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Obesity, Diabetes, Serum Glucose, and Risk of Primary Liver Cancer by Birth Cohort, Race/Ethnicity, and Sex: Multiphasic Health Checkup Study

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Abstract

Objective—Obesity and diabetes have been associated with liver cancer. However, recent US-based studies have suggested a lack of association between obesity and liver cancer among blacks and women.

Methods—We conducted a nested case-control study within the Multiphasic Health Checkup (MHC) cohort of Kaiser Permanente Northern California (KPNC) members. Liver cancer was diagnosed using the KPNC Cancer Registry. Detailed self-administered questionnaires and a standardized examination that included measurement of height and weight and a 1-hour glucose tolerance test were completed prior to diagnosis of liver cancer for cases (n=450) and matched controls (4,489). Height and weight were utilized to calculate BMI (kg/m²) as a measure of adiposity: underweight (15–<18.5 kg/m²), normal weight (18.5–<25 kg/m²), overweight (25–<30 kg/m²), and obese (≥30 kg/m²). Conditional logistic regression was used to estimate odds ratios (ORs) and 95% confidence intervals (CI) for the association between BMI, diabetes, and serum

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glucose with subsequent incidence of liver cancer, in models that were stratified by birth cohort, race/ethnicity, and sex.

Results—Compared to normal weight individuals, obese individuals had a 2.4-fold increased risk of liver cancer (OR=2.38, 95% CI: 1.68–3.36), and overweight individuals had a 32% increased risk (OR=1.32, 95% CI: 1.03–1.70). This association did not differ when stratified by birth cohort, race/ethnicity, or sex ($p_{\text{int}} > 0.05$). Among blacks and women, obesity was associated with at least a 2-fold increased risk of liver cancer (OR=2.29, 95% CI: 1.22–4.28 and OR=2.00, 95% CI: 1.14–3.52, respectively). More moderate increased odds ratios were noted for diabetes (OR=1.28, 95% CI: 0.65–2.54) and serum glucose ≥ 200 mg/dL (OR=1.63, 95% CI: 0.48–5.55), although the results did not attain statistical significance.

Conclusion—In summary, our finding of a positive association between obesity and liver cancer suggests that a higher BMI may increase the risk of liver cancer in the US, for both sexes and all race/ethnicities.

1. INTRODUCTION

Liver cancer usually develops on a background of oxidative stress and inflammation, triggered by chronic infection with hepatitis B or C virus (HBV or HCV), excess alcohol consumption, aflatoxin exposure, or obesity [1]. Obesity can cause chronic, low-grade systemic inflammation through increased levels of TNF- α , IL-6, leptin, free fatty acids, and TLR4 and decreased adiponectin levels [2]. This systemic inflammation is believed to contribute to metabolic dysregulation, including onset of insulin resistance and subsequent diabetes [3], and the development and progression of nonalcoholic fatty liver disease (NAFLD) to non-alcoholic steatohepatitis, fibrosis, cirrhosis; culminating in liver cancer development [2]. Diabetes further contributes to metabolic dysregulation and may lead to the development and progression of NAFLD [4] and risk of liver cancer, independent of obesity [5–7].

The incidence of primary liver cancer, which includes both hepatocellular carcinoma and intrahepatic cholangiocarcinoma, has been increasing in the United States (US) since 1980 [8], approximately ten years after the beginning of the obesity epidemic [9]. Although there is substantial evidence from prospective cohort studies that obesity is associated with increased risk of liver cancer [10], only two studies have investigated this association in a US population, where the risk factor profile may be different from other populations. Both cohort studies reported that obesity is associated with 64–94% increased risk of liver cancer, but the association may differ by race/ethnicity or sex. Additionally, both of these prospective studies were conducted after the start of the obesity epidemic in the US and therefore may have very different risk factor profiles [11](Campbell et al., Under Review). Diabetes has been consistently associated with a 2–2.5 fold increased risk of liver cancer [12–15], but few studies, all non-US, have investigated serum glucose measures [16, 17].

Thus, we examined the effects of adiposity on liver cancer risk by examining the association between obesity, diabetes, and serum glucose and subsequent risk of liver cancer in a racially and ethnically diverse US population of men and women, the majority of whom were recruited beginning in 1964 prior to the start of the obesity epidemic in the 1970s [9].

2. METHODS

2.1. Study Design and Population

We conducted a nested case-control study, within a large cohort, of the associations between body mass index, diabetes, and glucose and the risk of primary liver cancer.

The Multiphasic Health Checkup (MHC) cohort consists of Kaiser Permanente Northern California (KPNC) members who underwent a MHC at either the Kaiser Oakland or San Francisco Medical Center. Kaiser Permanente members presenting for a routine health examination, for any reason, were invited to complete a detailed questionnaire and standardized physical examination, including clinical and laboratory testing [18, 19]. Kaiser Permanente members are broadly representative of the San Francisco Bay region underlying census demographics [20, 21]. The present study includes cohort members who completed an examination between 1964 and 1992, with the majority of individuals (69.9%) enrolled between 1964 and 1973.

2.2. Exposure Measurements

Height and weight were measured during a standardized physical examination by trained examiners, using a written, systematic protocol and standardized instruments. These measurements were utilized to calculate BMI (kg/m^2) as a measure of adiposity and categorized according to the World Health Organization criteria [22]: underweight ($<18.5 \text{ kg}/\text{m}^2$), normal weight ($18.5\text{--}25 \text{ kg}/\text{m}^2$), overweight ($25\text{--}30 \text{ kg}/\text{m}^2$), and obese ($>30 \text{ kg}/\text{m}^2$). Individuals with a BMI of less than 15 were excluded. MHC cohort participants additionally underwent a 1-hour glucose tolerance test to determine serum glucose levels (mg/dL ; categorized as <140 , $140\text{--}199$, and ≥ 200). Finally, participants reported whether they had ever been diagnosed with diabetes or “sugar disease” – type was not specified.

2.3. Outcome Measurements

To determine cancer outcomes, the KPNC Cancer Registry was used. Prior to 1973, KPNC maintained a cancer registry for internal purposes. In 1973, the KPNC Cancer Registry was reorganized as part of the National Cancer Institute’s Surveillance, Epidemiology, and End Results programs in California. Incident primary liver cancer cases were defined according to the *International Classification of Disease for Oncology* diagnostic code of C22. We identified 450 cases of incident liver cancer occurring after the individual’s interview date through December 31, 2009 (mean follow-up = 22.5 years). The KPNC Cancer Registry has a follow-up rate of over 95% and a case ascertainment rate of over 98% [23].

To maximize power [24], ten controls were individually matched to each liver cancer case. However, for 25 cases, ten eligible controls could not be identified. Matching factors included period of enrollment in the MHC cohort (enrollment years 1964–1973, 1973–1977, 1978–1985, or 1985–1992), age at enrollment (± 1 year), date of (first, if two) blood draw (± 6 months), sex, and race (White, Black, Asian, or Other). If the case had two blood draws, date of second blood draw (± 12 months) was also included as a matching criterion. Matching on blood draw was conducted for a parent study, which examined the association between blood levels of environmental pollutants and liver cancer.

2.4. Statistical Analysis

Conditional logistic regression was performed on matched pairs of cases and controls to calculate odds ratios (ORs) and corresponding 95% confidence intervals (CIs) for the association of BMI, diabetes, and serum glucose with risk of liver cancer [25]. To better describe the relationship between BMI and liver cancer, cubic splines were also utilized. All analyses were conducted using SAS version 9.3 (SAS Institute, Cary, NC).

We examined effect measure modification of BMI by birth cohort (1884–1900, 1901–1924, 1925–1944, and 1945–1962). Relative to other birth cohorts, the 1945–1965 birth cohorts have a unique risk factor profile for liver cancer, including high prevalence of HCV infection [26] and obesity [27]. We also examined effect modification by race (white, black, Asian, other), sex, diabetes (yes/no), cigarette smoking (never/ever), and alcohol consumption (not current or current drinker). Departures from the multiplicative null were assessed using likelihood ratio tests to compare regression models with and without a multiplicative term [25].

Potential confounders included cigarette smoking (never, former, current), alcohol consumption (not current or current drinker), and education (<high school, high school, some college or technical school, college graduate, or post-college graduate). If elimination of a variable changed the log odds ratio by 10%, the variable was considered a confounder and included in the model [25]; no covariates met this criterion. Thus, the final models accounted for only the matching terms.

Adjusted population attributable fractions (PAFs) for BMI and diabetes were computed utilizing a method for estimating PAFs from population-based case-controls studies with an adjusted odds ratios [28, 29].

2.5. Sensitivity Analyses

Models adjusted for both smoking and alcohol consumption were examined as a sensitivity analysis. As an additional sensitivity analysis, we examined the association between obesity and liver cancer prior to the beginning of the obesity epidemic. Thus, we restricted the analysis to individuals who entered during the first enrollment period in the MHC study (1964–1973).

3. RESULTS

Characteristics of cases and controls are shown in Table 1. Cases were slightly older and were more likely to be smokers and have lower educational attainment than the controls. Cases and controls were similar in the distribution of alcohol consumption and year of birth.

As shown in Table 2, obese individuals had a 2.4-fold increased risk of liver cancer (OR=2.38, 95% CI: 1.68–3.36), and overweight individuals had a 32% increased risk (OR=1.32, 95% CI: 1.03–1.70). A trend of 33% increased liver cancer risk per 5-kg/m² was observed (OR=1.33, 95% CI: 1.15–1.53). When BMI was further stratified, severely obese individuals (BMI ≥ 40 kg/m²) had a nearly 5-fold increase in risk (OR=4.76, 95% CI: 1.48–15.37). This increasing trend with increasing BMI was also seen in the spline model (Figure

1). Although non-significant, the associations of diabetes and serum glucose with liver cancer were suggestive of an increased risk (OR=1.28, 95% CI: 0.65–2.54 and OR=1.63, 95% CI: 0.48–5.55, respectively). The population attributable fraction for obesity was 19.0% and for diabetes was 0.8%.

There was no evidence of effect measure modification by any covariate ($p > 0.05$) on the association between BMI and liver cancer in any of the models (Tables 3–5 and Supplemental Table 1). A trend of 17–36% increased liver cancer risk per 5-kg/m² was observed in each birth cohort. When results were stratified by race/ethnicity, obese white individuals had a 2.8-fold increased risk of liver cancer (OR=2.76, 95% CI: 1.69–4.51), obese black individuals had a 2.3-fold increased risk (OR=2.29, 95% CI: 1.22–4.28), and obese Asians had a 2.5-fold increased risk (OR=2.50, 95% CI: 0.74–8.47). While there was no evidence of effect measure modification by sex, the point estimate for the association between obesity and liver cancer was somewhat higher in men (OR=2.68, 95% CI: 1.73–4.16) than women (OR=2.00, 95% CI: 1.14–3.52). When we stratified by sex and race/ethnicity, we observed a 3-fold increased risk of liver cancer among obese black males (OR=3.05, 95% CI: 1.28, 7.26). Among white and Asian males, obese individuals were also at an increased risk of liver cancer (OR=3.37, 95% CI: 1.82–6.24 and OR=2.26, 95% CI: 0.57–8.95, respectively).

In the sensitivity analysis adjusted for smoking and drinking, the results were not substantially different than our main model (Supplemental Table 2). Similarly, when the study population was restricted to individuals who entered during the first enrollment period, results were robust for obesity (Supplemental Table 3).

4. DISCUSSION

This study examined the association between BMI, diabetes, and serum glucose and liver cancer. In this study, each 5-kg/m² increase in BMI was associated with a 33% increased risk of liver cancer. Obese individuals were at a 2.4 fold increased risk of liver cancer, while overweight individuals were at a 32% increased risk. Diabetes and serum glucose were possibly associated with an increased risk of liver cancer.

Previous studies have reported that adiposity is associated with an increased risk of liver cancer. In a recent meta-analysis of prospective studies, overweight and obesity were associated with an 18% and 83% increased risk of liver cancer, respectively [10]. Another meta-analysis reported a 39% increased risk of liver cancer with each 5 kg/m² increase [30]. Two recent studies from the US reported similar results to the prior meta-analyses [11] (Campbell et al., Under Review). Our results are more similar to a SEER-Medicare analysis, which reported a 2.5-fold increased risk of liver cancer associated with diabetes or obesity [31].

The US Liver Cancer Pooling Project examined the category of BMI ≥ 40 kg/m², but only reported a 2.5 fold increase in risk (Campbell et al., Under Review). In the current study, we report almost a 5-fold increase in risk of liver cancer. Additionally, the Liver Cancer Pooling Project (Campbell et al., Under Review) and the US Multiethnic Cohort Study [11] reported

differences in the association between obesity and liver cancer by race, specifically a lack of association between BMI and liver cancer among blacks. We did not find notable differences by race/ethnicity in our population. Conversely to what was reported by the Liver Cancer Pooling Project and Multiethnic Cohort Study and replicated in the Southern Communities Cohort Study, we found a 3-fold increased risk of liver cancer among obese black men. Differences between previous studies and our study could be due to prevalence of liver cancer risk factors, differing birth cohorts, or chance.

Disease incidence is affected by the changing prevalence of risk factors to which a population is exposed. If the prevalence of non-adipose liver cancer risk factors is high in a population (e.g., high prevalence rates of HBV or HCV infection), the “baseline” incidence proportion (i.e., the proportion of non-obese individuals being diagnosed with liver cancer) will be high and the proportion of cases associated with obesity will be relatively low. Thus, strength of effect, as measured by a ratio of proportions, depends on how common or rare other disease mechanisms are, in which obesity is not a factor [25]. Here, we hypothesize that the underlying prevalence of liver cancer risk factors, such as HBV/HCV infection, alcohol consumption, smoking, or other unknown risk factors, differs between these studies. This could cause the association between obesity and liver cancer among black males to be attenuated. In the Multiethnic Cohort/Southern Communities Cohort Study and Liver Cancer Pooling Project, the percentage of never-smokers among black males was slightly lower than the current report (31.8 and 30.8 vs. 35.5%), but the percentage of non-drinkers was higher (41.5 and 30.6 vs. 21.9%). Unfortunately, we lacked information on HBV and HCV in our cohort to investigate the differences in prevalence between the current study and previous studies.

In the current analysis, the strength of association between obesity and liver cancer among black males was attenuated when we included the 1945–1962 birth cohorts in the model (OR=3.05, 95% CI: 1.28–7.26) versus excluding these birth cohorts (OR=3.38, 95% CI: 1.18–9.68). The 1945–1965 birth cohorts are known to have a high prevalence of HCV infection, and within these birth cohorts, the prevalence of HCV infections among blacks is nearly twice what is reported in whites [26]. Although HCV is currently the main risk factor for liver cancer among US blacks [31], HCV is unlikely to be the main risk factor in the future, as the highest-risk 1945–1965 birth cohorts age out of the population and new second generation direct-acting antivirals are increasingly utilized to treat HCV infections, which have higher sustained virologic response rate, fewer side effects, and require a shorter course of treatment. However, the rates of obesity are forecast to continue to increase. In 2012, more than a third (34.9%) of adults were categorized as obese, with the highest rate of 47.8% among blacks (37.1% for black men and 56.6% for black women) [32]. By 2030, these rates are forecast to be between 39.5–50.7% [33]. Thus, obesity is likely to become an ever-more important risk factor for liver cancer among blacks, in addition to other groups.

The population attributable fraction is also affected by the prevalence of the exposure. In a recent study of SEER-Medicare, the population attributable fraction of diabetes and/or obesity was 36.6% [31]. In the current study, we report a population attributable fraction of 19.0% for obesity and 0.8% for diabetes. The lower population attributable fractions in our study reflect the lower prevalence of obesity (8.3% among controls) and diabetes (2.8%

among controls) relative to the SEER-Medicare study (34.7% of controls with diabetes and/or obesity), since the KPNC MHC cohort was primarily enrolled before the obesity epidemic in the US. Thus, we expect that the current attributable fraction for obesity and diabetes and liver cancer is higher than shown here and will increase in the future.

Diabetes has been consistently associated with a 2–2.5 fold increased risk of liver cancer [12–15]. A similar association was found in the US Liver Cancer Pooling Project (Campbell et al., Under Review). Two studies which have examined serum glucose also report an increased risk of liver cancer [16, 17]. In the current study, we report a possible increased risk of liver cancer associated with diabetes and serum glucose. However, our sample size was limited to determine a precise estimate of risk. In addition, the prevalence of diabetes was low.

While this analysis included information on several major confounders (e.g., smoking and alcohol consumption), smoking and/or drinking information was unavailable for approximately 38% of study participants. However, when we adjusted for these covariates among participants with information on smoking and drinking, our results did not substantially differ (Supplemental Table 2). Additionally, this study did not include information on other important potential confounders, such as HBV and HCV infection status. However, we did stratify by birth cohort and conducted a sensitivity analysis excluding the 1945–1965 birth cohorts, for whom the prevalence of HCV differs from other birth cohorts (data not shown). Information on histologic subtype of liver cancer (e.g., hepatocellular carcinoma, intrahepatic cholangiocarcinoma, etc.) was not available. Additionally, we only have single exposure measurement at baseline for BMI, diabetes, and glucose, which does not account for the within person variability over time. We also did not have glucose measurements available on all participants – only individuals recruited between 1974 and 1985 had these measurements available. Finally, we are limited in our interpretation of some estimates due to small sample size, especially for underweight participants and stratifications by birth cohort and race.

Strengths of this study include use of a racially and ethnically diverse population, with long-term follow-up and a comprehensive cancer registry. The study population is more racially and ethnically diverse than the US population, which allowed examination of the obesity-liver cancer association among minority groups. Additionally, BMI was measured during a standardized physical examination by trained examiners, using a systematic protocol and standardized instruments, and serum glucose was utilized as a biomarker of pre-diabetes and diabetes status in addition to self-reported diabetes status.

5. CONCLUSION

In summary, our finding of a positive association between obesity and liver cancer suggests that a higher BMI may increase the risk of liver cancer in the US. Further research is needed to elucidate the role of obesity and diabetes, specifically by race/ethnicity, sex, and birth cohort, in relation to liver cancer in the US.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1. Cubic spline graph of the adjusted ORs (represented by the solid line) and 95% CIs (represented by the dotted lines) for the association between body mass index at enrollment (kg/m^2) and risk of liver cancer (knots: 18.5, 25, 30; referent: 21.75).

Table 1

Distribution of Characteristics Among Liver Cancer Cases and Controls.

	Controls (N=4,489)		Liver Cancer Cases (N=450)	
	N	(%)	N	(%)
Age at Enrollment (years), mean (sd)	41.6	(11.5)	44.4	(11.7)
Race				
White	2309	(53.8)	224	(53.9)
Black	867	(20.2)	85	(20.4)
Asian/Pacific Islander	715	(16.7)	76	(18.3)
Other	404	(9.4)	31	(7.5)
Missing	194		34	
Sex				
Male	3027	(67.4)	303	(67.3)
Female	1462	(32.6)	147	(32.7)
Education				
High School or less	473	(15.0)	63	(25.3)
High School	951	(30.1)	74	(29.7)
Some College/Vocational	607	(19.2)	58	(23.3)
College Degree	559	(17.7)	32	(12.9)
Graduate Degree	566	(17.9)	22	(8.8)
Missing	1333		201	
Alcohol				
Not Current Drinker	729	(24.2)	60	(25.0)
Current	2277	(75.8)	180	(75.0)
Missing	1483		210	
Cigarette Smoking Status				
Non-Smoker	1272	(45.0)	88	(38.1)
Former Smoker	547	(19.4)	33	(14.3)
Current Smoker	1005	(35.6)	110	(47.6)
Missing	1665		219	
Birth Cohort				
1894–1900	79	(1.8)	10	(2.2)
1901–1924	1720	(38.3)	173	(38.4)
1925–1944	2014	(44.9)	197	(43.78)
1945–1962	676	(15.1)	70	(15.6)

Table 2

Adjusted * Odds Ratios (OR) and 95% Confidence Intervals (CI) for Associations Between Body Mass Index, Diabetes, and Serum Glucose at Enrollment and Risk of Liver Cancer.

	No. Controls	No. Liver Cancer Cases	OR†	(95% CI)
Body Mass Index, kg/m²				
<18.5	51	6	1.36	(0.57, 3.25)
18.5–<25	1,721	155	1.00	Referent
25–<30	1,217	139	1.32	(1.03, 1.70)
30	281	56	2.38	(1.68, 3.36)
Body Mass Index, per 5 kg/m²	3,270	356	1.33	(1.15, 1.53)
<i>p for trend</i>				<0.0001
Diabetes				
No	2,436	257	1.00	Referent
Yes	76	10	1.28	(0.65, 2.54)
Serum Glucose, mg/dL				
<140	861	158	1.00	Referent
140–199	43	12	1.39	(0.70, 2.76)
200	11	4	1.63	(0.48, 5.55)
Serum Glucose, per 10 mg/dL	915	174	1.00	(0.96, 1.05)
<i>p for trend</i>				0.99

* Stratified by matching factor.

Adjusted* Odds Ratios (OR) and 95% Confidence Intervals (CI) for Association Between Body Mass Index at Enrollment and Risk of Liver Cancer by Birth Cohort.

Table 3

	1894–1900				1901–1924			
	No. Controls	No. Liver Cancer Cases	OR	(95% CI)	No. Controls	No. Liver Cancer Cases	OR	(95% CI)
Body Mass Index, kg/m²								
<18.5	0	0	-	-	16	2	1.58	(0.35, 7.18)
18.5–<25	36	2	1.00	Referent	726	62	1.00	Referent
25<30	32	7	3.58	(0.70, 18.19)	609	69	1.33	(0.91, 1.94)
30	11	1	1.54	(0.13, 18.53)	134	22	2.00	(1.17, 3.44)
Body Mass Index, per 5 kg/m²	79	10	1.23	(0.59, 2.58)	1,485	155	1.36	(1.10, 1.69)
<i>p for trend</i>				0.6				0.004
	1925–1944				1945–1962			
	No. Controls	No. Liver Cancer Cases	OR	(95% CI)	No. Controls	No. Liver Cancer Cases	OR	(95% CI)
Body Mass Index, kg/m²								
<18.5	18	3	2.17	(0.61, 7.73)	17	1	0.54	(0.07, 4.28)
18.5–<25	725	64	1.00	Referent	234	27	1.00	Referent
25<30	488	48	1.13	(0.75, 1.71)	88	15	1.51	(0.76, 3.00)
30	110	30	3.37	(2.00, 5.69)	26	3	1.00	(0.28, 3.59)
Body Mass Index, per 5 kg/m²	1,341	145	1.33	(1.05, 1.68)	365	46	1.17	(0.79, 1.72)
<i>p for trend</i>				0.02				0.4

* Stratified by matching factor.

Adjusted* Odds Ratios (OR) and 95% Confidence Intervals (CI) for Association Between Body Mass Index at Enrollment and Risk of Liver Cancer by Race.

Table 4

	White				Black			
	No. Controls	No. Liver Cancer Cases	OR	(95% CI)	No. Controls	No. Liver Cancer Cases	OR	(95% CI)
Body Mass Index, kg/m²								
<18.5	28	1	0.44	(0.06, 3.33)	9	3	4.35	(1.05, 18.02)
18.5–<25	968	80	1.00	Referent	305	26	1.00	Referent
25<30	726	85	1.49	(1.06, 2.09)	289	28	1.18	(0.66, 2.09)
30	130	27	2.76	(1.69, 4.51)	120	22	2.29	(1.22, 4.28)
Body Mass Index, per 5 kg/m²	1,852	193	1.47	(1.22, 1.79)	723	79	1.18	(0.91, 1.54)
<i>p for trend</i>				<0.0001				0.2
Asian/Pacific Islander								
	Asian/Pacific Islander				Other			
	No. Controls	No. Liver Cancer Cases	OR	(95% CI)	No. Controls	No. Liver Cancer Cases	OR	(95% CI)
Body Mass Index, kg/m²								
<18.5	10	2	1.85	(0.35, 9.85)	4	0	-	-
18.5–<25	310	37	1.00	Referent	135	10	1.00	Referent
25<30	114	12	0.75	(0.38, 1.50)	86	13	2.43	(0.83, 7.09)
30	12	4	2.50	(0.74, 8.47)	19	2	8.31	(0.67, 102.83)
Body Mass Index, per 5 kg/m²	446	55	1.05	(0.67, 1.66)	244	25	3.12	(1.28, 7.61)
<i>p for trend</i>				0.8				0.01

* Stratified by matching factor.

Adjusted* Odds Ratios (OR) and 95% Confidence Intervals (CI) for Association Between Body Mass Index at Enrollment and Risk of Liver Cancer by Sex.

Table 5

	Men				Women			
	No. Controls	No. Liver Cancer Cases	OR	(95% CI)	No. Controls	No. Liver Cancer Cases	OR	(95% CI)
Body Mass Index, kg/m ²								
<18.5	22	4	2.19	(0.72, 6.61)	29	2	0.77	(0.18, 3.33)
18.5–<25	1,061	94	1.00	Referent	660	61	1.00	Referent
25<30	926	104	1.31	(0.97, 1.78)	291	35	1.41	(0.90, 2.23)
30	162	36	2.68	(1.73, 4.16)	119	20	2.00	(1.14, 3.52)
Body Mass Index, per 5 kg/m ²	2,171	238	1.37	(1.14, 1.66)	1,099	118	1.28	(1.03, 1.58)
<i>p for trend</i>				0.001				0.03

* Stratified by matching factor.