detected in 3 years after the entry are shown in Fig. 5, and they are in accord with the results of HRs.

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| MetS-developed group | | | | | | | | | | | | | | | | | | | | |
| At risk | 11248 | 10521 | 9821 | 9181 | 8739 | 8328 | 7926 | 7559 | 4148 | 725 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Censored | 0 | 648 | 1271 | 1799 | 2162 | 2488 | 2801 | 3085 | 6421 | 9825 | 10546 | 10546 | 10546 | 10546 | 10546 | 10546 | 10546 | 10546 | 10546 | 10546 |
| Events | 0 | 79 | 156 | 268 | 347 | 432 | 521 | 604 | 679 | 698 | 702 | 702 | 702 | 702 | 702 | 702 | 702 | 702 | 702 | 702 |
| MetS-free group | | | | | | | | | | | | | | | | | | | | |
| At risk | 171970 | 162616 | 154274 | 146596 | 140522 | 135253 | 130297 | 125670 | 71056 | 10915 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Censored | 0 | 8173 | 15517 | 22081 | 27141 | 31479 | 35659 | 39377 | 93119 | 153072 | 163962 | 163962 | 163962 | 163962 | 163962 | 163962 | 163962 | 163962 | 163962 | 163962 |
| Events | 0 | 1181 | 2179 | 3293 | 4307 | 5238 | 6014 | 6923 | 7795 | 7983 | 8008 | 8008 | 8008 | 8008 | 8008 | 8008 | 8008 | 8008 | 8008 | 8008 |
| MetS-persistent group | | | | | | | | | | | | | | | | | | | | |
| At risk | 13595 | 12542 | 11706 | 10901 | 10248 | 9699 | 9150 | 8668 | 4711 | 920 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Censored | 0 | 893 | 1583 | 2246 | 2779 | 3207 | 3646 | 4013 | 7879 | 11656 | 12573 | 12573 | 12573 | 12573 | 12573 | 12573 | 12573 | 12573 | 12573 | 12573 |
| Events | 0 | 160 | 306 | 448 | 568 | 689 | 799 | 914 | 1005 | 1019 | 1022 | 1022 | 1022 | 1022 | 1022 | 1022 | 1022 | 1022 | 1022 | 1022 |
| MetS-recovered group | | | | | | | | | | | | | | | | | | | | |
| At risk | 10034 | 9334 | 8713 | 8115 | 7657 | 7250 | 6873 | 6540 | 3720 | 682 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Censored | 0 | 604 | 1142 | 1643 | 2008 | 2334 | 2648 | 2919 | 5682 | 8700 | 9382 | 9382 | 9382 | 9382 | 9382 | 9382 | 9382 | 9382 | 9382 | 9382 |
| Events | 0 | 96 | 179 | 276 | 369 | 450 | 513 | 575 | 632 | 652 | 652 | 652 | 652 | 652 | 652 | 652 | 652 | 652 | 652 | 652 |

*Fig. 4:* Kaplan–Meier curves of MetS-free and MetS-developed groups, and MetS-recovered and MetS-persistent groups for the incidence of pancreatic cancer.

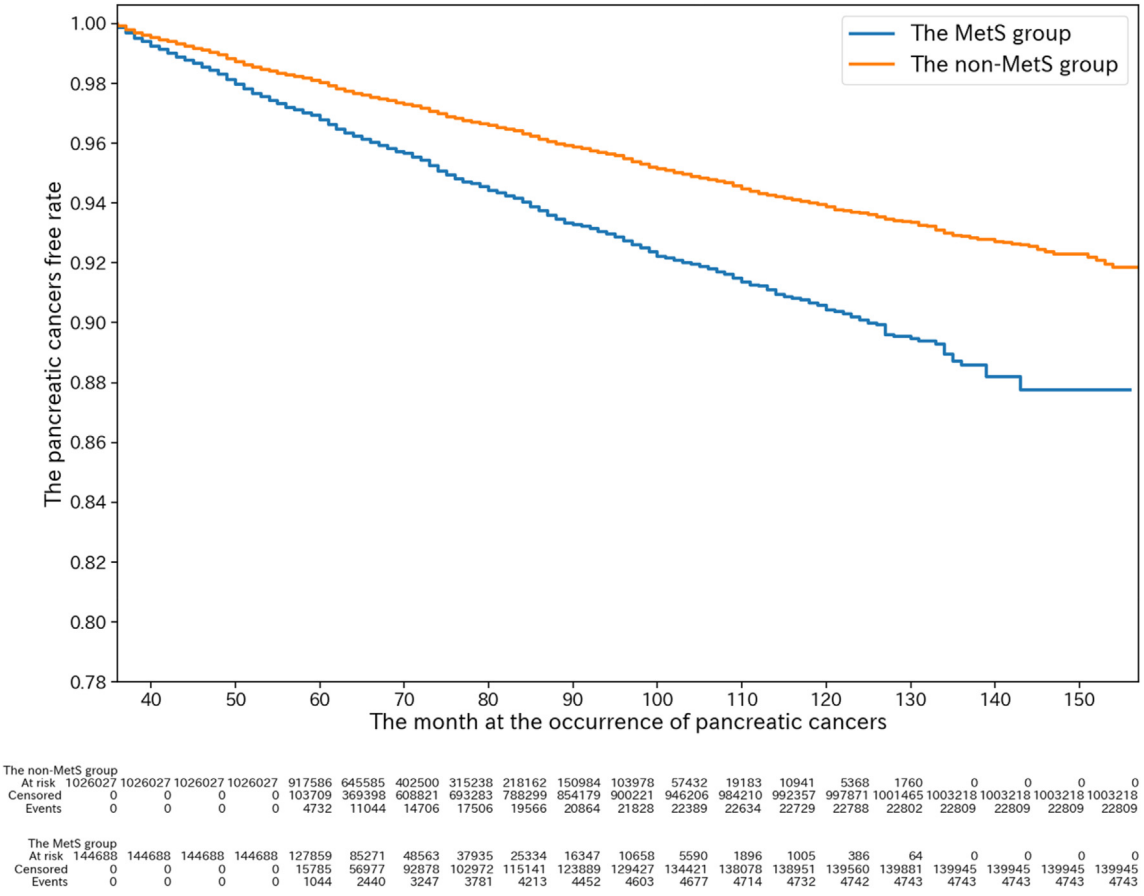


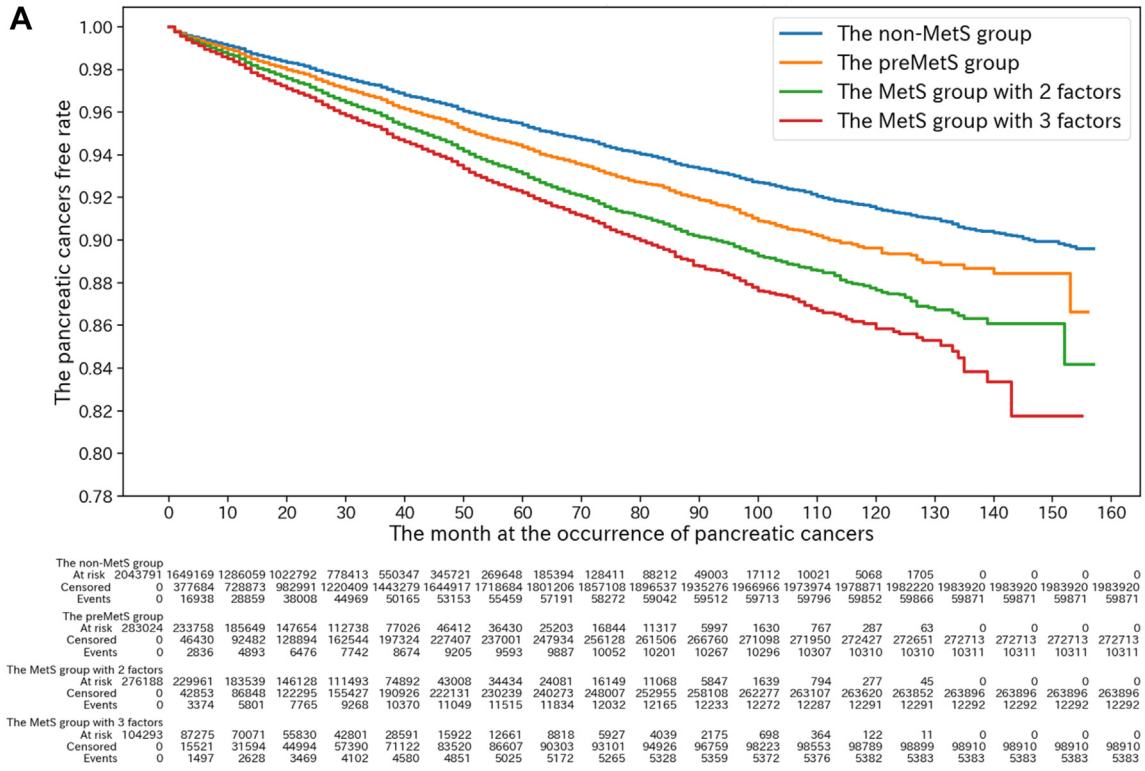

***Fig. 5:*** Kaplan–Meier analysis without the subjects with pancreatic cancer detected in 3 years after the entry.

The results of the Kaplan–Meier analysis of subjects with or without MetS or preMetS for the incidence of pancreatic cancer are shown in Fig. 6A and B, and they are in accord with the results of HRs shown in Fig. 2A and B. Fig. 7A shows HRs for MetS with 2 and 3 MetS components (HR, 1.27; 95% CI, 1.24–1.29; $p < 0.0001$; HR, 1.45; 95% CI, 1.41–1.49; $p < 0.0001$, respectively) and preMetS (HR, 1.14; 95% CI, 1.12–1.17; $p < 0.0001$). Fig. 7B depicts the HRs of the components or combinations of factors constituting MetS based on the Japanese guideline for the incidence of pancreatic cancer, indicating that the combinations of MetS components except dyslipidemia, hypertension and hypertension with dyslipidemia increase the risk of pancreatic cancer.

## Discussion

The present data confirmed strong associations between the presence of MetS and the incidence of pancreatic cancer, suggesting that MetS is links to the occurrence of pancreatic cancer. We propose that MetS, or even preMetS, is a new risk factor for pancreatic cancer. However, to reach this conclusion, we must consider several factors.

Pancreatic cancer, one of the most lethal of all human cancers,[2] has become very common in developed countries such as Europe, the United States, and Japan. Pancreatic cancer is the fourth and fifth leading cause of cancer death in the United States and Japan, respectively.[3] Because the incidence and mortality rates for pancreatic cancer are nearly comparable, implying that pancreatic cancer is lethal and difficult to treat, it is critical to investigate the priming or triggering mechanism for pancreatic cancer in order to prevent its onset. Interestingly and importantly, the incidence rates of pancreatic cancer in high-risk countries are approximately five to seven times higher than in low-risk countries, implying that environmental or genetic factors play an important role in the incidence of pancreatic cancer.[14] Indeed, germline diseases are said to increase the risk of pancreatic cancer,[15] and gene polymorphism also influences pancreatic cancer incidence.[16] Furthermore, several lines of evidence suggest that environmental factors play a role in the occurrence of pancreatic cancer. Smoking is the most significant risk factor for pancreatic cancer,[4] with the risk being twice or three times higher than in non-smokers. Moreover, quitting smoking may

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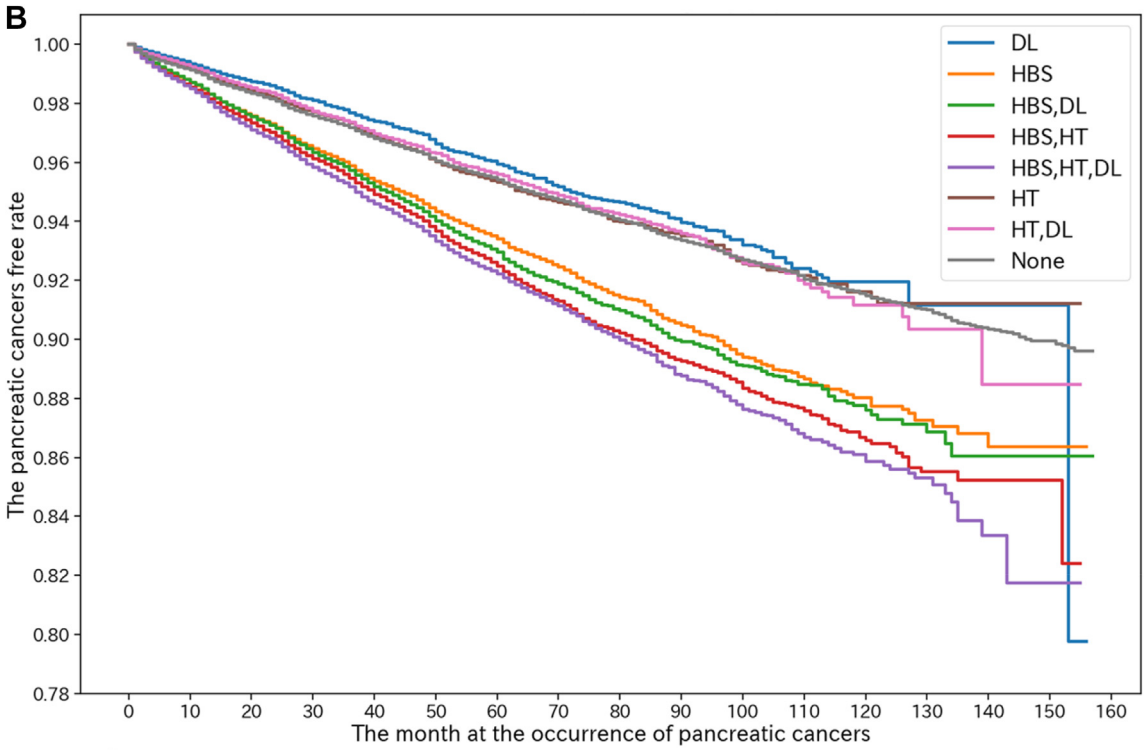
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| The non-MetS group | | | | | | | | | | | | | | | | | | | | |
| At risk | 2043791 | 1649169 | 1286059 | 1022792 | 778413 | 550347 | 345721 | 269648 | 185394 | 128411 | 88212 | 49003 | 17112 | 10021 | 5068 | 1705 | 0 | 0 | 0 | 0 |
| Censored | 0 | 377684 | 728873 | 982991 | 1220409 | 1443279 | 1644917 | 1718684 | 1801206 | 1857108 | 1896537 | 1935276 | 1966966 | 1973974 | 1978871 | 1982220 | 1983920 | 1983920 | 1983920 | 1983920 |
| Events | 0 | 16938 | 28859 | 38008 | 44969 | 50165 | 53153 | 55459 | 57191 | 58272 | 59042 | 59512 | 59713 | 59796 | 59852 | 59866 | 59871 | 59871 | 59871 | 59871 |
| The preMetS group | | | | | | | | | | | | | | | | | | | | |
| At risk | 283024 | 233758 | 185649 | 147654 | 112738 | 77026 | 46412 | 36430 | 25203 | 16844 | 11317 | 5997 | 1630 | 767 | 287 | 63 | 0 | 0 | 0 | 0 |
| Censored | 0 | 46430 | 92482 | 128894 | 162544 | 197324 | 227407 | 237001 | 247934 | 256128 | 261506 | 266760 | 271098 | 271950 | 272427 | 272651 | 272713 | 272713 | 272713 | 272713 |
| Events | 0 | 2836 | 4893 | 6476 | 7742 | 8674 | 9205 | 9593 | 9887 | 10052 | 10201 | 10267 | 10296 | 10307 | 10310 | 10310 | 10311 | 10311 | 10311 | 10311 |
| The MetS group with 2 factors | | | | | | | | | | | | | | | | | | | | |
| At risk | 276188 | 229961 | 183539 | 146128 | 111493 | 74892 | 43008 | 34434 | 24081 | 16149 | 11068 | 5847 | 1639 | 794 | 277 | 45 | 0 | 0 | 0 | 0 |
| Censored | 0 | 42853 | 86848 | 122295 | 155427 | 190926 | 222131 | 230239 | 240273 | 248007 | 252955 | 258108 | 262277 | 263107 | 263620 | 263852 | 263896 | 263896 | 263896 | 263896 |
| Events | 0 | 3374 | 5801 | 7765 | 9268 | 10370 | 11049 | 11515 | 11834 | 12032 | 12165 | 12233 | 12272 | 12287 | 12291 | 12291 | 12292 | 12292 | 12292 | 12292 |
| The MetS group with 3 factors | | | | | | | | | | | | | | | | | | | | |
| At risk | 104293 | 87275 | 70071 | 55830 | 42801 | 28591 | 15922 | 12661 | 8818 | 5927 | 4039 | 2175 | 698 | 364 | 122 | 11 | 0 | 0 | 0 | 0 |
| Censored | 0 | 15521 | 31594 | 44994 | 57390 | 71122 | 83520 | 86607 | 90303 | 93101 | 94926 | 96759 | 98223 | 98553 | 98789 | 98899 | 98910 | 98910 | 98910 | 98910 |
| Events | 0 | 1497 | 2628 | 3469 | 4102 | 4580 | 4851 | 5025 | 5172 | 5265 | 5328 | 5359 | 5372 | 5376 | 5382 | 5383 | 5383 | 5383 | 5383 | 5383 |

***Fig. 6:*** Kaplan–Meier curves for the incidence of the pancreatic cancer with preMetS or MetS with 2 or 3 factors (A) and for the incidence of pancreatic cancer among the eight groups with any combination of the three components of MetS (B) based on the Japanese criteria for MetS.

prevent 23% of pancreatic cancer in men.[17] Second, diet plays a role in increasing the risk of pancreatic cancer. Overall caloric intake and consumption of vegetables or fruits both increase or decrease the incidence of pancreatic cancer.[18] Third, obesity is an independent risk factor for pancreatic cancer, and increased physical activity decreased pancreatic cancer incidence.[19] T2D also increases the incidence of pancreatic cancer as well as other cancers.[20] Obesity[21] and lack of physical activity[22] and T2D[23] may result in hyperinsulinemia, which may prime carcinogenesis. Given the involvement of these three factors in pancreatic cancer, we have concluded that MetS is linked to pancreatic cancer.

The present study confirmed MetS as a potential risk factor for the incidence of pancreatic cancer. MetS has been characterized by adiponectin deficiency, which is independent of obesity, lack of exercise, and T2D. MetS is a cluster of risk factors for both T2D and CVD. However, there is no clear consensus on whether MetS is related to pancreatic cancer, although each factor for MetS is related to pancreatic cancer.[24] MetS is distinct from and independent of T2D, hypertension, dyslipidemia, or obesity. Amidst such circumstances, the present study demonstrated that MetS is tightly related to the incidence of pancreatic cancer.

MetS was defined by the modified criteria of NCEP/ATPIII as the presence of ≥3 hypertriglyceridemia actors: low plasma levels of HDL, hyperglycemia, high systemic blood pressure, and high BMI,[12] or by the Japanese criteria for abdominal circumference length ≥85 cm for men and ≥90 cm for women instead of BMI.[13] Interestingly, in Japan, MetS is predominantly and mainly characterized by the presence of high blood pressure,[25] whereas in the United States or Europe, the presence of glucose intolerance mainly contributes to the occurrence of MetS. The present study highlighted the significance of elevated blood glucose levels, rather than high blood pressure among the constituting factors of MetS in relation to the development of pancreatic cancer. The pathophysiology of MetS, which is based on obesity, especially abdominal obesity, independent of hypertension, dyslipidemia, and DM, is closely linked to the pathophysiology of pancreatic cancer. On the other hand, since preMetS judged by Japanese criteria is also linked to pancreatic cancer, and we found that the incidence of pancreatic cancer correspondingly increased as the number of the constituent factors of the MetS increased from one to five, we suggest that even early stages of MetS are linked to pancreatic cancer.

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|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| DL | | | | | | | | | | | | | | | | | | | | |
| At risk | 52227 | 43373 | 34202 | 27682 | 21471 | 15216 | 9888 | 7356 | 4795 | 2974 | 1858 | 888 | 273 | 127 | 43 | 11 | 0 | 0 | 0 | 0 |
| Censored | 0 | 8530 | 17460 | 23776 | 29812 | 35925 | 41162 | 43623 | 46146 | 47942 | 49039 | 49998 | 50609 | 50753 | 50837 | 50869 | 50879 | 50879 | 50879 | 50879 |
| Events | 0 | 324 | 565 | 769 | 944 | 1086 | 1177 | 1248 | 1286 | 1311 | 1330 | 1341 | 1345 | 1347 | 1347 | 1347 | 1348 | 1348 | 1348 | 1348 |
| HBS | | | | | | | | | | | | | | | | | | | | |
| At risk | 158531 | 131036 | 104151 | 82270 | 62318 | 42181 | 24488 | 19635 | 14228 | 10073 | 6835 | 3772 | 906 | 444 | 165 | 43 | 0 | 0 | 0 | 0 |
| Censored | 0 | 25553 | 51032 | 71852 | 90990 | 110549 | 127921 | 132537 | 137747 | 141784 | 144923 | 147940 | 150787 | 151242 | 151518 | 151640 | 151683 | 151683 | 151683 | 151683 |
| Events | 0 | 1942 | 3348 | 4409 | 5223 | 5801 | 6122 | 6359 | 6556 | 6674 | 6773 | 6819 | 6838 | 6845 | 6848 | 6848 | 6848 | 6848 | 6848 | 6848 |
| HBS,DL | | | | | | | | | | | | | | | | | | | | |
| At risk | 98444 | 82715 | 66196 | 53222 | 41045 | 28134 | 16419 | 13169 | 9552 | 6642 | 4540 | 2439 | 576 | 255 | 84 | 11 | 0 | 0 | 0 | 0 |
| Censored | 0 | 14527 | 30129 | 42356 | 53973 | 66466 | 77925 | 80993 | 84493 | 87315 | 89366 | 91442 | 93290 | 93607 | 93776 | 93849 | 93860 | 93860 | 93860 | 93860 |
| Events | 0 | 1202 | 2119 | 2866 | 3426 | 3844 | 4100 | 4282 | 4399 | 4487 | 4538 | 4563 | 4578 | 4582 | 4584 | 4584 | 4584 | 4584 | 4584 | 4584 |
| HBS,HT | | | | | | | | | | | | | | | | | | | | |
| At risk | 138091 | 114112 | 90611 | 71161 | 53420 | 35053 | 19346 | 15641 | 10928 | 7357 | 5091 | 2707 | 813 | 431 | 152 | 30 | 0 | 0 | 0 | 0 |
| Censored | 0 | 22093 | 44304 | 62732 | 79680 | 97465 | 112820 | 116292 | 120838 | 124317 | 126520 | 128868 | 130742 | 131115 | 131393 | 131515 | 131544 | 131544 | 131544 | 131544 |
| Events | 0 | 1886 | 3176 | 4198 | 4991 | 5573 | 5925 | 6158 | 6325 | 6417 | 6480 | 6516 | 6536 | 6545 | 6546 | 6546 | 6547 | 6547 | 6547 | 6547 |
| HBS,HT,DL | | | | | | | | | | | | | | | | | | | | |
| At risk | 104293 | 87275 | 70071 | 55830 | 42801 | 28591 | 15922 | 12661 | 8818 | 5927 | 4039 | 2175 | 698 | 364 | 122 | 11 | 0 | 0 | 0 | 0 |
| Censored | 0 | 15521 | 31594 | 44994 | 57390 | 71122 | 83520 | 86607 | 90303 | 93101 | 94926 | 96759 | 98223 | 98553 | 98789 | 98899 | 98910 | 98910 | 98910 | 98910 |
| Events | 0 | 1497 | 2628 | 3469 | 4102 | 4580 | 4851 | 5025 | 5172 | 5265 | 5328 | 5359 | 5372 | 5376 | 5382 | 5383 | 5383 | 5383 | 5383 | 5383 |
| HT | | | | | | | | | | | | | | | | | | | | |
| At risk | 72266 | 59349 | 47296 | 37702 | 28949 | 19629 | 12036 | 9439 | 6180 | 3797 | 2624 | 1337 | 451 | 196 | 79 | 9 | 0 | 0 | 0 | 0 |
| Censored | 0 | 12347 | 23990 | 33266 | 41742 | 50850 | 58324 | 60841 | 64041 | 66402 | 67544 | 68822 | 69702 | 69955 | 70072 | 70142 | 70151 | 70151 | 70151 | 70151 |
| Events | 0 | 570 | 980 | 1298 | 1575 | 1787 | 1906 | 1986 | 2045 | 2067 | 2098 | 2107 | 2113 | 2115 | 2115 | 2115 | 2115 | 2115 | 2115 | 2115 |
| HT,DL | | | | | | | | | | | | | | | | | | | | |
| At risk | 39653 | 33134 | 26732 | 21745 | 17028 | 11705 | 7243 | 5624 | 3601 | 2150 | 1437 | 701 | 250 | 108 | 41 | 4 | 0 | 0 | 0 | 0 |
| Censored | 0 | 6233 | 12415 | 17207 | 21774 | 26995 | 31386 | 32954 | 34942 | 36375 | 37069 | 37798 | 38245 | 38385 | 38451 | 38488 | 38492 | 38492 | 38492 | 38492 |
| Events | 0 | 286 | 506 | 701 | 851 | 953 | 1024 | 1075 | 1110 | 1128 | 1147 | 1154 | 1158 | 1160 | 1161 | 1161 | 1161 | 1161 | 1161 | 1161 |
| None | | | | | | | | | | | | | | | | | | | | |
| At risk | 2043791 | 1649169 | 1286059 | 1022792 | 778413 | 550347 | 345721 | 269648 | 185394 | 128411 | 88212 | 49003 | 17112 | 10021 | 5068 | 1705 | 0 | 0 | 0 | 0 |
| Censored | 0 | 377684 | 728873 | 982991 | 1220409 | 1443279 | 1644917 | 1718684 | 1801206 | 1857108 | 1896537 | 1935276 | 1966966 | 1973974 | 1978871 | 1982220 | 1983920 | 1983920 | 1983920 | 1983920 |
| Events | 0 | 16938 | 28859 | 38008 | 44969 | 50165 | 53153 | 55459 | 57191 | 58272 | 59042 | 59512 | 59713 | 59796 | 59852 | 59866 | 59871 | 59871 | 59871 | 59871 |

*Fig. 6:* (continued)

On the other hand, Park et al.[8] recently showed that MetS and dynamic change in MetS status are associated with risks of pancreatic cancer. We also confirmed dynamism of MetS during the observation period, and that the improvement MetS decreases the incidence of pancreatic cancer, and that newly onset of MetS in non-MetS group increases the incidence of pancreatic cancer, which is consonant with Park et al.[8]

Then, we must consider which molecular factor(s) in the pathophysiology of MetS may be linked to the incidence of pancreatic cancer. Molecular mechanisms of MetS culminate in (1) insulin, (2) adipokines, and (3) reactive oxygen species (ROS).[24] To begin with, insulin is a major anabolic hormone that can stimulate cell proliferation.[26] 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 p21 ras/MAPK pathway for cell proliferation as well as the PI3K/AKT cell survival pathway.[27] The proliferative and antiapoptotic effects of IGF-1 are important in tumorigenesis because overexpression of IGF-1 stimulates and suppression of IGF-1 reduces mammary tumor development in mutant mice treated with a carcinogen.[27]

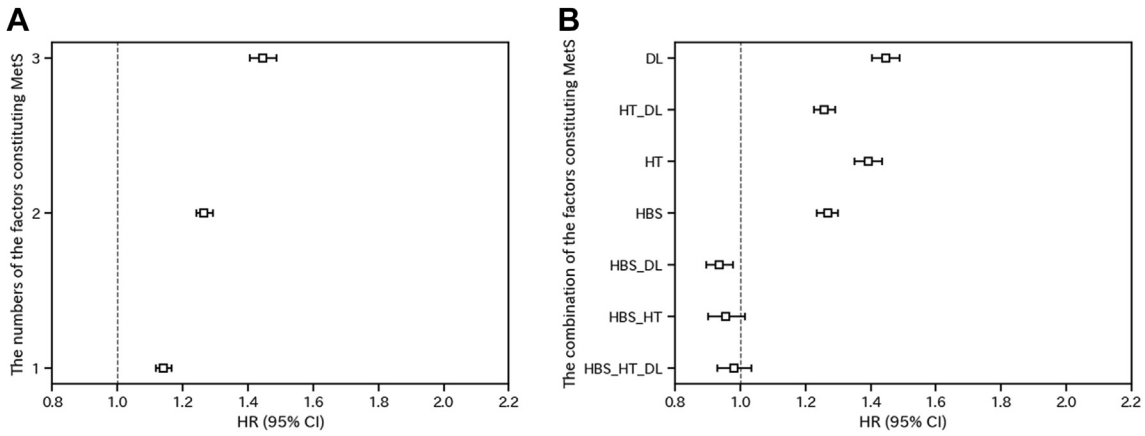


*Fig. 7:* HRs for the incidence of the pancreatic cancer with and without MetS (A) and for the incidence of pancreatic cancer among the eight groups with any combination of the three components of MetS (B) based on the Japanese criteria for MetS. (A) HRs of preMetS, MetS with 2 factors, and MetS with 3 factors are 1.14 (95% CI, 1.12–1.17; p < 0.0001), 1.27 (95% CI, 1.24–1.29; p < 0.0001), and 1.45 (95% CI, 1.41–1.49; p < 0.0001), respectively. (B) the independent factor or combinations of constituting factors for MetS increased HRs in the groups of dyslipidemia (DL, 0.98 (95% CI, 0.93–1.04), p = 0.48), hypertension (HT) with DL (0.96 (95% CI, 0.90–1.01), p = 0.14), HT (0.93 (95% CI, 0.89–0.98), p < 0.0001), high blood glucose levels (HGS) (1.27 (95% CI, 1.24–1.30), p < 0.0001), DL with HBS (1.39 (95% CI, 1.35–1.44), p < 0.0001), HBS with HT (1.26 (95% CI, 1.23–1.29), p < 0.0001) and HBS with HT and DL (1.45 (95% CI, 1.41–1.49), p < 0.0001).

On the other hand, adipokines are a diverse group of signaling molecules involved in a variety of processes including appetite and energy balance, inflammation, insulin resistance/sensitivity, angiogenesis, lipid metabolism, cell proliferation, and atherosclerosis.[28] Many of these functions are related to either MetS or cancer, and they may act as a link between these two pathologies. Adiponectin, an adipokine, has been linked to MetS because obesity lowers plasma adiponectin levels, and adiponectin has insulin-sensitizing effects that ameliorates insulin resistance and T2D.[29]

Excess glucose or lipids, as well as high blood pressure, promote the formation of ROS, which can cause cancers. ROS can damage DNA through a variety of processes, including DNA base modification, deletions, frame shifts, strand breaks, DNA protein cross-links, and chromosomal rearrangements.[30] DNA damage can occur in genes involved in cell proliferation, such as ras, or cell survival, such as p53, resulting in cancer progression.

It is important how long it takes for MetS to affect the incidence of pancreatic cancer. Even when we excluded the subjects with pancreatic cancer that occurred in 3 years after the entry as the sub-analysis, the probability of the incidence of pancreatic cancer is similar, suggesting that MetS may affect incidence of pancreatic cancer on monthly basis.

As for limitation of this study, since this is a retrospective study, there were a significant amount of missing data (Table 2) and we excluded the subjects with missing data. This operation may cause the bias for the conclusion. However, when compared the 1,825,660 and 2,731,898 subjects with and without the parameters for the diagnosis of MetS and important risk factors, respectively (Table 2), there are small differences of the numerical data: The subjects with missing data were younger and had a higher prevalence of smoking than the subjects without missing data. We should consider such a selection bias for understanding of the present results. Secondly, there may be racial differences in whether MetS regulates the incidence of pancreatic cancer. The incidence of pancreatic cancer is high in Japan as well as in the United States or Europe,[14] suggesting that the present conclusion may be applicable globally. Thirdly, since the cohort of the present study is obtained from the employees of general corporations and their family members, as well as all medical treatments received by insured individuals at all treatment facilities, the average age of the cohort may be younger than the average Japanese people. In 2020, the average age of the Japanese population is 48.9 years old, and the cohort of the present study has a similar age to the average Japanese population. Nevertheless, the present cohort may be lacking in very old people over the age of 80.

In conclusion, this is an additional and confirmatory study to show that MetS is linked to pancreatic cancer. Since the incidence and mortality rates of pancreatic cancer are the same, it is critical to prevent pancreatic cancer than to treat it.

#### Contributors

The followings are the role of each author to this study; Study conceptualization and design: MK, YH; Data curation, JK; Data formal analysis: YH, NK, KK, MY and TW; Project administration: HF, TH, SI, YY; Visualization: SI, YY; Figures and Tables: HF, YH; Writing and editing: MK.

All authors have read and approved the manuscript and the agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Yohei Miyashita, Naoki Kimoto and Masafumi Kitakaze have verified the underlying data of this study.

#### Data sharing statement

The data analyzed in this study are available from the corresponding author upon reasonable request, depending on the nature of the request.

#### Declaration of interests

Relationships to industry do not exist for YM, TH, HF, JK, NK, KK, YY, MY, and TW. SI reports grants from Japan Society for the Promotion of Science outside the submitted work. MK reports personal fees from Daiichi-sankyo, personal fees from Viatris, grants and personal fees from Ono, grants from Novartis, grants and personal fees from Tanabe-mitsubishi, grants from Takeda, grants and personal fees from Astra Zeneca, grants and personal fees from Boehringer-ingelheim, grants from Kowa, personal fees from Otsuka, personal fees from Eli Lilly outside the submitted work.

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