Impact of Body Mass Index on Obesity-Related Cancer and Cardiovascular Disease Mortality; The Japan Collaborative Cohort Study

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**Aim:** We aimed to examine the association of obesity-related cancer and cardiovascular disease (CVD) with body mass index (BMI) and the estimated population attributable fraction in lean Asians.

**Methods:** We studied 102,535 participants aged 40–79 years without histories of cancer or CVD at baseline between 1988 and 2009. The cause-specific hazard ratios (csHRs) of BMI categories (<18.5, 18.5–20.9, 21.0–22.9 [reference], 23.0–24.9, 25.0–27.4, and ≥27.5 kg/m²) were estimated for each endpoint. The events considered were mortalities from obesity-related cancer (esophageal, colorectal, liver, pancreatic, kidney, female breast, and endometrial cancer) and those from CVD (coronary heart disease and stroke). Population attributable fractions (PAFs) were calculated for these endpoints.

**Results:** During a 19.2-year median follow-up, 2906 died from obesity-related cancer and 4532 died from CVD. The multivariable-adjusted csHRs (95% confidence interval) of higher BMI categories (25–27.4 and ≥27.5 kg/m²) for obesity-related cancer mortality were 0.93 (0.78, 1.10) and 1.18 (0.92, 1.50) in men and 1.25 (1.04, 1.50) and 1.48 (1.19, 1.84) in women, respectively. The corresponding csHRs for CVD mortality were 1.27 (1.10, 1.46) and 1.59 (1.30, 1.95) in men and 1.10 (0.95, 1.28) and 1.44 (1.21, 1.72) in women, respectively. The PAF of a BMI ≥25 kg/m² for obesity-related cancer was −0.2% in men and 6.7% in women and that for CVD was 5.0% in men and 4.5% in women.

**Conclusion:** A BMI ≥25 kg/m² is associated with an increased risk of obesity-related cancer in women and CVD in both sexes.

**Key words:** Body mass index, Overweight, Obesity, Cancer, Cardiovascular disease

**Introduction**
Cardiovascular disease (CVD) and cancer are major causes of death in Japan¹. Recent studies have shown several shared risk factors between CVD and cancer². Obesity is a risk factor that increases the
mortality rate of CVD and some types of cancer referred to as obesity-related cancer3, 4).

The body mass index (BMI) is an easy and efficient tool for population-based estimates of the health risks related to obesity. An increased BMI is an established risk factor for CVD and obesity-related cancers death3, 4). Globally, CVD and cancer account for approximately 70% and 10%, respectively, of deaths due to a BMI ≥ 25 kg/m²5).

In Westerners, a BMI ≥ 25 kg/m² is associated with an increased risk of CVD mortality and obesity-related cancer mortality6, 7). However, in East Asians, a BMI ≥ 25 kg/m² is associated with an increased risk of CVD mortality9), but the BMI at which the risk of obesity-related cancer mortality increases is unclear. Colon and ≥ 60-year-old female breast cancer mortality is associated with an extremely high BMI (BMI ≥ 30 kg/m²) in Asians (mainly East Asia)8). In our previous study, colon cancer mortality was associated with a BMI ≥ 28 kg/m² in Japanese women9). In contrast, rectal cancer is associated with an increased mortality rate at a lower degree of increased BMI than that of colon cancer in Asians10). East Asians have a lower rate of obesity than Westerners. Therefore, the population impact of controlling obesity on CVD and obesity-related cancers needs to be estimated. Additionally, the detailed associations of obesity with these two outcomes in the Japanese population need to be described.

Aim

This study aimed to determine the associations of BMI with both CVD mortality and overall obesity-related cancer mortality and compare the magnitude of these associations in a large-scale nationally representative cohort of Japanese people. Additionally, we investigated the public health impact of BMI on the risk of CVD and obesity-related cancer mortality by calculating the population attributable fraction (PAF). Our findings could be used to inform public health strategies regarding the healthy weight for CVD and cancer, which are major causes of death in Japan. Obesity-related cancer was defined in accordance with the World Cancer Research Fund American Institute for Cancer Research (WCRF/AICR): esophageal adenocarcinoma, pancreatic cancer, liver cancer, colorectal cancer, kidney cancer, postmenopausal breast cancer, and endometrial cancer10).

Methods

Study Population

The Japan Collaborative Cohort (JACC) Study for Evaluation of Cancer Risks, which was sponsored by the Ministry of Education, Culture, Sports, Science and Technology, conducted a baseline survey from 1988 to 1990 in 45 areas throughout Japan. Participants (n = 110,585; 46,395 men and 64,190 women) aged 40–79 years completed self-administered questionnaires about their lifestyles and medical histories. The sampling methods used and other details of this survey have been described previously11-13). The participants were followed up until death or up to the end of 2009 for most areas (follow-up concluded at the end of 1999 for four areas, 2003 for four areas, and 2008 for two areas). Those who moved out were treated as censored cases because subsequent deaths could not be confirmed. Participants were excluded from the analysis if they had a medical history of cancer or CVD (n = 8050; 3429 men and 4621 women). Therefore, 102,535 participants (42,966 men and 59,569 women) were included in the present analysis.

The study design and informed consent procedure were approved by the ethics committees of the Hokkaido University School of Medicine and Nagoya University School of Medicine.

Definition of Variables

A self-administered questionnaire assessed weight, height, sociodemographic information, medical history, and health behavior. The BMI was calculated by dividing the self-reported weight in kg by the square of the self-reported height in m. The BMI was divided into six categories (underweight: < 18.5 kg/m², low normal: 18.5–20.9 kg/m², mid normal: 21.0–22.9 kg/m² [reference], high normal: 23.0–24.9 kg/m², low overweight: 25.0–27.4 kg/m², and high overweight or obesity: ≥ 27.5 kg/m²) according to the World Health Organization and Asia-Pacific classification14).

We adjusted for age (years), education level (attended school until 13, 13–15, 16–18, or > 19 years), area of residence (Hokkaido, Tohoku, Kanto, Chubu, Kinki, Chugoku, or Kyushu region), smoking status (current smoker of ≥ 20 cigarettes/day, < 20 cigarettes/day, past, or never), alcohol drinking (current drinker of ≥ 46.0 g/day ethanol, 23.0–45.9 g/day ethanol, < 23.0 g/day ethanol, past, or never) according to evidence in a previous study15), physical activity (walking ≥ 0.5 h/day or sport ≥ 5 h/week, walking < 0.5 h/day and sport < 5 h/week), history of liver disease (yes or no), history of blood transfusion.
(yes or no), menopause (yes or no), hormone replacement therapy in women (yes or no), age at menarche (<13, 13 to <15, 15 to <17, or ≥ 17 years), age at first delivery (no, <21, 21 to <26, 26 to <31, or ≥ 31 years), and parity number (0, 1, 2, or ≥ 3) as potential confounding factors. We also used a history of hypertension (yes or no) and a history of diabetes (yes or no) as potential mediation factors.

Outcomes and Mortality Surveillance

The outcomes were death from obesity-related cancer or CVD (coronary heart disease and stroke). Death from obesity-related cancer was defined as that from esophageal, colon, rectal, liver, pancreatic, kidney, female breast, or endometrial cancer reported by the WCRF/AICR as having convincing evidence of an association with obesity.10

The date and cause of death were confirmed by the official death certificates, with permission of the Director-General of the Prime Minister's Office. The cause-specific mortality was adjusted for the transition to the International Classification of Diseases (10th revision), and was determined for CVD (coronary heart disease [I20–I25] and stroke [I60–I69]) and obesity-related cancer (esophageal [C15], colon [C18], rectal [C19–C20], liver [C22], pancreatic [C25], breast [C50], endometrial [C54], and kidney [C64] cancer). We used esophageal cancer rather than esophageal adenocarcinoma, and breast cancer rather than postmenopausal breast cancer because they could not be identified from death certificates. Approximately two thirds (103/157) of breast cancer deaths were in women who were menopausal at baseline. The Hisayama Study reported that the concordance rate between causes of death in death certificates and those in autopsy reports was 0.92 for cancer mortality and 0.68 for cardiovascular mortality, respectively.16

Statistical Analysis

Any missing data for the above-mentioned variables and a history of cancer and CVD were imputed using multiple imputation in the Missing Values option of SPSS. This method generates 50 datasets with imputed missing values. The results from each dataset were combined by using Rubin's rule to pool parameter estimates.17

Sociodemographic characteristics, the medical history, and health behavior of the participants at baseline are summarized by the number and frequency (%) for each sex. Sex- and cause-specific mortality rates were calculated per 1000 person-years. Additionally, to evaluate the etiological effect of covariates, we applied a cause-specific Cox proportional hazard model.18 The model was stratified by sex because breast cancer was included in obesity-related cancer in women only. The multivariable-adjusted Cox model included age, education level, area of residence, smoking status, alcohol drinking, physical activity, a history of liver disease, and a history of blood transfusion. For women, the variables of age at menarche, age at first delivery, parity number, menopausal status, and hormone replacement therapy were added to the model. Further adjustment was performed for a history of hypertension and a history of diabetes to evaluate their mediation effects. A linear trend was tested by treating BMI as a continuous variable, which provided cause-specific hazard ratios (csHRs) by a 1 kg/m² increase in BMI.

We tested for a difference between pairs of Cox regression coefficients (i.e., csHRs) using the following formula: \((\text{csHR}_1 - \text{csHR}_2)/([\text{SE}(\text{csHR}_1)]^2 + [\text{SE}(\text{csHR}_2)]^2)^{1/2}\), where \(b_1\) is the coefficient for each BMI category for obesity-related cancer, \(b_2\) is the corresponding coefficient for CVD, \(\text{SE}(b_1)\) is the standard error of the variable for obesity-related cancer, and \(\text{SE}(b_2)\) is the corresponding standard error for CVD in the multivariable model.19 The test statistic was compared with a standard normal distribution to yield a \(P\) value for the difference.

Additionally, we performed stratified analyses according to age (40–64 and 65–79 years) because cancer mortality rate and CVD mortality rate differ by age group.19 In an attempt to avoid reverse causality, we also performed an analysis excluding participants with <5 years of follow-up (2876 men and 2500 women). Because some of the breast cancer and esophageal cancer cases included in obesity-related cancer defined in this analysis may not have been associated with obesity, we performed an analysis excluding breast cancer and esophageal cancer from the defined obesity-related cancer.

The PAF was used to estimate the public health impact of exposure in populations. The PAF was defined as the proportion of death in the population over a specified time that would have been prevented if exposure to the risk factor had been eliminated. In our analysis, the PAF for each specific cause of death was calculated using the following equation: \(\text{PAF} = P_d \left(\right.\frac{HR_a - 1}{HR_a}\left.\right)\), where \(P_d\) is the proportion of participants exposed among those who died of a particular cause of death, and HRa is the csHR in the multivariable-adjusted model for that cause of death.20 We also attempted an additional estimation of the PAF using the proportion of obese Japanese people reported in the 2019 National Health and Nutrition Survey21 (PAF2019). PAF2019 was defined as
During the median 19.2 (interquartile range, 11.6–21.0) years of follow-up, 2906 participants died from obesity-related cancer (total: 1606 men and 1300 women; esophageal cancer: 196 men and 30 women; pancreatic cancer: 311 men and 323 women; liver cancer: 560 men and 307 women; colon cancer: 275 men and 306 women; rectal cancer: 205 men and 120 women; kidney cancer: 57 men and 24 women; breast cancer: 157 women; endometrial cancer: 34 women) and 4532 died from CVD (total: 2369 men and 2163 women; coronary heart disease: 836 men and 650 women; stroke: 1533 men and 1513 women). We censored 16,396 (total: 9377 men and 7019 women) participants who died from death secondary to causes other than obesity-related cancer or CVD. We also censored 5930 participants because of being lost to follow-up.

All analyses were conducted using IBM SPSS ver.24 (IBM Corporation, Armonk, NY, USA). Two-tailed probability values of <0.05 were considered to indicate statistical significance.

### Results

During the median 19.2 (interquartile range, 11.6–21.0) years of follow-up, 2906 participants died from obesity-related cancer (total: 1606 men and 1300 women; esophageal cancer: 196 men and 30 women; pancreatic cancer: 311 men and 323 women; liver cancer: 560 men and 307 women; colon cancer: 275 men and 306 women; rectal cancer: 205 men and 120 women; kidney cancer: 57 men and 24 women; breast cancer: 157 women; endometrial cancer: 34 women) and 4532 died from CVD (total: 2369 men and 2163 women; coronary heart disease: 836 men and 650 women; stroke: 1533 men and 1513 women). We censored 16,396 (total: 9377 men and 7019 women) participants who died from death secondary to causes other than obesity-related cancer or CVD. We also censored 5930 participants because of being lost to follow-up.

Of the 110,585 participants, 61,631 (55.7%) had missing data. The percentage of missing values across 16 variables ranged from 1.3% to 26.5% (Supplementary Table 1).

Table 1 shows the baseline characteristics of the

### Table 1. Baseline characteristics of the study participants, 1988–1990, JACC Study

| Body mass index (kg/m²) | <18.5 | 18.5–20.9 | 21.0–22.9 | 23.0–24.9 | 25.0–27.4 | ≥27.5 | P value |
|-------------------------|-------|-----------|-----------|-----------|-----------|-------|--------|
| **Men**                 |       |           |           |           |           |       |        |
| Number of participants  | 2399  | 9987      | 12,223    | 10,299    | 5999      | 2060  |        |
| Age (years)             | 62.6 (10.4) | 58.3 (10.3) | 56.9 (10.2) | 55.8 (10.2) | 55.3 (10.3) | 54.7 (10.4) | <0.001 |
| College or higher education (%) | 365 (15.2) | 1638 (16.4) | 2115 (17.3) | 1870 (18.2) | 1121 (18.7) | 343 (16.6) | <0.001 |
| Current smoker (%)      | 1487 (61.9) | 6060 (60.7) | 6778 (55.5) | 5161 (50.1) | 2887 (48.1) | 934 (45.3) | <0.001 |
| Alcohol intake ≥ 46 g/day (%) | 204 (8.4) | 1047 (10.4) | 1346 (11.0) | 1206 (11.7) | 716 (11.9) | 266 (12.9) | <0.001 |
| Sports ≥ 5h/week or walking ≥ 30min/day (%) | 1600 (66.7) | 6696 (67.1) | 8026 (65.7) | 6558 (63.7) | 3658 (61.0) | 1180 (57.3) | 0.017 |
| History of hypertension (%) | 385 (16.1) | 1592 (16.0) | 2285 (18.7) | 2212 (21.5) | 1528 (25.5) | 594 (28.8) | <0.001 |
| History of diabetes mellitus (%) | 169 (7.0) | 631 (6.3) | 772 (6.3) | 664 (6.5) | 447 (7.5) | 163 (7.9) | 0.017 |
| History of liver disease (%) | 199 (8.3) | 779 (7.8) | 970 (7.9) | 767 (7.4) | 504 (8.4) | 190 (9.2) | 0.192 |
| History of blood transfusion (%) | 429 (17.9) | 1137 (11.4) | 1099 (9.0) | 819 (7.9) | 421 (7.0) | 154 (7.5) | <0.001 |
| **Women**               |       |           |           |           |           |       |        |
| Number of participants  | 3858  | 12,453    | 15,896    | 13,726    | 9188      | 4448  |        |
| Age (years)             | 61.0 (10.8) | 57.2 (10.5) | 56.8 (10.4) | 56.9 (10.5) | 57.6 (10.7) | 57.5 (10.5) | <0.001 |
| College or higher education (%) | 423 (11.0) | 1351 (10.8) | 1698 (10.7) | 1278 (9.3) | 820 (8.9) | 325 (7.3) | <0.001 |
| Current smoker (%)      | 293 (7.6) | 748 (6.0) | 812 (5.1) | 695 (5.1) | 479 (5.2) | 316 (7.1) | <0.001 |
| Alcohol intake ≥ 46 g/day (%) | 50 (1.3) | 152 (1.2) | 210 (1.3) | 202 (1.5) | 126 (1.4) | 75 (1.7) | 0.248 |
| Sports ≥ 5h/week or walking ≥ 30min/day (%) | 2569 (66.6) | 8520 (68.4) | 10,649 (67.0) | 8885 (64.7) | 5834 (63.5) | 2704 (60.8) | <0.001 |
| History of hypertension (%) | 562 (14.6) | 1895 (15.2) | 3078 (19.4) | 3253 (23.7) | 2762 (30.1) | 1720 (38.7) | <0.001 |
| History of diabetes mellitus (%) | 139 (3.6) | 399 (3.2) | 609 (3.8) | 529 (3.9) | 406 (4.4) | 279 (6.3) | <0.001 |
| History of liver disease (%) | 203 (5.3) | 627 (5.0) | 802 (5.0) | 735 (5.4) | 531 (5.8) | 281 (6.3) | 0.010 |
| History of blood transfusion (%) | 516 (13.4) | 1319 (10.6) | 1565 (9.8) | 1413 (10.3) | 902 (9.8) | 467 (10.5) | <0.001 |
| Menopause (%)           | 2678 (69.4) | 7922 (63.6) | 10,318 (64.9) | 9111 (66.4) | 6292 (68.5) | 3069 (69.0) | <0.001 |
| Hormone replacement therapy (%) | 188 (4.9) | 559 (4.5) | 742 (4.7) | 623 (4.5) | 431 (4.7) | 241 (5.4) | 0.378 |
| No history of parity (%) | 219 (5.7) | 487 (3.9) | 559 (3.5) | 480 (3.5) | 307 (3.3) | 169 (3.8) | <0.001 |
| Age ≥ 31 years at first delivery (%) | 384 (9.9) | 1019 (8.2) | 1168 (7.3) | 1026 (7.5) | 723 (7.9) | 402 (9.0) | 0.623 |
| Age <13 years at menarche (%) | 154 (4.0) | 672 (5.4) | 944 (5.9) | 914 (6.7) | 633 (6.9) | 351 (7.9) | <0.001 |

Data are expressed as the mean (standard deviation) for continuous variables and as numbers (%) for categorical variables.
study participants according to BMI categories. Men with a lower BMI tended to be older, and were more likely to be current smokers and have a history of transfusion. Men and women with a higher BMI were more likely to have hypertension and tended to be engaged in lower physical activity.

CVD mortality rates (3.44/1000 person-years in men and 2.17/1000 in women) were higher than obesity-related cancer mortality rates (2.33/1000 person-years in men and 1.31/1000 in women).

A BMI ≥ 27.5 kg/m² was associated with increased multivariable-adjusted csHRs of CVD mortality in men (Table 2). The csHR of BMI ≥ 27.5 kg/m² with obesity-related cancer mortality in men was also higher than 1, but this was not significant. However, a positive association between a BMI ≥ 27.5 kg/m² and obesity-related cancer was found when the analysis was restricted to men aged 40–64 years (Supplementary Tables 2 and 3). The positive association of a BMI ≥ 25.0 kg/m² with CVD mortality and obesity-related cancer mortality in women (Table 3). The csHRs of BMI ≥ 25.0 kg/m² with CVD mortality was not significantly different from those of BMI ≥ 25.0 kg/m² with obesity-related cancer mortality in women. There was a positive linear trend (multivariable-adjusted csHRs for a 1 kg/m² increase in BMI) between BMI and obesity-related cancer mortality in women. A BMI ≥ 18.5 kg/m² was associated with an increased multivariable-adjusted csHR of mortality from CVD in both sexes. In contrast, a BMI ≥ 18.5 kg/m² tended to be associated with an increased multivariable-adjusted csHR of mortality from obesity-related cancer only in men. Further adjustment for possible mediating factors, such as hypertension or diabetes, attenuated the association of a higher BMI with CVD, but did little to change the association of a higher BMI with obesity-related cancer in both sexes.

Stratifying the analyses by age did not change the results, except for obesity-related cancer in men (Supplementary Tables 2, 3, 4 and 5). Results of a secondary analysis that excluded participants with <5 years of follow-up were essentially the same (Supplementary Tables 6 and 7). There were no

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**Table 2. Comparison of cause-specific hazard ratios for death from obesity-related cancer and cardiovascular disease in men, 1988–2009, JACC study**

| Body mass index (kg/m²) | <18.5 | 18.5–20.9 | 21.0–22.9 | 23.0–24.9 | 25.0–27.4 | ≥ 27.5 | per 1 kg/m² |
|-------------------------|-------|-----------|-----------|-----------|-----------|--------|------------|
| Number of participants  | 2399  | 9987      | 12,223    | 10,299    | 5999      | 2060   |
| Person-years            | 32,152| 154,933   | 197,613   | 169,787   | 99,073    | 34,338 |
| Obesity-related cancer<sup>a</sup> | | | | | |
| Number of deaths       | 110   | 409       | 455       | 358       | 192       | 81     |
| Crude mortality rate (per 1000 person-years) | 3.43  | 2.64      | 2.30      | 2.11      | 1.94      | 2.36   |
| csHR                   | 1.11  | 1.04      | 1.00      | 0.98      | 0.93      | 1.18   |
| (95% CI)               | (0.89–1.39) | (0.91–1.20) | (0.85–1.13) | (0.78–1.10) | (0.92–1.50) | (0.977–1.012) |
| +histories of           |       |           |           |           |           |        |
| hypertension and diabetes | (0.93–1.21) | (0.93–1.21) | (0.85–1.13) | (0.77–1.10) | (0.91–1.49) | (0.975–1.111) |
| Cardiovascular disease<sup>c</sup> | | | | | |
| Number of deaths       | 207   | 617       | 614       | 473       | 326       | 132    |
| Crude mortality rate (per 1000 person-years) | 6.44  | 3.98      | 3.11      | 2.78      | 3.29      | 3.84   |
| csHR                   | 1.28  | 1.11      | 1.00      | 1.02      | 1.27      | 1.59   |
| (95% CI)               | (1.08–1.52) | (0.99–1.24) | (0.90–1.15) | (1.10–1.46) | (1.30–1.95) | (0.996–1.021) |
| +histories of           |       |           |           |           |           |        |
| hypertension and diabetes | (1.15–1.62) | (1.02–1.29) | (0.88–1.13) | (1.04–1.39) | (1.20–1.80) | (0.984–1.013) |
| P value for difference<sup>d</sup> | 0.330 | 0.526     | –         | 0.696     | 0.006     | 0.065  |

<sup>a</sup>Obesity-related cancer included esophageal, colon, rectal, liver, pancreatic, and kidney cancer.

<sup>b</sup>The multivariable adjusted model was adjusted using the following variables: age, education level, area of residence, smoking status, alcohol drinking, physical activity, and histories of liver disease and blood transfusion.

<sup>c</sup>Cardiovascular disease included coronary heart disease and stroke.

<sup>d</sup>P value for the difference associated with the null hypothesis that the risk factor variable of interest has the same association with obesity-related cancer and cardiovascular disease in the multivariable model.
In contrast, obesity-related cancer mortality was associated with a high normal weight and heavier only in women. A BMI of $\geq 27.5$ kg/m$^2$ was significantly positively associated with obesity-related cancer in men aged 40–64 years at baseline.

Positive associations between obesity-related cancer mortality and a BMI $\geq 25.0$ kg/m$^2$ and a BMI as a continuous variable were found in women, but not in men, in this study. A previous study showed that most deaths from obesity-related cancer were associated with a BMI $\geq 25$ kg/m$^2$ and a BMI as a continuous variable in men and women in the American population$^7$. There are several possible explanations for the sex difference in the association of BMI with mortality. First, in this study, men had higher CVD risk factors than women, which might have weakened the association of BMI with obesity-related cancer mortality as a result of mortality from CVD occurring before mortality from obesity-related cancer. Second, few older men in this study were high overweight or obese. A larger study is required for more accurate point estimates. Third, the distribution of BMI in the present sample might have been skewed toward lower values. A total of 19% of male participants and 23% female participants had a BMI

significant changes in the association of BMI with obesity-related cancer when esophageal and breast cancers were excluded from the definition of obesity-related cancer (Supplementary Tables 8 and 9).

The PAFs according to BMI categories for obesity-related cancer are shown in Fig. 1 and those for CVD are shown in Fig. 2. A total of 7% of obesity-related cancer mortality was significantly attributable to a BMI $\geq 25.0$ kg/m$^2$ in women. In both sexes, a significant portion of CVD mortality was attributable to a BMI $\geq 27.5$ kg/m$^2$ and a BMI $< 18.5$ kg/m$^2$. The PAF$_{2019}$ of overweight or obesity relative to a normal weight was $-0.7\%$ for obesity-related cancer and $9.3\%$ for CVD in men, and $5.1\%$ for obesity-related cancer and $5.1\%$ for CVD in women.

**Discussion**

This study investigated whether the association of BMI with CVD differed from that with obesity-related cancer in a large-scale community-based cohort of Japanese men and women. We found that CVD mortality was associated with overweight and obesity in men and high overweight and obesity in women. In contrast, obesity-related cancer mortality was associated with a high normal weight and heavier only in women. A BMI of $\geq 27.5$ kg/m$^2$ was significantly positively associated with obesity-related cancer in men aged 40–64 years at baseline.

Positive associations between obesity-related cancer mortality and a BMI $\geq 25.0$ kg/m$^2$ and a BMI as a continuous variable were found in women, but not in men, in this study. In contrast, a previous study showed that most deaths from obesity-related cancer were associated with a BMI $\geq 25$ kg/m$^2$ and a BMI as a continuous variable in men and women in the American population$^7$. There are several possible explanations for the sex difference in the association of BMI with mortality. First, in this study, men had higher CVD risk factors than women, which might have weakened the association of BMI with obesity-related cancer mortality as a result of mortality from CVD occurring before mortality from obesity-related cancer. Second, few older men in this study were high overweight or obese. A larger study is required for more accurate point estimates. Third, the distribution of BMI in the present sample might have been skewed toward lower values. A total of 19% of male participants and 23% female participants had a BMI

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**Table 3. Comparison of cause-specific hazard ratios for death from obesity-related cancer and cardiovascular disease in women, 1988–2009, JACC study**

| Body mass index (kg/m$^2$) | <18.5 | 18.5–20.9 | 21.0–22.9 | 23.0–24.9 | 25.0–27.4 | $\geq$ 27.5 | per 1 kg/m$^2$ |
|----------------------------|-------|-----------|-----------|-----------|-----------|-------------|----------------|
| Number of participants     | 3858  | 12,453    | 15,896    | 13,726    | 9188      | 4448        |                |
| Person-years               | 58,432| 206,379   | 268,818   | 232,324   | 154,971   | 74,334      |                |
| Obesity-related cancer$^a$ |       |           |           |           |           |             |                |
| Number of deaths           | 77    | 258       | 301       | 307       | 225       | 132         |                |
| Crude mortality rate (per 1000 person-years) | 1.32 | 1.25 | 1.12 | 1.32 | 1.45 | 1.77 |                |
| csHR                      | 0.94  | 1.08      | 1.00      | 1.17      | 1.25      | 1.48        | 1.011          |
| (95% CI)                   | (0.71–1.23) | (0.91–1.29) | (Reference) | (0.99–1.39) | (1.04–1.50) | (1.19–1.84) | (1.003–1.019) |
| +histories of hypertension and diabetes | 0.94 | 1.09 | 1.00 | 1.17 | 1.24 | 1.46 | 1.010          |
| Cardiovascular disease$^c$ |       |           |           |           |           |             |                |
| Number of deaths           | 253   | 441       | 508       | 409       | 333       | 218         |                |
| Crude mortality rate (per 1000 person-years) | 4.33 | 2.14 | 1.89 | 1.76 | 2.15 | 2.94 |                |
| csHR                      | 1.46  | 1.03      | 1.00      | 0.95      | 1.10      | 1.44        | 1.001          |
| (95% CI)                   | (1.24–1.73) | (0.89–1.18) | (Reference) | (0.82–1.09) | (0.95–1.28) | (1.21–1.72) | (0.989–1.013) |
| +histories of hypertension and diabetes | 1.59 | 1.07 | 1.00 | 0.92 | 1.04 | 1.29 | 0.988          |
| $P$ value for difference$^d$ | 0.006 | 0.638 | – | 0.058 | 0.300 | 0.849 |                |

$^a$ Obesity-related cancer included esophageal, colon, rectal, liver, pancreatic, breast, endometrial, and kidney cancer.

$^b$ The multivariable adjusted model was adjusted using the following variables: age, education level, area of residence, smoking status, alcohol drinking, physical activity, histories of liver disease and blood transfusion, menopausal status, hormone replacement therapy, age at menarche, age at first delivery, and parity number.

$^c$ Cardiovascular disease included coronary heart disease and stroke.

$^d$ $P$ value for the difference associated with the null hypothesis that the risk factor variable of interest has the same association with obesity-related cancer and cardiovascular disease in the multivariable model.

csHR, cause-specific hazard ratio; CI, confidence interval.
cancer, and ≥ 60-year-old female breast cancer in Asians). In this study, in the lowest BMI category, the percentage of obesity-related cancer mortality that was due to rectal, colon, and ≥ 60-year-old female breast cancer was 24% (26/110) in men and 42% (32/77) in women. This finding might partly account for the different association between men and women.

There are several definitions of obesity-related cancer. The WCRF/AICR and the International Agency for Research on Cancer have reported established obesity-related cancers. Fewer types of obesity-related cancer have been established in the Japanese population (convincing: liver, colorectal, and postmenopausal breast cancer; probable:

![Fig. 1.](image1) Population attributable fraction for obesity-related cancer mortality according to body mass index, 1988–2009, JACC study. Population attributable fractions are shown in parentheses. *P < 0.05.

![Fig. 2.](image2) Population attributable fraction for cardiovascular disease mortality according to body mass index, 1988–2009, JACC study. Population attributable fractions are shown in parentheses. *P < 0.05.
suggest that cancer mortality. However, our findings of obesity-related cancer may have distorted the association between BMI and obesity-related endometrial cancer. As a result, our definition of obesity-related cancer instead of postmenopausal breast cancer and esophageal adenocarcinoma. As a result, our definition of obesity-related cancer may have distorted the association between BMI and obesity-related cancer mortality. However, our findings (Supplementary Tables 8 and 9) suggest that including esophageal and breast cancers in the definition of obesity-related cancer did not change the association between obesity-related cancer and BMI.

In this study, an increased and decreased BMI were associated with CVD mortality. The lowest CVD mortality rate was observed when the BMI was 21.0–24.9 kg/m² in men and women. This finding is broadly consistent with that of a pooled analysis of seven large-scale cohort studies in Japan, which showed an optimal BMI of 21.0–27.0 kg/m². This finding could be important for the development of public health policy related to a healthy weight. The association between an increased BMI and CVD mortality found in the present study has also been reported in Japanese and Western populations. However, the association between a decreased BMI and CVD mortality is not evident in the Western population. Our previous study showed that a decreased BMI was more strongly associated with stroke than with coronary heart disease. The Japanese population has a higher hemorrhagic stroke mortality rate than that in the Western population, which might explain the association of decreased BMI with CVD mortality. However, the mortality rate of CVD in Koreans, whose hemorrhagic stroke mortality rate is as high as that in Japanese, is lower with a lower BMI, which is inconsistent with our study.

In this study, adjustment for a history of hypertension and diabetes appeared to weaken the association of BMI with CVD, but not for obesity-related cancer. We speculate that the association of BMI with obesity-related cancer is not likely to be mediated by hypertension and diabetes compared with the association between BMI and CVD. Hypertension is strongly associated with CVD mortality. However, the association between hypertension and mortality from sites other than the kidney in cancer is unclear, which could explain the difference in the mediating effects.

The attributable burden of a higher BMI on obesity-related cancer was considered low, but significant in women. This result is compatible with a previous report that the PAF for the incidence of obesity-related cancer (esophageal adenocarcinoma, and colon, rectal, pancreatic, kidney, breast [postmenopausal], and endometrial cancer) was lower in East Asia compared with that in Europe and America. The attributable burden of a higher BMI on CVD is also smaller than that of a higher BMI on CVD in the American population. The attributable burden of a lower BMI for CVD was similar to that of a higher BMI in both sexes in this study. The attributable burden of a lower BMI for obesity-related cancer was also similar to that of a higher BMI for obesity-related cancer in men in this study. These results suggest the need for public health measures of CVD mortality and obesity-related cancer mortality in people with a lower BMI in Japan, where many people have a low normal weight or an underweight BMI. However, the PAF in data in our study suggest that obesity control should be a priority because the obesity rate in Japan has increased since the baseline time of this study.

There are several limitations to the present study. First, the association of a low BMI at baseline with CVD and obesity-related cancer may have been confounded by health problems or disease processes (e.g., smoking or an underlying disease that affected food intake or body weight). However, a sensitivity analysis excluding the early occurrence of outcomes and dropouts did not change the results. Second, weight and height were self-reported and were not validated by actual measurements in the present study. However, a previous validation study in a Japanese population showed that self-reported weight and height were strongly correlated with measured weight and height. Third, the baseline data were obtained at one time point only. Changes in body weight simultaneously affect changes in CVD risk and individual CVD risk factors. Changes in BMI or confounding factors over the follow-up period might have distorted associations. Fourth, we estimated cause-specific Cox models for each death and treated all other deaths as censoring events by assuming that censoring events were non-informative. Therefore, we assumed that CVD mortality and obesity-related cancer mortality occurred independently. However, patients with cancer are at a higher risk for CVD death, which might violate the independence assumption. Fifth, we used the mortality rate rather than the incidence rate. The ratio of the mortality rate to the incidence rate varies depending on the type of cancer. The ratios for colorectal, kidney, breast, and endometrial cancer are lower than those for esophageal, pancreatic, and liver cancer in Japan.
which might have distorted the association of BMI with obesity-related cancer mortality. Finally, there was a missing value rate of 15%. Some variables, such as smoking status and alcohol intake, might be missing not at random (e.g., heavy smokers were less likely to report their smoking status). Nevertheless, we assumed a missing at random mechanism and applied multiple imputations to deal with the missing data. However, there was no substantial difference in the results between complete case analysis (data not shown) and multiple imputation analysis.

**Conclusion**

Female overweight and obesity are associated with obesity-related cancer mortality and CVD mortality. However, male overweight and obesity are not associated with CVD mortality. The burden of obesity-related cancer is greater with a higher BMI in women. The burden of CVD is greater at higher and lower BMIs in both sexes. Our findings could be helpful for designing preventive strategies for CVD and obesity-related cancer from the viewpoint of obesity control in the Japanese population.

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**Conflict of Interest**

The authors declare no conflicts of interest associated with this manuscript.

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Supplementary Table 1. Number of all participants with missing values for body mass index and other variables at baseline, 1988-1990, JACC Study

| No question item in the questionnaire | Men \((n=46,395)\) | Women \((n=64,190)\) | Total \((n=110,585)\) | Menopausal status was assessed by self-reported age at menopause or the reason for menopause. No answer provided was treated as not having menopause. |
|--------------------------------------|-----------------|-----------------|-----------------|-------------------------------------------------|
| Body mass index                      | 2455 (5.3)      | 4149 (6.7)      | 6604 (6.0)      | 528 (0.5)                                        |
| History of cancer                    | 9669 (20.8)     | 13,866 (22.6)   | 23,535 (21.3)   | 5750 (5.2)                                       |
| History of cardiovascular disease    | 5994 (12.9)     | 8667 (14.1)     | 14,661 (13.3)   | –                                               |
| Education level                      | 12,716 (27.4)   | 16,590 (27.0)   | 29,306 (26.5)   | 22,379 (20.2)                                    |
| Smoking status                       | 2256 (4.9)      | 8704 (14.2)     | 10,960 (9.9)    | –                                               |
| Alcohol intake                       | 9558 (20.6)     | 12,736 (20.7)   | 22,294 (20.2)   | 6934 (6.3)                                       |
| Physical activity                    | 7799 (16.8)     | 10,465 (17.0)   | 18,264 (16.5)   | 15,128 (13.7)                                    |
| History of hypertension              | 4929 (10.6)     | 6877 (11.2)     | 11,806 (10.7)   | –                                               |
| History of diabetes mellitus         | 5885 (12.7)     | 8619 (14.0)     | 14,504 (13.1)   | –                                               |
| History of liver disease             | 9769 (21.1)     | 13,524 (22.0)   | 22,293 (21.1)   | 10,031 (9.1)                                    |
| History of blood transfusion         | 7966 (17.2)     | 11,055 (18.0)   | 19,021 (17.2)   | 5590 (5.1)                                       |
| Menopause                            | –               | 831 (1.3)       | –               | 831 (1.3)                                        |
| Hormone replacement therapy          | –               | 15,938 (24.8)   | –               | 8395 (13.1)                                      |
| Parity number                        | –               | 7217 (11.2)     | –               | 831 (1.3)                                        |
| Age at first delivery                | –               | 8960 (14.0)     | –               | 3393 (5.3)                                       |
| Age at menarche                      | –               | 6249 (9.7)      | –               | 831 (1.3)                                        |

Data are expressed as numbers (%).

Supplementary Table 2. Comparison of cause-specific hazard ratios for death from obesity-related cancer and cardiovascular disease in men aged 40–64 years, 1988–2009, JACC study

| Body mass index (kg/m²) | < 18.5 | 18.5–20.9 | 21.0–22.9 | 23.0–24.9 | 25.0–27.4 | ≥ 27.5 | per 1 kg/m² |
|-------------------------|--------|-----------|-----------|-----------|-----------|--------|-------------|
| Number of participants  | 1294   | 7994      | 9367      | 8293      | 4929      | 1724   |             |
| Person-years            | 20,395 | 119,650   | 161,191   | 143,778   | 85,070    | 29,949 |             |
| Obesity-related cancer  |        |           |           |           |           |        |             |
| Number of deaths        | 53     | 246       | 296       | 254       | 148       | 67     |             |
| Crude mortality rate (per 1000 person-years) | 2.58 | 2.06 | 1.84 | 1.77 | 1.74 | 2.22 |             |
| csHR  Multivariable adjustedb | 1.17 | 1.04 | 1.00 | 1.02 | 1.04 | 1.37 | 1.012 |
| (95% CI)                | (0.86–1.60) | (0.88–1.24) | [Reference] | (0.86–1.21) | (0.85–1.27) | (1.04–1.80) | (0.989–1.036) |
| +histories of hypertension and diabetes | 1.18 | 1.04 | 1.00 | 1.02 | 1.03 | 1.36 | 1.011 |
| Cardiovascular diseasec |        |           |           |           |           |        |             |
| Number of deaths        | 63     | 245       | 271       | 242       | 179       | 76     |             |
| Crude mortality rate (per 1000 person-years) | 3.09 | 2.05 | 1.68 | 1.68 | 2.10 | 2.54 |             |
| csHR  Multivariable adjustedb | 1.51 | 1.13 | 1.00 | 1.09 | 1.42 | 1.82 | 1.030 |
| (95% CI)                | (1.13–2.02) | (0.94–1.35) | [Reference] | (0.91–1.31) | (1.17–1.74) | (1.39–2.37) | (1.004–1.056) |
| +histories of hypertension and diabetes | 1.57 | 1.16 | 1.00 | 1.05 | 1.31 | 1.62 | 1.014 |
| P value for differenced | 0.250  | 0.550    | –         | 0.586    | 0.028    | 0.150  |             |

a Obesity-related cancer included esophageal, colon, rectal, liver, pancreatic, and kidney cancer.
b The multivariable adjusted model was adjusted using the following variables: age, education level, area of residence, smoking status, alcohol drinking, physical activity, and histories of liver disease and blood transfusion.
c Cardiovascular disease included coronary heart disease and stroke.
d P value for the difference associated with the null hypothesis that the risk factor variable of interest has the same association with obesity-related cancer and cardiovascular disease in the multivariable model.
csHR, cause-specific hazard ratio; CI, confidence interval.
### Supplementary Table 3. Comparison of cause-specific hazard ratios for death from obesity-related cancer and cardiovascular disease in men aged 65–79 years, 1988–2009, JACC study

| Body mass index (kg/m²) | <18.5 | 18.5–20.9 | 21.0–22.9 | 23.0–24.9 | 25.0–27.4 | ≥ 27.5 | per 1 kg/m² |
|----------------------|-------|-----------|-----------|-----------|-----------|--------|-------------|
| Number of participants | 1105  | 2893      | 2855      | 2005      | 1070      | 336    |
| Person-years         | 11,755| 35,283    | 36,424    | 26,007    | 14,001    | 4389   |
| Obesity-related cancer<sup>a</sup> |       |           |           |           |           |        |
| Number of deaths     | 58    | 162       | 159       | 104       | 45        | 15     |
| Crude mortality rate (per 1000 person-years) | 4.92  | 4.60      | 4.37      | 3.99      | 3.18      | 3.33   |
| csHR                 | 1.08  | 1.04      | 1.00      | 0.92      | 0.71      | 0.76   |
| (95% CI)             | (0.78–1.49) | (0.83–1.31) | (0.71–1.20) | (0.50–1.02) | (0.43–1.34) | (0.930–0.994) |
| +histories of hypertension and diabetes | 1.10  | 1.05      | 1.00      | 0.92      | 0.71      | 0.74   |
| (0.79–1.52) | (0.84–1.33) | [Reference] | (0.71–1.20) | (0.49–1.01) | (0.42–1.32) | (0.926–0.991) |
| Cardiovascular disease<sup>c</sup> |       |           |           |           |           |        |
| Number of deaths     | 144   | 372       | 343       | 231       | 147       | 56     |
| Crude mortality rate (per 1000 person-years) | 12.27 | 10.53     | 9.42      | 8.87      | 10.49     | 12.75  |
| csHR                 | 1.18  | 1.09      | 1.00      | 0.97      | 1.13      | 1.39   |
| (95% CI)             | (0.95–1.45) | (0.93–1.27) | (0.81–1.15) | (0.92–1.39) | (1.02–1.90) | (0.978–1.016) |
| +histories of hypertension and diabetes | 1.26  | 1.13      | 1.00      | 0.95      | 1.09      | 1.32   |
| (1.02–1.55) | (0.97–1.32) | [Reference] | (0.80–1.14) | (0.97–1.80) | (0.967–1.008) |
| P value for difference<sup>d</sup> | 0.662 | 0.761     | –         | 0.786     | 0.027     | 0.068  |

<sup>a</sup> Obesity-related cancer included esophageal, colon, rectal, liver, pancreatic, and kidney cancer.

<sup>b</sup> The multivariable adjusted model was adjusted using the following variables: age, education level, area of residence, smoking status, alcohol drinking, physical activity, and histories of liver disease and blood transfusion.

<sup>c</sup> Cardiovascular disease included coronary heart disease and stroke.

<sup>d</sup> P value for the difference associated with the null hypothesis that the risk factor variable of interest has the same association with obesity-related cancer and cardiovascular disease in the multivariable model.

### Supplementary Table 4. Comparison of cause-specific hazard ratios for death from obesity-related cancer and cardiovascular disease in women aged 40–64 years, 1988–2009, JACC study

| Body mass index (kg/m²) | <18.5 | 18.5–20.9 | 21.0–22.9 | 23.0–24.9 | 25.0–27.4 | ≥ 27.5 | per 1 kg/m² |
|----------------------|-------|-----------|-----------|-----------|-----------|--------|-------------|
| Number of participants | 2230  | 9076      | 12,065    | 10,648    | 6957      | 3348   |
| Person-years         | 37,603| 159,601   | 213,847   | 187,466   | 122,838   | 58,486 |
| Obesity-related cancer<sup>a</sup> |       |           |           |           |           |        |
| Number of deaths     | 34    | 136       | 176       | 194       | 128       | 74     |
| Crude mortality rate (per 1000 person-years) | 0.90  | 0.85      | 0.82      | 1.03      | 1.04      | 1.27   |
| csHR                 | 1.03  | 1.04      | 1.00      | 1.22      | 1.17      | 1.40   |
| (95% CI)             | (0.70–1.51) | (0.83–1.31) | (0.98–1.50) | (0.92–1.48) | (1.05–1.86) | (0.998–1.020) |
| +histories of hypertension and diabetes | 1.04  | 1.05      | 1.00      | 1.21      | 1.16      | 1.37   |
| (0.70–1.53) | (0.83–1.32) | [Reference] | (0.98–1.50) | (0.92–1.47) | (1.03–1.82) | (0.997–1.020) |
| Cardiovascular disease<sup>c</sup> |       |           |           |           |           |        |
| Number of deaths     | 65    | 118       | 156       | 139       | 108       | 76     |
| Crude mortality rate (per 1000 person-years) | 1.73  | 0.74      | 0.73      | 0.74      | 0.88      | 1.30   |
| csHR                 | 2.09  | 1.02      | 1.00      | 0.97      | 1.09      | 1.58   |
| (95% CI)             | (1.54–2.84) | (0.79–1.31) | (0.77–1.23) | (0.84–1.42) | (1.18–2.11) | (0.976–1.023) |
| +histories of hypertension and diabetes | 2.31  | 1.07      | 1.00      | 0.93      | 1.00      | 1.30   |
| (1.70–3.14) | (0.83–1.37) | [Reference] | (0.74–1.18) | (0.77–1.30) | (0.97–1.75) | (0.951–1.003) |
| P value for difference<sup>d</sup> | 0.662 | 0.761     | –         | 0.786     | 0.027     | 0.068  |

<sup>a</sup> Obesity-related cancer included esophageal, colon, rectal, liver, pancreatic, breast, endometrial, and kidney cancer.

<sup>b</sup> The multivariable adjusted model was adjusted using the following variables: age, education level, area of residence, smoking status, alcohol drinking, physical activity, histories of liver disease and blood transfusion, menopausal status, hormone replacement therapy, age at menarche, age at first delivery, and parity number.

<sup>c</sup> Cardiovascular disease included coronary heart disease and stroke.

<sup>d</sup> P value for the difference associated with the null hypothesis that the risk factor variable of interest has the same association with obesity-related cancer and cardiovascular disease in the multivariable model.

csHR, cause-specific hazard ratio; CI, confidence interval.
### Supplementary Table 5. Comparison of cause-specific hazard ratios for death from obesity-related cancer and cardiovascular disease in women aged 65–79 years, 1988–2009, JACC study

| Body mass index (kg/m²) | <18.5 | 18.5–20.9 | 21.0–22.9 | 23.0–24.9 | 25.0–27.4 | ≥ 27.5 | per 1 kg/m² |
|------------------------|-------|-----------|-----------|-----------|-----------|--------|-------------|
| Number of participants | 1628  | 3378      | 3831      | 3078      | 2231      | 1099   |             |
| Person-years           | 20,829| 46,778    | 54,971    | 44,858    | 32,133    | 15,847 |             |
| Obesity-related cancer |       |           |           |           |           |        |             |
| Number of deaths       | 44    | 122       | 125       | 113       | 98        | 58     |             |
| Crude mortality rate (per 1000 person-years) | 2.09 | 2.61 | 2.28 | 2.53 | 3.04 | 3.65 | |
| csHR                   | 0.88  | 1.13      | 1.00      | 1.09      | 1.35      | 1.58   | (0.60–1.30) |
| (95% CI)               |       | (0.86–1.49) | [Reference] | (0.83–1.44) | (1.01–1.81) | (1.13–2.22) | (1.002–1.028) |
| +histories of          | 0.89  | 1.14      | 1.00      | 1.08      | 1.35      | 1.58   | (0.60–1.30) |
| hypertension and diabetes |       | (0.86–1.50) | [Reference] | (0.83–1.44) | (1.01–1.81) | (1.12–2.21) | (1.002–1.028) |
| Cardiovascular disease |       |           |           |           |           |        |             |
| Number of deaths       | 188   | 324       | 352       | 271       | 225       | 142    |             |
| Crude mortality rate (per 1000 person-years) | 9.02 | 6.92 | 6.40 | 6.04 | 7.00 | 8.96 | |
| csHR                   | 1.32  | 1.02      | 1.00      | 0.94      | 1.12      | 1.38   | (1.08–1.61) |
| (95% CI)               |       | (0.86–1.20) | [Reference] | (0.78–1.12) | (0.93–1.34) | (1.11–1.72) | (0.988–1.016) |
| +histories of          | 1.41  | 1.06      | 1.00      | 0.92      | 1.07      | 1.27   | (1.15–1.73) |
| hypertension and diabetes |       | (0.89–1.25) | [Reference] | (0.77–1.10) | (0.89–1.29) | (1.02–1.58) | (0.976–1.010) |
| P value for difference | 0.072 | 0.510     | –         | 0.360     | 0.275     | 0.519  |             |
| aObesity-related cancer included esophageal, colon, rectal, liver, pancreatic, breast, endometrial, and kidney cancer. | | | | | | | |
| bThe multivariable adjusted model was adjusted using the following variables: age, education level, area of residence, smoking status, alcohol drinking, physical activity, histories of liver disease and blood transfusion, menopausal status, hormone replacement therapy, age at menarche, age at first delivery, and parity number. | | | | | | | |
| cCardiovascular disease included coronary heart disease and stroke. | | | | | | | |
| dP value for the difference associated with the null hypothesis that the risk factor variable of interest has the same association with obesity-related cancer and cardiovascular disease in the multivariable model. | | | | | | | |
| csHR, cause-specific hazard ratio; CI, confidence interval. | | | | | | | |

### Supplementary Table 6. Comparison of cause-specific hazard ratios for death from obesity-related cancer and cardiovascular disease in men excluding participants with less than 5 years of follow-up, 1988–2009, JACC study

| Body mass index (kg/m²) | <18.5 | 18.5–20.9 | 21.0–22.9 | 23.0–24.9 | 25.0–27.4 | ≥ 27.5 | per 1 kg/m² |
|------------------------|-------|-----------|-----------|-----------|-----------|--------|-------------|
| Number of participants | 2081  | 9224      | 11,460    | 9692      | 5676      | 1958   |             |
| Person-years           | 31,333| 152,852   | 195,532   | 168,132   | 98,213    | 34,058 |             |
| Obesity-related cancer |       |           |           |           |           |        |             |
| Number of deaths       | 84    | 330       | 371       | 304       | 160       | 74     |             |
| Crude mortality rate (per 1000 person-years) | 2.16 | 1.90 | 1.90 | 1.81 | 1.63 | 2.17 | |
| csHR                   | 1.14  | 1.06      | 1.00      | 1.01      | 0.93      | 1.29   | (0.88–1.47) |
| (95% CI)               |       | (0.93–1.23) | [Reference] | (0.86–1.18) | (0.77–1.13) | (1.00–1.68) | (0.979–1.018) |
| +histories of          | 1.15  | 1.06      | 1.00      | 1.01      | 0.92      | 1.28   | (0.89–1.48) |
| hypertension and diabetes |       | (0.91–1.24) | [Reference] | (0.86–1.18) | (0.76–1.12) | (0.99–1.66) | (0.977–1.017) |
| Cardiovascular disease |       |           |           |           |           |        |             |
| Number of deaths       | 162   | 533       | 524       | 409       | 291       | 115    |             |
| Crude mortality rate (per 1000 person-years) | 5.18 | 3.49 | 2.68 | 2.43 | 2.96 | 3.38 | |
| csHR                   | 1.24  | 1.13      | 1.00      | 1.03      | 1.32      | 1.61   | (1.03–1.30) |
| (95% CI)               |       | (1.00–1.29) | [Reference] | (0.90–1.18) | (1.13–1.53) | (1.30–2.00) | (0.998–1.023) |
| +histories of          | 1.32  | 1.17      | 1.00      | 1.01      | 1.25      | 1.49   | (1.09–1.60) |
| hypertension and diabetes |       | (1.03–1.33) | [Reference] | (0.88–1.15) | (1.08–1.46) | (1.20–1.85) | (0.987–1.016) |
| P value for difference | 0.578 | 0.488     | –         | 0.856     | 0.004     | 0.202  |             |
| aObesity-related cancer included esophageal, colon, rectal, liver, pancreatic, and kidney cancer. | | | | | | | |
| bThe multivariable adjusted model was adjusted using the following variables: age, education level, area of residence, smoking status, alcohol drinking, physical activity, and histories of liver disease and blood transfusion. | | | | | | | |
| cCardiovascular disease included coronary heart disease and stroke. | | | | | | | |
| dP value for the difference associated with the null hypothesis that the risk factor variable of interest has the same association with obesity-related cancer and cardiovascular disease in the multivariable model. | | | | | | | |
| csHR, cause-specific hazard ratio; CI, confidence interval. | | | | | | | |
**Supplementary Table 7.** Comparison of cause-specific hazard ratios for death from obesity-related cancer and cardiovascular disease in women excluding participants with less than 5 years of follow-up, 1988–2009, JACC study

| Body mass index (kg/m²) | < 18.5 | 18.5–20.9 | 21.0–22.9 | 23.0–24.9 | 25.0–27.4 | ≥ 27.5 | per 1 kg/m² |
|------------------------|--------|-----------|-----------|-----------|-----------|---------|-------------|
| Number of participants | 3570   | 11,880    | 15,294    | 13,214    | 8847      | 4265    |             |
| Person-years           | 57,663 | 204,854   | 267,214   | 230,970   | 154,023   | 73,828  |             |
| Obesity-related cancer |        |           |           |           |           |         |             |
| Number of deaths       | 61     | 217       | 254       | 266       | 196       | 118     |             |
| Crude mortality rate (per 1000 person-years) | 1.06 | 1.06 | 0.95 | 1.15 | 1.27 | 1.60 |             |
| csHR                   | 0.92   | 1.09      | 1.00      | 1.20      | 1.29      | 1.59    |             |
| (95% CI)               | (0.68–1.24) | (0.90–1.32) | [Reference] | (1.01–1.44) | (1.06–1.57) | (1.27–2.00) | (1.005–1.020) |
| +histories of          | 0.93   | 1.09      | 1.00      | 1.20      | 1.28      | 1.57    | 1.012       |
| hypertension and diabetes | (0.69–1.25) | (0.90–1.33) | [Reference] | (1.01–1.44) | (1.06–1.56) | (1.25–1.98) | (1.004–1.019) |
| Cardiovascular disease |        |           |           |           |           |         |             |
| Number of deaths       | 211    | 383       | 453       | 368       | 293       | 198     |             |
| Crude mortality rate (per 1000 person-years) | 3.65 | 1.87 | 1.70 | 1.59 | 1.90 | 2.68 |             |
| csHR                   | 1.41   | 1.01      | 1.00      | 0.95      | 1.09      | 1.47    | 1.004       |
| (95% CI)               | (1.18–1.69) | (0.87–1.17) | [Reference] | (0.82–1.11) | (0.93–1.27) | (1.23–1.76) | (0.993–1.015) |
| +histories of          | 1.53   | 1.05      | 1.00      | 0.93      | 1.04      | 1.33    | 0.994       |
| hypertension and diabetes | (1.27–1.83) | (0.90–1.22) | [Reference] | (0.80–1.08) | (0.89–1.21) | (1.11–1.59) | (0.980–1.009) |

P value for difference | 0.015 | 0.529 | – | 0.048 | 0.183 | 0.595 |

*a* Obesity-related cancer included esophageal, colon, rectal, liver, pancreatic, breast, endometrial, and kidney cancer.

*b* The multivariable adjusted model was adjusted using the following variables: age, education level, area of residence, smoking status, alcohol drinking, physical activity, histories of liver disease and blood transfusion, menopausal status, hormone replacement therapy, age at menarche, age at first delivery, and parity number.

*c* Cardiovascular disease included coronary heart disease and stroke.

*d* P value for the difference associated with the null hypothesis that the risk factor variable of interest has the same association with obesity-related cancer and cardiovascular disease in the multivariable model.

csHR, cause-specific hazard ratio; CI, confidence interval.

**Supplementary Table 8.** Cause-specific hazard ratios for death from obesity-related cancer excluding esophageal cancer in men, 1988–2009, JACC study

| Body mass index (kg/m²) | < 18.5 | 18.5–20.9 | 21.0–22.9 | 23.0–24.9 | 25.0–27.4 | ≥ 27.5 | per 1 kg/m² |
|------------------------|--------|-----------|-----------|-----------|-----------|---------|-------------|
| Number of participants | 2399   | 9987      | 12,223    | 10,299    | 5999      | 2060    |             |
| Person-years           | 32,152 | 154,933   | 197,613   | 169,787   | 99,073    | 34,338  |             |
| Obesity-related cancer |        |           |           |           |           |         |             |
| Number of deaths       | 91     | 350       | 395       | 319       | 181       | 72      |             |
| Crude mortality rate (per 1000 person-years) | 2.82 | 2.26 | 1.99 | 1.88 | 1.83 | 2.09 |             |
| csHR                   | 1.04   | 1.03      | 1.00      | 1.01      | 1.01      | 1.20    | 1.005       |
| (95% CI)               | (0.81–1.32) | (0.89–1.19) | [Reference] | (0.87–1.17) | (0.84–1.17) | (0.84–1.21) | (0.987–1.022) |
| +histories of          | 1.04   | 1.03      | 1.00      | 1.01      | 1.00      | 1.18    | 1.003       |
| hypertension and diabetes | (0.82–1.33) | (0.89–1.20) | [Reference] | (0.86–1.17) | (0.83–1.20) | (0.91–1.54) | (0.985–1.022) |

*a* Obesity-related cancer included colon, rectal, liver, pancreatic, and kidney cancer.

*b* The multivariable adjusted model was adjusted using the following variables: age, education level, area of residence, smoking status, alcohol drinking, physical activity, and histories of liver disease and blood transfusion.

csHR, cause-specific hazard ratio; CI, confidence interval.
**Supplementary Table 9.** Cause-specific hazard ratios for death from obesity-related cancer excluding esophageal and female breast cancers in women, 1988–2009, JACC study

| Body mass index (kg/m²) | <18.5 | 18.5–20.9 | 21.0–22.9 | 23.0–24.9 | 25.0–27.4 | ≥ 27.5 | per 1 kg/m² |
|-------------------------|-------|-----------|-----------|-----------|-----------|--------|-------------|
| Number of participants  | 3858  | 12,453    | 15,896    | 13,726    | 9188      | 4448   |
| Person-years            | 58,432| 206,379   | 268,818   | 232,324   | 154,971   | 74,334 |
| Obesity-related cancer  |       |           |           |           |           |        |
| Number of deaths        | 68    | 217       | 254       | 265       | 192       | 117    |
| Crude mortality rate (per 1000 person-years) | 1.17 | 1.05 | 0.95 | 1.14 | 1.23 | 1.57 |
| csHR                    | 0.95  | 1.08      | 1.00      | 1.20      | 1.26      | 1.55   |
| Multivariable adjusted  | (95% CI) |     |           |           |           |        |
| +histories of hypertension and diabetes | (0.71–1.27) | (0.89–1.31) | [Reference] | (1.00–1.44) | (1.03–1.53) | (1.22–1.95) | (1.003–1.019) |

*a* Obesity-related cancer included colon, rectal, liver, pancreatic, endometrial, and kidney cancer.

*b* The multivariable adjusted model was adjusted using the following variables: age, education level, area of residence, smoking status, alcohol drinking, physical activity, histories of liver disease and blood transfusion, menopausal status, hormone replacement therapy, age at menarche, age at first delivery, and parity number.

csHR, cause-specific hazard ratio; CI, confidence interval.