The official journal of the Japan Atherosclerosis Society and
the Asian Pacific Society of Atherosclerosis and Vascular Diseases

Original Article

J Atheroscler Thromb, 2022; 29: 1547-1562. http://doi.org/10.5551/jat.63143

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

Masaaki Matsunaga[1], Hiroshi Yatsuya[2], Hiroyasu Iso[3], Yuanying Li[1], Kazumasa Yamagishi[4], Naohito Tanabe[5], Yasuhiko Wada[6], Atsuhiko Ota[1], Koji Tamakoshi[7] and Akiko Tamakoshi[8]; The JACC Study Group

[1]Department of Public Health, Fujita Health University School of Medicine, Aichi, Japan
[2]Department of Public Health and Health Systems, Graduate School of Medicine, Nagoya University, Aichi, Japan
[3]Public Health, Department of Social Medicine, Graduate School of Medicine, Osaka University, Osaka, Japan
[4]Department of Public Health Medicine, Faculty of Medicine, and Health Services Research and Development Center, University of Tsukuba, Ibaraki, Japan
[5]Department of Health and Nutrition, Faculty of Human Life Studies, University of Niigata Prefecture, Niigata, Japan
[6]Wakayama Prefectural Shingu Public Health Center, Wakayama, Japan
[7]Department of Nursing, Nagoya University School of Health Science, Aichi, Japan
[8]Department of Public Health, Graduate School of Medicine, Hokkaido University, Hokkaido, Japan

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/m^2) 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/m^2) 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/m^2 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/m^2 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 Japan[1)]. Recent studies have shown several shared risk factors between CVD and cancer[2)]. Obesity is a risk factor that increases the

Address for correspondence: Hiroshi Yatsuya, Department of Public Health and Health Systems, Graduate School of Medicine, Nagoya University, 65 Tsurumai-cho, Showa-ku, Nagoya, Aichi 466-8550, Japan E-mail: h828@med.nagoya-u.ac.jp

Received: July 4, 2021 Accepted for publication: October 26, 2021

mortality rate of CVD and some types of cancer referred to as obesity-related cancer[3, 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 death[3, 4]. Globally, CVD and cancer account for approximately 70% and 10%, respectively, of deaths due to a BMI ≥ 25 kg/m^2 [5].

In Westerners, a BMI ≥ 25 kg/m^2 is associated with an increased risk of CVD mortality and obesity-related cancer mortality[6, 7]. However, in East Asians, a BMI ≥ 25 kg/m^2 is associated with an increased risk of CVD mortality[3], 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/m^2) in Asians (mainly East Asia)[8]. In our previous study, colon cancer mortality was associated with a BMI ≥ 28 kg/m^2 in Japanese women[9]. In contrast, rectal cancer is associated with an increased mortality rate at a lower degree of increased BMI than that of colon cancer in Asians[8]. 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 cancer[10].

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 previously[11-13]. 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/m^2, low normal: 18.5–20.9 kg/m^2, mid normal: 21.0–22.9 kg/m^2 [reference], high normal: 23.0–24.9 kg/m^2, low overweight: 25.0–27.4 kg/m^2, and high overweight or obesity: ≥ 27.5 kg/m^2) according to the World Health Organization and Asia-Pacific classification[14].

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 study[15], 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/m^2 increase in BMI.

We tested for a difference between pairs of Cox regression coefficients (i.e., csHRs) using the following formula: $(b_1-b_2)/\{[SE(b_1)]^2+[SE(b_2)]^2\}^{1/2}$, where b_1 is the coefficient for each BMI category for obesity-related cancer, b_2 is the corresponding coefficient for CVD, $SE(b_1)$ is the standard error of the variable for obesity-related cancer, and $SE(b_2)$ 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[1]. 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: $PAF=P_d(HR_a-1)/HR_a$, where P_d is the proportion of participants exposed among those who died of a particular cause of death, and HR_a 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 Survey[21] (PAF_{2019}). PAF_{2019} was defined as

Table 1. Baseline characteristics of the study participants, 1988–1990, 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	≥ 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)	<0.001
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.

follows: P_e (HR_a–1)/{(P_e (HR_a–1)+1}, where P_e is the proportion of the population exposed to overweight or obesity (BMI ≥ 25.0 kg/m^2) in 2019 and HR_a is the multivariable-adjusted HR of CVD mortality or obesity-related cancer mortality in overweight or obesity (BMI ≥ 25.0 kg/m^2) relative to normal (BMI of 18.5–24.9 kg/m^2)[22]. However, bias is reportedly present in PAF_{2019} calculated using adjusted hazard ratios.

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 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/m^2)	< 18.5	18.5–20.9	21.0–22.9	23.0–24.9	25.0–27.4	≥ 27.5	per 1 kg/m^2
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[a]							
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 Multivariable adjusted[b]	1.11	1.04	1.00	0.98	0.93	1.18	0.994
(95% CI)	(0.89–1.39)	(0.91–1.20)	[Reference]	(0.85–1.13)	(0.78–1.10)	(0.92–1.50)	(0.977–1.012)
+histories of	1.06	1.06	1.00	0.98	0.92	1.16	0.993
hypertension and diabetes	(0.93–1.21)	(0.93–1.21)	[Reference]	(0.85–1.13)	(0.77–1.10)	(0.91–1.49)	(0.975–1.011)
Cardiovascular disease[c]							
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 Multivariable adjusted[b]	1.28	1.11	1.00	1.02	1.27	1.59	1.008
(95% CI)	(1.08–1.52)	(0.99–1.24)	[Reference]	(0.90–1.15)	(1.10–1.46)	(1.30–1.95)	(0.996–1.021)
+histories of	1.37	1.15	1.00	1.00	1.20	1.47	0.998
hypertension and diabetes	(1.15–1.62)	(1.02–1.29)	[Reference]	(0.88–1.13)	(1.04–1.39)	(1.20–1.80)	(0.984–1.013)
P value for difference[d]	0.330	0.526	–	0.696	0.006	0.065	

[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.

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/m^2 was associated with increased multivariable-adjusted csHRs of CVD mortality in men **(Table 2)**. The csHR of BMI ≥ 27.5 kg/m^2 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/m^2 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/m^2 with CVD mortality was greater than that with obesity-related cancer mortality in men (*P* value for the difference = 0.006 for a BMI of 25.0–27.4 kg/m^2 and *P* value for the difference = 0.065 for a BMI ≥ 27.5 kg/m^2). In contrast, a BMI ≥ 25.0 kg/m^2 was positively associated with CVD mortality and obesity-related cancer mortality in women **(Table 3)**. The csHRs of BMI ≥ 25.0 kg/m^2 with CVD mortality was not significantly different from those of BMI ≥ 25.0 kg/m^2 with obesity-related cancer mortality in women. There was a positive linear trend (multivariable-adjusted csHRs for a 1 kg/m^2 increase in BMI) between BMI and obesity-related cancer mortality in women. A BMI < 18.5 kg/m^2 was associated with an increased multivariable-adjusted csHR of mortality from CVD in both sexes. In contrast, a BMI < 18.5 kg/m^2 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

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	≥ 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 Multivariable adjusted[b]	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	0.94	1.09	1.00	1.17	1.24	1.46	1.010
hypertension and diabetes	(0.72–1.24)	(0.91–1.30)	[Reference]	(0.99–1.38)	(1.04–1.49)	(1.17–1.82)	(1.002–1.018)
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 Multivariable adjusted[b]	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	1.59	1.07	1.00	0.92	1.04	1.29	0.988
hypertension and diabetes	(1.34–1.88)	(0.93–1.23)	[Reference]	(0.80–1.07)	(0.90–1.21)	(1.08–1.54)	(0.974–1.003)
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.

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 ≥ 25.0 kg/m^2 in women. In both sexes, a significant portion of CVD mortality was attributable to a BMI ≥ 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 ≥ 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 ≥ 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 ≥ 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

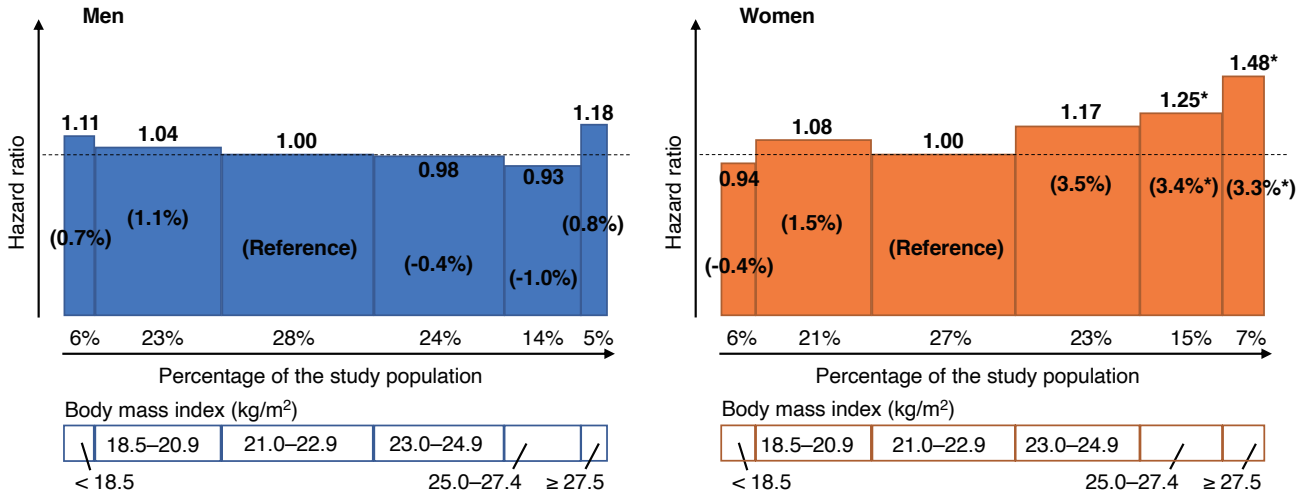

Fig. 1. Population attributable fraction for obesity-related cancer mortality according to body mass index, 1988–2009, JACC study
Population attributable fractions are shown in parentheses. *$P<0.05$.

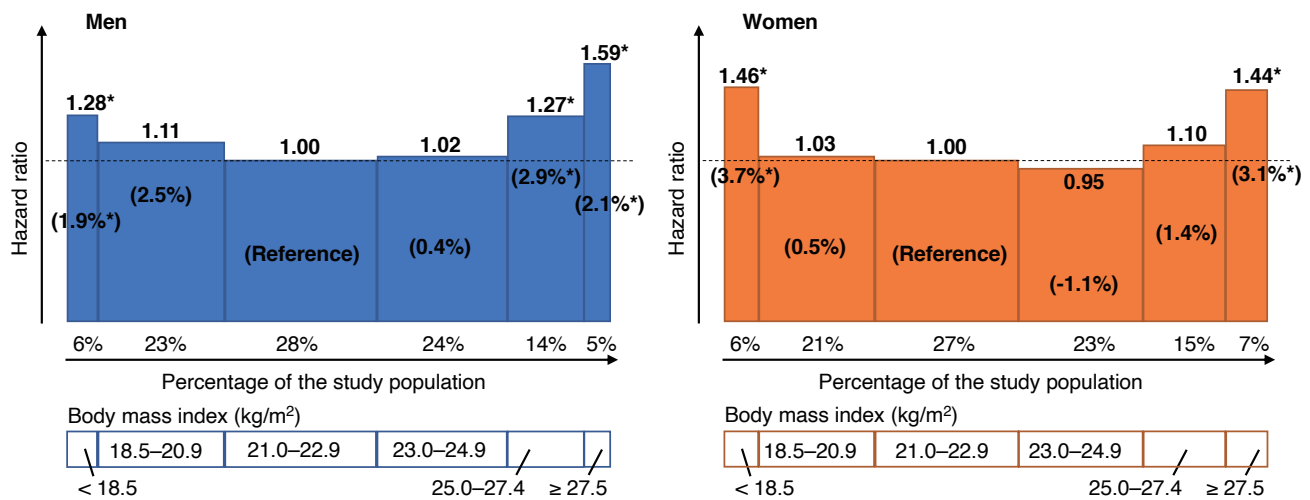

Fig. 2. Population attributable fraction for cardiovascular disease mortality according to body mass index, 1988–2009, JACC study
Population attributable fractions are shown in parentheses. *$P<0.05$.

≥ 25.0 kg/m^2, while over half of Caucasians have a BMI ≥ 25.0 kg/m^2 [23]. Therefore, the present study might have had a reduced chance of detecting an association between an increased BMI and obesity-related cancer, especially in men. The association of the lowest BMI category with obesity-related cancer mortality tended to differ between men and women. This association in women is consistent with the notion that the risk of obesity-related cancer is related to a high BMI. This association in men was generally null. The reason why we did not observe a similar association in men and women is unclear. A linear association of BMI with obesity-related cancer mortality has been reported for rectal cancer, colon cancer, and ≥ 60-year-old female breast cancer in Asians[8]. 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[4, 10]. Fewer types of obesity-related cancer have been established in the Japanese population (convincing: liver, colorectal, and postmenopausal breast cancer; probable:

premenopausal breast, male pancreatic, and endometrial cancer) compared with obesity-related cancer reported by these agencies[24]. Nevertheless, our study showed that the definition of obesity-related cancer based on the WCRF/AICR report could be applied to the Japanese population. However, we used breast cancer and esophageal cancer to define 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/m^2 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/m^2 [25]. 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[25] and Western populations[6]. However, the association between a decreased BMI and CVD mortality is not evident in the Western population[6]. Our previous study showed that a decreased BMI was more strongly associated with stroke than with coronary heart disease[26]. The Japanese population has a higher hemorrhagic stroke mortality rate than that in the Western population[27], 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[27], is lower with a lower BMI[28], 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[2, 29]. Hypertension is strongly associated with CVD mortality[26]. However, the association between hypertension and mortality from sites other than the kidney in cancer is unclear[30], 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[31]. The attributable burden of a higher BMI on CVD is also smaller than that of a higher BMI on CVD in the American population[32]. 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$_{2019}$ 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[33]. Third, the baseline data were obtained at one time point only. Changes in body weight simultaneously affect changes in CVD risk[34, 35] and individual CVD risk factors[34]. 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[36], 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[37],

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 only 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.

Acknowledgements

The authors appreciate Drs Kunio Aoki and Yoshiyuki Ohno, Nagoya University School of Medicine, and Dr Haruo Sugano, Cancer Institute, Tokyo, who greatly contributed to the initiation of the JACC Study. A list of the names of all of the members of the JACC Study is available at: http://publichealth.med.hokudai.ac.jp/jacc/member.html. We also thank Ellen Knapp, PhD, from Edanz (https://jp.edanz.com/ac) for editing a draft of this manuscript.

Financial Support

This work was supported by Grants-in-Aid for Scientific Research from the Ministry of Education, Culture, Sports, Science and Technology of Japan (MEXT) (Monbusho); Grants-in-Aid for Scientific Research on Priority Areas of Cancer; Grants-in-Aid for Scientific Research on Priority Areas of Cancer Epidemiology from MEXT (MonbuKagaku-sho) (numbers 61010076, 62010074, 63010074, 1010068, 2151065, 3151064, 4151063, 5151069, 6279102, 11181101, 17015022, 18014011, 20014026, 20390156, and 26293138); a JSPS Kakenhi grant (number JP 16H06277) (CoBiA); a Grant-in-Aid from the Ministry of Health, Labour and Welfare; and Health and Labor Sciences research grants, Japan (Research on Health Services: H17–Kenkou–007; Comprehensive Research on Cardiovascular Disease and Life–Related Disease: H18–Junkankitou [Seishuu]–Ippan–012; H19–Junkankitou [Seishuu]–Ippan–012; H20–Junkankitou [Seishuu]–Ippan–013; H23–Junkankitou [Seishuu]–Ippan–005; H26-Junkankitou [Seisaku]-Ippan-001; H29–Junkankitou–Ippan–003; and 20FA1002). The study sponsors had no involvement in the study design, collection, analysis, and interpretation of data, the writing of the manuscript, or the decision to submit the manuscript for publication.

Conflict of Interest

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

References

1) Ministry of Health Labour and Welfare. Vital statistics. Vital, Health and Social Statistics Office, the Counsellor for Vital, Health and Social Statistics, the Director-General for Statistics and Information Policy, 2018. https://www.mhlw.go.jp/english/database/db-hw/dl/81-1a2en.pdf (Access date: October 4, 2021)
2) Koene RJ, Prizment AE, Blaes A, and Konety SH: Shared risk factors in cardiovascular disease and cancer. Circulation, 2016; 133: 1104-1114
3) Chen Y, Copeland WK, Vedanthan R, Grant E, Lee JE, Gu D, Gupta PC, Ramadas K, Inoue M, Tsugane S, Tamakoshi A, Gao Y-T, Yuan J-M, Shu X-O, Ozasa K, Tsuji I, Kakizaki M, Tanaka H, Nishino Y, Chen C-J, Wang R, Yoo K-Y, Ahn Y-O, Ahsan H, Pan W-H, Chen C-S, Pednekar MS, Sauvaget C, Sasazuki S, Yang G, Koh W-P, Xiang Y-B, Ohishi W, Watanabe T, Sugawara Y, Matsuo K, You S-L, Park SK, Kim D-H, Parvez F, Chuang S-Y, Ge W, Rolland B, McLerran D, Sinha R, Thornquist M, Kang D, Feng Z, Boffetta P, Zheng W, He J, and Potter JD: Association between body mass index and cardiovascular disease mortality in east Asians and south Asians: pooled analysis of prospective data from the Asia Cohort Consortium. BMJ, 2013; 347: f5446
4) Lauby-Secretan B, Scoccianti C, Loomis D, Grosse Y, Bianchini F, and Straif K: Body fatness and cancer — viewpoint of the IARC Working Group. N Engl J Med, 2016; 375: 794-798
5) GBD 2015 Obesity Collaborators: Health effects of overweight and obesity in 195 countries over 25 years. N Engl J Med, 2017; 377: 13-27.
6) Prospective Studies Collaboration: Body-mass index and cause-specific mortality in 900 000 adults: collaborative analyses of 57 prospective studies. Lancet, 2009; 373: 1083-1096.
7) Calle EE, Rodriguez C, Walker-Thurmond K, and Thun MJ: Overweight, obesity, and mortality from cancer in a prospectively studied cohort of U.S. adults. N Engl J Med, 2003; 348: 1625-1638
8) Parr CL, Batty GD, Lam TH, Barzi F, Fang X, Ho SC, Jee SH, Ansary-Moghaddam A, Jamrozik K, Ueshima H,

Woodward M, and Huxley RR; Asia-Pacific Cohort Studies Collaboration: Body-mass index and cancer mortality in the Asia-Pacific Cohort Studies Collaboration: pooled analyses of 424,519 participants. Lancet Oncol, 2010; 11: 741-752
9) Tamakoshi K, Wakai K, Kojima M, Watanabe Y, Hayakawa N, Toyoshima H, Yatsuya H, Kondo T, Tokudome S, Hashimoto S, Suzuki K, Ito Y, and Tamakoshi A; JACC Study Group: A prospective study of body size and colon cancer mortality in Japan: the JACC Study. Int J Obes Relat Metab Disord, 2004; 28: 551-558
10) World Cancer Research Fund/American Institute for Cancer Research. Body fatness & weight gain. https://www.wcrf.org/dietandcancer/exposures/body-fatness (Access date: October 4, 2021)
11) Ohno Y and Tamakoshi A; JACC Study Group JS: Japan collaborative cohort study for evaluation of cancer risk sponsored by monbusho (JACC study). J Epidemiol, 2001; 11: 144-150
12) Tamakoshi A, Ozasa K, Fujino Y, Suzuki K, Sakata K, Mori M, Kikuchi S, and Iso H: Cohort profile of the Japan collaborative cohort study at final follow-up. J Epidemiol, 2013; 23: 227-232
13) Tamakoshi A, Yoshimura T, Inaba Y, Ito Y, Watanabe Y, Fukuda K, and Iso H: Profile of the JACC study. J Epidemiol, 2005; 15: S4-S8
14) WHO Expert Consultation: Appropriate body-mass index for Asian populations and its implications for policy and intervention strategies. Lancet, 2004; 363: 157-163
15) Ikehara S, Iso H, Toyoshima H, Date C, Yamamoto A, Kikuchi S, Kondo T, Watanabe Y, Koizumi A, Wada Y, Inaba Y, and Tamakoshi A; Japan Collaborative Cohort Study Group: Alcohol consumption and mortality from stroke and coronary heart disease among Japanese men and women. Stroke, 2008; 39: 2936-2942
16) Hasuo Y, Ueda K, Kiyohara Y, Wada J, Kawano H, Kato I, Yanai T, Fujii I, Omae T, and Fujishima M: Accuracy of diagnosis on death certificates for underlying causes of death in a long-term autopsy-based population study in Hisayama, Japan; with special reference to cardiovascular diseases. J Clin Epidemiol, 1989; 42: 577-584
17) Rubin DB: Multiple Imputation for Nonresponse in Surveys, Wiley-Interscience, Hoboken, New Jersey, 2004
18) Austin PC, Lee DS, and Fine JP: Introduction to the analysis of survival data in the presence of competing risks. Circulation, 2016; 133: 601-609
19) Allison PD: Event History and Survival Analysis 2nd Ed, SAGE Publications, Los Angeles, California, 2014
20) Greenland S: Re: "Confidence limits made easy: interval estimation using a substitution method." Am J Epidemiol, 1999; 149: 884
21) Ministry of Health Labour and Welfare. The national health and nutrition survey in Japan, 2019 (article in Japanese). https://www.mhlw.go.jp/content/000710991.pdf (Access date: October 4, 2021)
22) Flegal KM, Panagiotou OA, and Graubard BI: Estimating population attributable fractions to quantify the health burden of obesity. Ann Epidemiol, 2015; 25: 201-207
23) Yatsuya H, Li Y, Hilawe EH, Ota A, Wang C, Chiang C, Zhang Y, Uemura M, Osako A, Ozaki Y, and Aoyama A: Global trend in overweight and obesity and its association with cardiovascular disease incidence. Circ J, 2014; 78: 2807-2818
24) National Cancer Center, Epidemiology and Prevention Division. Development and Evaluation of Cancer Prevention Strategies in Japan (article in Japanese). https://epi.ncc.go.jp/cgi-bin/cms/public/index.cgi/nccepi/can_prev/outcome/index (Access date: October 4, 2021)
25) Sasazuki S, Inoue M, Tsuji I, Sugawara Y, Tamakoshi A, Matsuo K, Wakai K, Nagata C, Tanaka K, Mizoue T, and Tsugane S: Body mass index and mortality from all causes and major causes in Japanese: results of a pooled analysis of 7 large-scale cohort studies. J Epidemiol, 2011; 21: 417-430
26) Matsunaga M, Yatsuya H, Iso H, Yamashita K, Li Y, Yamagishi K, Tanabe N, Wada Y, Wang C, Ota A, Tamakoshi K, and Tamakoshi A; JACC Study Group: Similarities and differences between coronary heart disease and stroke in the associations with cardiovascular risk factors: the Japan collaborative cohort study. Atherosclerosis, 2017; 261: 124-130
27) Ueshima H, Sekikawa A, Miura K, Turin TC, Takashima N, Kita Y, Watanabe M, Kadota A, Okuda N, Kadowaki T, Nakamura Y, and Tomonori O: Cardiovascular disease and risk factors in Asia. Circulation, 2008; 118: 2702-2709
28) Jee SH, Sull JW, Park J, Lee S-Y, Ohrr H, Guallar E, and Samet JM: Body mass index and mortality in Korean men and women. N Engl J Med, 2006; 355: 779-787
29) Li Y, Yatsuya H, Tanaka S, Iso H, Okayama A, Tsuji I, Sakata K, Miyamoto Y, Ueshima H, Miura K, Murakami Y, and Okamura T; EPOCH-JAPAN Research Group: Estimation of 10-year risk of death from coronary heart disease, stroke, and cardiovascular disease in a pooled analysis of Japanese cohorts: EPOCH-JAPAN. J Atheroscler Thromb, 2021; 28: 816-825
30) Grossman E, Messerli FH, Boyko V, and Goldbourt U: Is there an association between hypertension and cancer mortality? Am J Med, 2002; 112: 479-486
31) Arnold M, Pandeya N, Byrnes G, Renehan AG, Stevens GA, Ezzati M, Ferlay J, Miranda JJ, Romieu I, Dikshit R, Forman D, and Soerjomataram I: Global burden of cancer attributable to high body-mass index in 2012: a population-based study. Lancet Oncol, 2015; 16: 36-46
32) Flegal KM, Graubard BI, Williamson DF, and Gail MH: Cause-specific excess deaths associated with underweight, overweight, and obesity. JAMA, 2007; 298: 2028-2037
33) Wada K, Tamakoshi K, Tsunekawa T, Otsuka R, Zhang H, Murata C, Nagasawa N, Matsushita K, Sugiura K, Yatsuya H, and Toyoshima H: Validity of self-reported height and weight in a Japanese workplace population. Int J Obes, 2005; 29: 1093-1099
34) Honda T, Ishida Y, Oda M, Noguchi K, Chen S, Sakata S, Oishi E, Furuta Y, Yoshida D, Hirakawa Y, Hata J, Kitazono T, and Ninomiya T: Changes in body weight and concurrent changes in cardiovascular risk profiles in community residents in Japan: the Hisayama study. J Atheroscler Thromb, 2022; 29: 252-267
35) Okada C, Kubota Y, Eshak ES, Cui R, Tamakoshi A, and Iso H; the JACC Study Group: Weight change and mortality from cardiovascular diseases: the Japan collaborative cohort study. J Atheroscler Thromb, 2021;

28: 25-33
36) Sturgeon KM, Deng L, Bluethmann SM, Zhou S, Trifiletti DM, Jiang C, Kelly SP, and Zaorsky NG: A population-based study of cardiovascular disease mortality risk in US cancer patients. Eur Heart J, 2019; 40: 3889-3897
37) Matsuda T and Saika K: Cancer burden in Japan based on the latest cancer statistics: need for evidence-based cancer control programs. Ann. Cancer Epidemiol, 2018; 2: 2

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

	Men (n=46,395)	Women (n=64,190)	Total (n=110,585)	No question item in the questionnaire
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 (%).
In some institutions, some questions items were not asked in the questionnaire.
Menopausal status was assessed by self-reported age at menopause or the reason for menopause. No answer provided was treated as not having menopause.

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/m^2)	<18.5	18.5–20.9	21.0–22.9	23.0–24.9	25.0–27.4	≥ 27.5	per 1 kg/m^2
Number of participants	1294	7094	9367	8293	4929	1724	
Person-years	20,395	119,650	161,191	143,778	85,070	29,949	
Obesity-related cancer[a]							
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 adjusted[b]	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	1.18	1.04	1.00	1.02	1.03	1.36	1.011
hypertension and diabetes	(0.87–1.61)	(0.88–1.25)	[Reference]	(0.85–1.21)	(0.84–1.27)	(1.03–1.79)	(0.988–1.035)
Cardiovascular disease[c]							
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 adjusted[b]	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	1.57	1.16	1.00	1.05	1.31	1.62	1.014
hypertension and diabetes	(1.17–2.11)	(0.97–1.39)	[Reference]	(0.88–1.26)	(1.08–1.60)	(1.24–2.12)	(0.991–1.038)
P value for difference[d]	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/m^2)	< 18.5	18.5–20.9	21.0–22.9	23.0–24.9	25.0–27.4	≥ 27.5	per 1 kg/m^2
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[a]							
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 Multivariable adjusted[b]	1.08	1.04	1.00	0.92	0.71	0.76	0.961
(95% CI)	(0.78–1.49)	(0.83–1.31)	[Reference]	(0.71–1.20)	(0.50–1.02)	(0.43–1.34)	(0.930–0.994)
+histories of	1.10	1.05	1.00	0.92	0.71	0.74	0.958
hypertension and diabetes	(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[c]							
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 Multivariable adjusted[b]	1.18	1.09	1.00	0.97	1.13	1.39	0.997
(95% CI)	(0.95–1.45)	(0.93–1.27)	[Reference]	(0.81–1.15)	(0.92–1.39)	(1.02–1.90)	(0.978–1.016)
+histories of	1.26	1.13	1.00	0.95	1.09	1.32	0.987
hypertension and diabetes	(1.02–1.55)	(0.97–1.32)	[Reference]	(0.80–1.14)	(0.89–1.34)	(0.97–1.80)	(0.967–1.008)
P value for difference[d]	0.662	0.761	–	0.786	0.027	0.068	

[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 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/m^2)	< 18.5	18.5–20.9	21.0–22.9	23.0–24.9	25.0–27.4	≥ 27.5	per 1 kg/m^2
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[a]							
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 Multivariable adjusted[b]	1.03	1.04	1.00	1.22	1.17	1.40	1.009
(95% CI)	(0.70–1.51)	(0.83–1.31)	[Reference]	(0.98–1.50)	(0.92–1.48)	(1.05–1.86)	(0.998–1.020)
+histories of	1.04	1.05	1.00	1.21	1.16	1.37	1.008
hypertension and diabetes	(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[c]							
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 Multivariable adjusted[b]	2.09	1.02	1.00	0.97	1.09	1.58	0.999
(95% CI)	(1.54–2.84)	(0.79–1.31)	[Reference]	(0.77–1.23)	(0.84–1.42)	(1.18–2.11)	(0.976–1.023)
+histories of	2.31	1.07	1.00	0.93	1.00	1.30	0.977
hypertension and diabetes	(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[d]	0.005	0.876	–	0.165	0.703	0.556	

[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 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/m^2)	< 18.5	18.5–20.9	21.0–22.9	23.0–24.9	25.0–27.4	≥ 27.5	per 1 kg/m^2
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[a]							
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 Multivariable adjusted[b]	0.88	1.13	1.00	1.09	1.35	1.58	1.015
(95% CI)	(0.60–1.30)	(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	1.09	1.35	1.57	1.015
hypertension and diabetes	(0.60–1.30)	(0.86–1.50)	[Reference]	(0.83–1.44)	(1.01–1.81)	(1.12–2.21)	(1.002–1.028)
Cardiovascular disease[c]							
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 Multivariable adjusted[b]	1.32	1.02	1.00	0.94	1.12	1.38	1.002
(95% CI)	(1.08–1.61)	(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	0.993
hypertension and diabetes	(1.15–1.73)	(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[d]	0.072	0.510	–	0.360	0.275	0.519	

[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 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/m^2)	< 18.5	18.5–20.9	21.0–22.9	23.0–24.9	25.0–27.4	≥ 27.5	per 1 kg/m^2
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[a]							
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 Multivariable adjusted[b]	1.14	1.06	1.00	1.01	0.93	1.29	0.998
(95% CI)	(0.88–1.47)	(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	0.997
hypertension and diabetes	(0.89–1.48)	(0.91–1.24)	[Reference]	(0.86–1.18)	(0.76–1.12)	(0.99–1.66)	(0.977–1.017)
Cardiovascular disease[c]							
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 Multivariable adjusted[b]	1.24	1.13	1.00	1.03	1.32	1.61	1.010
(95% CI)	(1.03–1.30)	(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	1.001
hypertension and diabetes	(1.09–1.60)	(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[d]	0.578	0.488	–	0.856	0.004	0.202	

[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 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/m^2)	< 18.5	18.5–20.9	21.0–22.9	23.0–24.9	25.0–27.4	≥ 27.5	per 1 kg/m^2
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[a]							
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 Multivariable adjusted[b]	0.92	1.09	1.00	1.20	1.29	1.59	1.012
(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[c]							
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 Multivariable adjusted[b]	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[d]	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/m^2)	< 18.5	18.5–20.9	21.0–22.9	23.0–24.9	25.0–27.4	≥ 27.5	per 1 kg/m^2
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[a]							
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 Multivariable adjusted[b]	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/m^2)	< 18.5	18.5–20.9	21.0–22.9	23.0–24.9	25.0–27.4	≥ 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	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 Multivariable adjusted[b]	0.95	1.08	1.00	1.20	1.26	1.55	1.011
(95% CI)	(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)
+histories of	0.96	1.08	1.00	1.20	1.25	1.53	1.010
hypertension and diabetes	(0.72–1.29)	(0.89–1.32)	[Reference]	(1.00–1.44)	(1.03–1.53)	(1.21–1.93)	(1.002–1.019)

[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.