RESEARCH ARTICLE

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Pooled Analysis of the Associations between Body Mass Index, Total Cholesterol, and Liver Cancer-related Mortality in Japan

Shigekazu Ukawa[1,2], Akiko Tamakoshi[1]*, Yoshitaka Murakami[3], Yutaka Kiyohara[4], Michiko Yamada[5], Masato Nagai[6,7], Atsushi Satoh[8], Katsuyuki Miura[9,10], Hirotsugu Ueshima[9,10], Tomonori Okamura[11], EPOCH-JAPAN Research Group

Abstract

Objective: We employed a large-scale pooled analysis to investigate the association of liver cancer-related mortality with being overweight/obese and total cholesterol (TC) levels, since limited and inconsistent data on these associations exist in Japan. **Methods:** A total of 59,332 participants (23,853 men and 35,479 women) from 12 cohorts without a history of cancer who were followed for a median of 14.3 years were analyzed. A sex-specific stratified Cox proportional hazards model adjusted for age and other potential confounders was used to calculate hazard ratios (HRs) and 95% confidence intervals (CI) for liver cancer-related mortality. **Results:** A total of 447 participants (266 men and 181 women) died of liver cancer within the follow-up period. Individuals classified as having a high BMI (≥25.0 kg/m^2) and low TC levels (<160 mg/dL) had a significantly increased risk for liver cancer-related mortality (HR 7.05, 95% CI 4.41–11.26 in men; HR 8.07, 95% CI 4.76–13.67 in women) when compared with those in the intermediate BMI (18.5–24.9 kg/m^2) and TC (160–219 mg/dL) categories. These associations remained after limiting the follow-up duration to >5 years. **Conclusion:** Being overweight/obese, combined with low TC levels, was strongly associated with liver cancer-related mortality in the EPOCH-JAPAN.

Keywords: Obesity- cholesterol- body mass index- liver cancer- pooled analysis

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Introduction

Over the past few decades, the percentage of the worldwide population with a body mass index (BMI) of ≥25 kg/m^2 has been increasing significantly, and about 40% of the adult population in industrialized countries is classified as having excess body weight (Ng et al., 2014).

Liver cancer is the second leading cause of cancer-related death worldwide, accounting for 745,000 deaths in 2012 (WHO, 2014), and is the fifth leading cause of cancer-related death in Japan. Although obesity has been shown to be associated with an increased risk of primary liver cancer in Western countries (Chen et al., 2012; Wang et al., 2012), inconsistent results were observed in the Japanese population (Parr et al., 2010; Saunders et al., 2010; Tanaka et al., 2012; Li et al., 2013). The major explanation regarding the biological mechanisms underlying the association between being overweight/obese and liver cancer is the non-alcoholic fatty liver disease (NAFLD) and non-alcoholic steatohepatitis (NASH)-related liver cancer histopathogenic pathway (Borena et al., 2012). In patients with NAFLD, cholesterol metabolism is characterized by increased hepatic cholesterol synthesis and diminished triglyceride and low-density lipoprotein cholesterol uptake; consequently, these patients experience hyperlipidemia (Hendrikx et al., 2014).

Two prospective Japanese cohort studies showed a significant inverse association between serum total cholesterol (TC) levels and the risk of liver cancer (Okamura et al., 2007; Iso et al., 2009). However, the association between liver cancer and being overweight/obese in

*[1]Department of Public Health, Faculty of Medicine and Graduate School of Medicine, Hokkaido University, Hokkaido, [2]Research Unit of Advanced Interdisciplinary Care Science, Osaka City University Graduate School of Human Life Science, Osaka, [3]Department of Medical Statistics, Toho University, Faculty of Medicine, [11]Department of Preventive Medicine and Public Health, Keio University School of Medicine, Tokyo, [4]Department of Environmental Medicine, Graduate School of Medical Sciences, Kyushu University, Fukuoka, [5]Department of Clinical Studies, Radiation Effects Research Foundation, Hiroshima, [6]Tohoku Medical Megabank Organization, Tohoku University, Sendai, [7]Graduate School of Medicine, Tohoku University, Miyagi, [8]Department of Preventive Medicine and Public Health, Fukuoka University, Fukuoka, [9]Department of Public Health, [10]Center for Epidemiologic Research in Asia, Shiga University of Medical Science, Shiga, Japan. *For Correspondence: tamaa@med.hokudai.ac.jp*

view of the degree of serum TC has not been reported yet. This study aimed to elucidate the associations between BMI and TC levels and liver cancer-related mortality by conducting the largest pooled analysis of pooled cohort data in the Japanese population to date.

Materials and Methods

Study population and data collection

The Evidence for Cardiovascular Prevention from Observational Cohorts in Japan (EPOCH-JAPAN) is a pooled analysis of individual participant data from 13 cohorts that has been described in detail elsewhere (Murakami et al., 2008; Fujiyoshi et al., 2012; Nagasawa et al., 2012; Nakamura et al., 2012; Asayama et al., 2014; Satoh et al., 2015). Studies were included in the EPOCH-JAPAN pooled analysis if they conducted health examinations, had >1,000 participants, and followed up patients for >10 years. Consequently, nationwide and regional cohort studies were included in this study.

Of the 101,977 participants (41,886 men and 60,091 women) from 12 of the 13 cohorts that provided data on liver cancer-related mortality, we excluded participants aged <50 or ≥80 years (n = 34,909), those with a previous history of cancer (n = 5,551), and those with missing BMI data (n = 358). Another 1,823 participants were excluded because of missing data on TC levels (n = 1,819) or familial hypercholesterolemia (TC levels of >500 mg/dL; n = 4) (Raal and Santos, 2012). A total of 59,332 participants (23,853 men and 35,479 women) were analyzed in the present study.

TC levels were measured enzymatically in all cohort studies except the National Integrated Project for Prospective Observation of Non-Communicable Disease And its Trends in the Aged (NIPPON DATA) 80 cohort study, in which levels were measured using the Lipid Standardization Program administered by the Lieberman-Burchard direct method.

Outcome

The primary outcome of this study was death due to primary liver cancer (International Classification of Disease [ICD] code 155 for ICD-9 and C22 for ICD-10). Causes of death were coded based on ICD-9 until the end of 1994 and ICD-10 starting in 1995. In the majority of studies, date and cause of death were confirmed by the National Vital Statistics of the Ministry of Health, Labor, and Welfare, Japan. Other sources included autopsy, medical records, health examination, and questionnaires.

Statistical analysis

Three different categories of BMI and TC levels were used in this study (BMI: <18.5, 18.5–24.9, and ≥25.0 kg/m^2; TC: <160, 160–219, and ≥220 mg/dL); their combinations were created as dummy variables. Sex-specific multivariable hazard ratios (HRs) and confidence intervals (CIs) for liver cancer-related mortality were estimated using a cohort-stratified Cox proportional hazards model. Age (continuous), systolic blood pressure (SBP; continuous), smoking status (never, former, and current smokers), alcohol consumption (never, former, and current alcohol drinkers) were included in the multivariable models. Heterogeneity for the associations between cohort studies and combinations of BMI and TC categories for liver cancer-related mortality was assessed by likelihood ratio tests with a cross-product term for each categorical variable. Furthermore, interactions between combinations of BMI and TC categories for liver cancer-related mortality were evaluated using a cross-product term for each categorical variable. To investigate potential reverse causation, we performed a secondary analysis of the population excluding participants followed for less than the first 5 years from the baseline in each cohort. An alpha level of 0.05 was considered statistically significant. All statistical analyses were performed using SAS 9.4 (SAS Institute Inc., Cary, NC, USA).

Results

During 849,360 person-years (327,212 for men and 522,148 for women) of follow-up (median follow-up period, 14.3 years), 447 individuals (266 men and 181 women) died due to liver cancer.

Table 1 shows the characteristics of the study participants by cohort. The numbers of study participants ranged from 449 men in the Tanno-Sobetsu cohort and 311 women in the YKK cohort to 6,458 men and 10,737 women in the Japan Collaborative Cohort (JACC) study. Mean age (± standard deviation [SD]) ranged between 54.5 ± 2.9 and 54.2 ± 2.6 years for men and women, respectively, in the YKK workers cohort to 65.4 ± 7.0 and 64.2 ± SD 6.7 years for men and women, respectively in the Osaki cohort. BMI levels were highest in the Osaki cohort for men and the Tanno-Sobetsu cohort for women (23.6 ± 2.9 and 24.4 ± 3.5 kg/m^2, respectively) and lowest in the NIPPON DATA 80 cohort for men and the YKK and Suita cohorts for women (22.2 ± 2.9, 22.6 ± 2.6, and 22.6 ± 3.4 kg/m^2, respectively). We found the highest TC levels in the Suita cohort for both men and women (202.3 ± 35.7 and 224.0 ± 36.8 mg/dL, respectively) and the lowest TC levels in the Tanno-Sobetsu cohort (185.0 ± 30.1 in men and 201.7 ± 35.0 mg/dL in women).

The baseline distributions of study participants according to BMI and TC levels are depicted in Table 2. For all BMI categories, male participants in the highest TC category (≥220 mg/dL) were younger, had lower systolic blood pressure, and were less likely to be current smokers and alcohol drinkers than those in the lowest TC category (<160 mg/dL). Among women, participants in the highest TC category had a higher blood pressure and were less likely to be current-smokers than those in the lowest TC category.

The HRs for liver cancer-related mortality according to BMI and TC levels are shown in Figures 1A and B. When compared with men who were classified as having both intermediate BMI and TC levels (18.5–22.4 kg/m^2 and 160–219 mg/dL, respectively), those in the lowest TC category (<160 mg/dL) had a significantly increased risk for liver cancer-related mortality irrespective of their BMI category (HR 4.37, 95% CI 2.30–8.28; HR 4.02, 95% CI 2.95–5.48; and HR 7.05, 95% CI 4.41–11.26 for the low,

Table 1. Characteristics of the Study Participants in Each Cohort

		Follow- up period	Age	BMI	TC	SBP	DBP	Smoking status			Alcohol drinking		
Cohort name	n	(years)	(years)	(kg/m²)	(mg/dl)	(mm Hg)	(mm Hg)	Never	Former	Current	Never	Former	Current
Men													
Tanno-Sobetsu	449	9,489	56.4±4.9	23.0±2.8	185.0±30.1	134.7±21.0	83.4±10.0	107 (27.9)	-	277 (72.1)	123 (32.2)	-	259 (67.8)
Osaki	5,465	59,761	65.4±7.0	23.6±2.9	193.5±33.4	133.9±17.1	80.3±10.7	1116 (21.5)	1621 (31.3)	2446 (47.2)	877 (16.7)	447 (8.5)	3941 (74.9)
Ohasama	697	8,405	63.4±7.3	23.0±2.9	185.1±33.6	135.5±17.3	76.6±11.1	361 (51.8)	-	336 (48.2)	278 (39.9)	-	419 (60.1)
Oyabe	1,217	11,681	63.0±7.0	22.6±2.7	180.6±33.0	132.9±20.6	79.2±11.6	557 (45.8)	-	660 (54.2)	319 (26.2)	-	898 (93.8)
YKK workers	568	8,863	54.5±2.9	22.7±2.6	201.7±34.1	125.4±17.1	78.0±12.6	142 (26.2)	87 (16.1)	313 (57.7)	111 (21.2)	15 (2.9)	398 (96.0)
Suita	2,061	26,223	63.9±8.2	22.7±3.0	202.3±35.7	134.7±22.5	80.5±12.4	352 (17.2)	745 (36.5)	945 (46.3)	478 (27.4)	124 (7.1)	1142 (65.5)
RERF	926	14,566	62.2±7.7	22.3±2.9	201.2±37.3	137.7±21.3	86.0±11.2	112 (13.0)	289 (33.5)	461 (53.5)	133 (16.3)	59 (7.2)	625 (96.5)
Hisayama	788	9,481	62.3±7.8	22.7±2.9	196.1±41.6	137.2±20.6	80.6±11.1	144 (18.3)	265 (33.6)	379 (48.1)	26 (4.7)	65 (11.8)	461 (93.5)
JACC study	6,458	103,970	61.4±6.7	22.7±2.8	186.8±34.3	137.0±19.3	81.3±11.4	1444 (23.3)	1613 (26.0)	3148 (50.7)	1258 (20.1)	355 (5.7)	4659 (74.3)
NIPPON DATA 80	1,961	34,836	61.4±8.0	22.2±2.9	185.3±33.4	145.8±21.9	85.6±12.6	321 (16.4)	431 (22.0)	1205 (61.6)	468 (23.9)	165 (8.4)	1323 (67.6)
NIPPON DATA 90	1,726	22,307	62.1±7.8	22.8±3.0	197.2±37.1	144.0±20.7	85.4±11.9	368 (21.3)	491 (28.4)	867 (50.2)	589 (34.1)	158 (9.2)	979 (56.7)
Osaka	1,537	17,630	62.4±7.1	23.2±2.8	201.4±34.6	139.0±20.8	84.7±11.4	291 (19.0)	487 (31.7)	757 (43.3)	286 (18.6)	122 (8.0)	1126 (73.4)
Women													
Tanno-Sobetsu	502	11,310	56.1±4.3	24.4±3.5	201.7±35.0	139.8±21.4	84.4±9.9	407 (92.5)	-	33 (7.5)	417 (94.8)	-	23 (5.2)
Osaki	7,783	86,987	64.2±6.7	24.3±3.2	215.1±33.3	131.6±18.2	78.1±11.0	5496 (94.0)	97 (1.7)	252 (4.3)	4731 (77.4)	180 (2.9)	1204 (19.7)
Ohasama	1,124	15,049	61.3±7.0	23.9±3.3	208.6±36.3	130.6±16.2	73.3±10.4	1104 (98.2)	-	20 (1.8)	1070 (95.2)	-	54 (4.8)
Oyabe	2,528	25,623	60.9±6.8	23.4±3.1	206.5±35.9	127.9±19.5	75.2±10.5	2475 (97.9)	-	53 (2.1)	2243 (88.7)	-	285 (11.3)
YKK workers	311	5,087	54.2±2.6	22.6±2.6	221.9±40.9	121.2±18.7	74.7±12.8	256 (99.2)	0 (0)	2 (0.8)	223 (83.8)	1 (0.4)	42 (15.8)
Suita	2,108	29,075	63.0±8.1	22.6±3.4	224.0±36.8	133.5±22.6	78.1±11.9	1744 (84.9)	88 (4.3)	221 (10.8)	1488 (72.1)	39 (1.9)	537 (26.0)
RERF	2,097	36,820	63.7±7.5	23.1±3.6	221.3±38.8	135.6±22.4	82.2±11.6	1787 (86.7)	74 (3.6)	201 (9.7)	1178 (61.8)	35 (1.8)	692 (36.3)
Hisayama	1,076	13,882	62.8±8.2	22.9±3.3	220.5±40.5	134.8±21.7	76.0±10.6	984 (91.4)	21 (2.0)	71 (6.6)	978 (91.0)	14 (1.3)	83 (7.7)
JACC study	10,737	186,433	60.3±6.6	23.4±3.2	208.5±40.5	134.0±19.3	78.9±11.0	9786 (95.9)	113 (1.1)	303 (3.0)	8375 (80.9)	109 (1.1)	1864 (18.0)
NIPPON DATA 80	2,532	50,480	61.5±7.8	23.1±3.5	201.9±33.8	143.0±22.0	82.7±11.8	2225 (78.9)	68 (2.7)	238 (9.4)	2076 (82.2)	42 (1.7)	408 (16.2)
NIPPON DATA 90	2,201	30,465	62.0±7.8	23.4±3.3	218.9±37.7	141.9±20.0	82.5±11.7	1970 (89.5)	57 (2.6)	174 (7.9)	2075 (94.3)	21 (1.0)	105 (4.8)
Osaka	2,480	30,937	61.3±7.5	23.5±3.4	223.7±35.6	137.9±20.6	81.6±11.2	2293 (92.6)	44 (1.8)	139 (5.6)	2129 (86.0)	56 (2.3)	291 (11.8)

RERF, the Radiation Research Foundation; JACC study, the Japan Collaborative Cohort study; NIPPON DATA, National Integrated Project for Prospective Observation of Non-communicable Disease And its Trends in the Aged; TC, total serum cholesterol levels; SBP, systolic blood pressure; DBP, diastolic blood pressure; BMI, body mass index (kg/m²); Values are expressed as mean±standard deviation or numbers (%); In the studies of Tanno-Sobetsu, Ohasama and Oyabe, former smokers were categorized as never smokers; In the studies of Tanno-Sobetsu, Ohasama, and Oyabe, former drinkers were categorized as never drinkers.

Table 2. Baseline Distribution of the Study Participants According to BMI and TC

BMI (kg/m²)	<18.5			18.5-24.9			≥25.0		
TC (mg/dl)	<160	160-219	≥220	<160	160-219	≥220	<160	160-219	≥220
Men									
Person-years	4,026	9,549	2,098	43,480	150,205	45,558	7,870	44,595	19,831
No. of case (n)	11	3	2	86	84	14	24	32	10
Age (years)	66.3±7.3	66.0±7.8	65.9±7.4	63.0±7.5	62.6±7.4	62.3±7.5	62.0±7.5	62.0±7.2	61.0±7.2
SBP	133.2±22.7	133.1±22.9	129.5±18.5	136.2±20.3	135.9±20.2	136.3±19.8	140.0±19.0	140.6±19.0	141.1±18.8
DBP	77.5±12.0	78.3±11.9	77.4±11.0	80.2±11.6	80.9±11.7	81.9±11.5	84.0±11.3	84.8±11.0	86.2±11.4
Smoking									
Never	44 (12.4)	95 (13.1)	30 (18.6)	605 (19.4)	2368 (13.1)	730 (22.7)	138 (24.5)	907 (28.9)	398 (28.0)
Former	60 (16.9)	180 (24.8)	51 (31.7)	595 (19.0)	2609 (24.8)	1,010 (31.4)	138 (24.5)	955 (30.5)	431 (30.4)
Current	251 (70.7)	452 (62.2)	80 (49.7)	1924 (61.6)	5464 (62.2)	1,472 (45.8)	288 (51.1)	1273 (60.6)	590 (41.6)
Alcohol drinking									
Never	86 (24.2)	223 (30.9)	57 (35.8)	587 (18.7)	2,288 (21.8)	794 (24.7)	101 (17.9)	691 (21.9)	354 (24.7)
Former	32 (9.0)	59 (8.2)	21 (13.2)	194 (6.2)	665 (6.3)	232 (7.2)	30 (5.3)	176 (5.6)	101 (7.0)
Current	238 (66.9)	440 (60.9)	81 (50.9)	2,364 (75.2)	7,542 (71.9)	2,192 (68.1)	434 (76.8)	2,289 (72.5)	980 (68.3)
Women									
Person-years	2,859	16,498	7,574	21,369	186,130	132,538	6,841	77,358	70,981
No. of case (n)	1	7	2	24	68	15	19	35	10
Age	64.1±8.7	63.6±7.7	64.1±7.6	61.1±7.8	61.4±7.3	61.9±7.1	61.9±7.7	61.7±7.1	62.2±6.9
SBP	125.8±21.3	128.6±21.0	129.3±20.6	131.7±20.8	131.8±19.7	133.9±20.0	137.4±21.6	137.9±19.5	140.8±20.1
DBP	73.0±11.4	75.0±11.6	74.6±11.4	76.4±11.2	77.5±11.0	78.8±11.2	80.6±11.3	81.5±11.1	83.2±11.3
Smoking									
Never	171 (88.2)	940 (87.9)	461 (88.7)	1,264 (93.5)	10,807 (93.9)	77,49 (92.4)	401 (93.9)	4,519 (94.0)	4,215 (93.1)
Former	3 (1.5)	17 (1.6)	21 (4.0)	12 (0.9)	174 (1.5)	160 (1.9)	3(0.7)	78 (1.6)	94 (2.1)
Current	30 (10.3)	113 (10.6)	38 (7.3)	76 (5.6)	534 (4.6)	477 (5.7)	23 (5.4)	208 (4.3)	218 (4.8)
Alcohol drinking									
Never	156 (81.7)	877 (82.4)	439 (84.3)	1,125 (83.1)	9,497 (81.4)	6,851 (81.2)	366 (83.9)	3,924 (80.8)	3,748 (81.8)
Former	3 (1.6)	20 (1.9)	9 (1.7)	13 (1.0)	148 (1.3)	138 (1.6)	7 (1.6)	72 (1.5)	87 (1.9)
Current	32 (16.8)	167 (15.7)	73 (14.0)	216 (16.0)	1,983 (17.1)	1,445 (17.1)	63 (14.4)	862 (17.7)	747 (16.3)

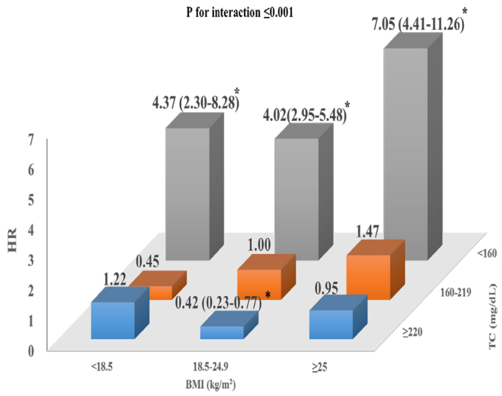
Values are expressed as mean±standard deviation or numbers (%). BMI, body mass index (kg/m2); TC, total serum cholesterol levels; SBP, systolic blood pressure; DBP, diastolic blood pressure; In the studies of Tanno-Sobetsu, Ohasama and Oyabe, former smokers were categorized as never smokers; In the studies of Tanno-Sobetsu, Ohasama, and Oyabe, former drinkers were categorized as never drinkers.

intermediate, and high BMI categories, respectively) after adjusting for potential confounders. In women, those classified as having intermediate and high BMI and low TC also showed a significantly increased risk for liver cancer-related mortality (HR 2.88, 95% CI 1.72–4.80; HR 8.07, 95% CI 4.76–13.67, respectively), as compared with those having intermediate BMI (18.5–22.4 kg/m^2) and TC (160–219 mg/dL). On the other hand, individuals classified as being in the intermediate BMI and high TC category had a significantly decreased risk for liver cancer-related mortality irrespective of their sex (HR 0.42, 95% CI 0.23–0.44 for men and HR 0.26, 95% CI 0.15–0.46 for women). Women with high BMI and TC had significantly decreased risks for liver cancer-related mortality (HR 0.29, 95% CI 0.14–0.5). These associations remained after limiting participants' follow-up periods to >5 years (Figures 1C and D). Tests for heterogeneity between cohort studies and combinations of BMI and TC levels were statistically significant among men (P = 0.01 for men; P = 0.93 for women). The tests for the interactions between combinations of BMI and TC levels were statistically significant (P < 0.001 in both men and women).

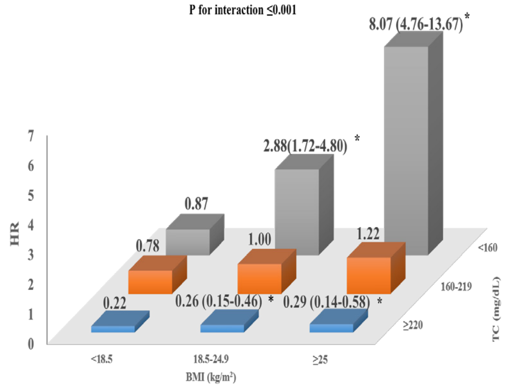
Discussion

In this large pooled analysis, we found that being overweight/obese, combined with low TC levels, showed the strongest association with liver cancer-related mortality, with a significant interaction between BMI and TC in both men and women. Our results also show that participants with TC levels ≥160 mg/dL did not have an increased risk for liver cancer-related mortality, irrespective of BMI category.

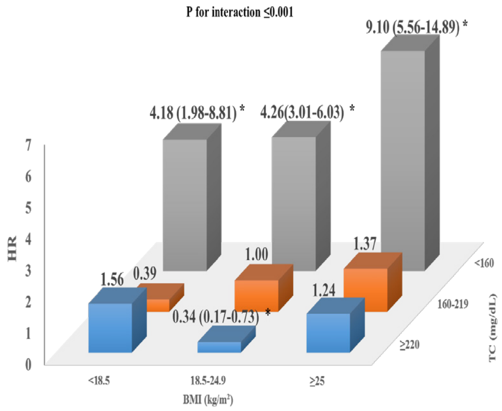
Previous studies reported inconsistent results regarding the association between being overweight/obese and liver cancer-related mortality in the Japanese population. A systematic review (Saunders et al., 2010) and epidemiologic study of Japanese individuals that analyzed the data of nine cohorts and three case-control studies Tanaka et al., (2012) reported that study subjects who were overweight/obese had a higher risk of liver cancer-related mortality. In contrast, a pooled analysis of 39 cohorts from Asia (including 424,519 Japanese participants), Australia, and New Zealand did not show this association



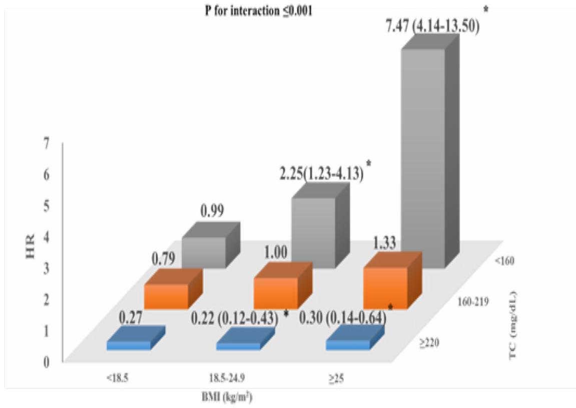
A. Men



B. Women



C. Men excluding participants followed for more than first five years from the baseline



D. Women excluding participants followed for more than first five years from the baseline

Figure 1. Hazard Ratios of Mortality from Liver Cancer According to BMI with TC; BMI, Body Mass Index, TC, Serum Total Cholesterol, HR, Hazard ratio, *, P<0.05; The Hazard Ratios Were Calculated Using a Cox Proportional Hazards Regression Model after Adjustment for Age, Smoking and Alcohol Drinking Status, and Systolic Blood Pressure. Analyses were stratified by cohort. The interaction between BMI and TC was assessed using likelihood ratio tests.

(Parr et al., 2010). A nationwide cohort study in Japan reported that only men who were overweight/obese (BMI ≥25 kg/m²) and who had a history of liver disease had a higher risk of mortality from liver cancer (Li et al., 2013). In Western countries, NAFLD and NASH are thought to contribute to the association between being overweight/obese and liver cancer-related mortality (Borena et al., 2012). The estimated prevalence rates of NAFLD and NASH in the Japanese population are 29.7 and 2.7%, respectively (Eguchi et al., 2012). It has been suggested that about 12% of NASH-associated hepatic cirrhosis further progresses to liver cancer (Ascha et al., 2010). The majority of patients with NAFLD are hyperlipidemic (Hendrikx et al., 2014). In this study, we used TC level to evaluate hyperlipidemic status because a large prospective study indicated no association between triglyceride levels and incidence of hepatocellular carcinoma (Borena et al., 2012). However, our results indicate no increased risk for liver cancer-related mortality among study participants who were overweight/obese and had high TC levels.

The majority of liver cancer cases in Japan (about 70%) are related to hepatitis C infection (Goh et al., 2015). Hepatitis C virus infection and subsequent liver cirrhosis are known to cause low blood cholesterol levels (Eisenberg and Levy, 1975); this has been positively associated with liver cancer incidence (Iso et al., 2009) and mortality (Okamura et al., 2007; Nago et al., 2011). A cross-sectional study indicated that low serum TC levels among patients with chronic hepatitis C were an independent predictor for fibrosis (Forns et al., 2002) and subsequent liver cancer (Tanaka et al., 2004). It has also been shown that obesity plays a critical role in the pathogenesis of fibrosis evolving to cirrhosis (Thein et al., 2008) and liver cancer (Masuzaki et al., 2009) in people with hepatitis C infection (Miyaaki et al., 2011). Although we had no data concerning the presence or absence of hepatitis C infection, our results suggest that the association between being overweight/obese and liver cancer-mortality in the Japanese population might interacted with hepatitis C infection.

The main strength of our study is that we conducted a large-scale pooled analysis of >100,000 Japanese individuals included in 12 cohort studies (including nationwide and regional cohort studies) with a long follow-up period of >10 years. However, our study also has several limitations. First, we could not obtain information on the use of cholesterol-lowering medications in all

12 cohort studies. The baseline surveys of the cohorts included in the EPOCH-JAPAN pooled analysis were performed before or around 1990. The first statin, which is the medication that is mainly used for treating hypercholesterolemia in Japan, was introduced in 1989 (Mabuchi, 1998); therefore, the lack of data on cholesterol-lowering drugs might not have affected our data significantly. Second, data on the histological types of liver cancer were not available for all cases. However, the most prevalent (90%) type of primary liver cancer in Japan is hepatocellular carcinoma (Ikai et al., 2007), which is involved in hepatic cholesterol synthesis. Thus, this might have had little effect on our results. Third, we could not obtain information on the individuals' history of cancer in 43.6% of participants in nine cohorts. Further epidemiological studies are needed to clarify the impact of hepatitis C infection on the results.

In conclusion, this large-scale pooled analysis of Japanese individuals demonstrated that being overweight/obese, concurrent with low TC levels, was associated with an increased risk for liver cancer-related mortality. Further epidemiological studies in the Japanese population that take into account data on hepatitis C virus infection are needed to elucidate the association between being overweight/obese and liver cancer-related mortality.

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