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Alcohol consumption, tobacco smoking, and subsequent risk of renal cell carcinoma: The JPHC study

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Abstract

The effects of alcohol consumption and tobacco smoking on renal cell carcinoma (RCC) incidence have not been well-investigated in Asian populations. Here, we evaluated these effects in a large Japanese prospective cohort. We collected data on eligible participants in the Japan Public Health Center-based Prospective Study, and undertook multivariable-adjusted Cox proportional hazards regression to estimate hazard ratios (HRs) and corresponding 95% confidence intervals (CIs) of RCC incidence. We identified 340 cases (230 men and 110 women) among the 105 663 eligible participants (50 262 men and 55 741 women), who were followed for an average of 19.1 years, with a cumulative total of 2 020 364 person-years. A slightly inverse but nonsignificant association was observed between alcohol drinking and RCC incidence. In contrast, the risk of RCC was increased in those with heavy smoking (≥40 pack-years) when men and women were combined (HR 1.50; 95% CI, 1.01-2.25). We identified no significant association between alcohol consumption and RCC incidence. In contrast, heavy smoking (≥40 pack-years) was associated with a significant increase in incidence.

KEYWORDS

cohort study, epidemiology, Renal cell carcinoma, Alcohol, Smoking

1 | INTRODUCTION

By incidence, cancers of the kidney, renal pelvis, and ureter were the ninth most common cancers in Japan in 2017, accounting for approximately 30 000 cases that year.[1] Furthermore, the age-standardized incidence of these cancers, which together are considered to represent renal cell cancer (RCC), is still increasing. [2-4] The latest GLOBOCAN estimate reports that RCC is the 15th most common cancer worldwide, and is positively associated with the human development index.[5] Despite this association, the cumulative risk of RCC incidence in Japan is low, at 0.59%, compared to 1.5% in other developed regions.[6] Some registry studies in the United States have reported that the adjusted incidence rate of RCC in non-Hispanic Asians and Pacific Islanders was lowest among several ethnicities.[7,8]

Several risk factors of RCC incidence have been closely studied, including age, sex, race, obesity, diabetes mellitus, hypertension, chronic renal failure, tobacco smoking, and alcohol consumption. [9-16] The IARC demonstrated that the categories of tobacco smoking and alcohol consumption for RCC incidence showed "sufficient evidence" and "evidence suggesting lack of carcinogenicity", respectively.[17] Of

interest, several large prospective studies reported that alcohol consumption had an inverse association with RCC incidence, suggesting that improving insulin sensitivity and antioxidant compounds in alcoholic beverages conferred preventive effects.[9-11,15,18] To date, however, most participants in these studies were Europe and North America, and although some subjects in the prospective multiethnic cohort study by Setiawan et al of RCC incidence were Asian, analysis in this study did not include stratification by ethnicity or mention ethnic differences.

Despite this, several behavioral and genetic susceptibility discrepancies between Asian and non-Asian populations following smoking and drinking have been identified.[19-25] Moreover, some prospective studies and pooled analyses - mainly conducted in Europe and North America populations owing to healthy cohort bias.[9,10,12,14] Given these limitations, the findings of these studies cannot be generalized to Asian populations.

Here, we evaluated the effects of alcohol consumption and tobacco smoking on RCC incidence in a large Japanese prospective cohort.

2 | MATERIALS AND METHODS

2.1 | Study population

The protocol of the Japan Public Health Center-based Prospective Study (JPHC Study) has been reported in detail elsewhere.[26] In brief, the JPHC Study began in 1990 (Cohort I) and 1993-1994 (Cohort II) and included Japanese residents (n = 140 420) aged 40-69 years from 11 public health center (PHC) areas. In the present study, participants from one PHC area in Tokyo in Cohort I (n = 7097) were excluded because cancer incidence data were not available. We also excluded 293 participants with: (a) non-Japanese nationality (n = 51); (b) late-reported relocation out of a study area before the start of follow-up (n = 207); (c) incorrect date of birth (n = 7); and (d) duplicate enrollment (n = 28). After the above exclusion criteria, the remaining 132 744 subjects were first considered as eligible in the present study.

2.2 | Study approval

The present study was approved by the Institutional Review Board of the National Cancer Center, Japan (approval no. 2001-021).

2.3 | Baseline survey

A self-administered questionnaire was distributed to all registered Japanese residents in 1990 for Cohort I and in 1993-1994 for Cohort II. Completion of the questionnaire after receiving a briefing about the study's purposes and methods was considered informed consent.

Among eligible subjects, 50 262 men (72.8%) and 55 741 women (77.4%) returned responses. The questionnaire included items on the history of smoking and alcohol consumption, current height and weight, medical history, including diabetes, hypertension, and chronic renal failure, and other lifestyle-related factors. [26] We excluded participants who did not answer the baseline questionnaires, leaving 106 003 participants considered eligible for analysis (Figure 1).

2.4 | Assessment of exposure

Information on alcohol drinking habits was based on a validated self-administered food frequency questionnaire at baseline. The questionnaires for Cohort I and Cohort II differed slightly: participants in Cohort I first reported their average frequency of alcohol consumption in terms of <1 day/month, 1-3 days/month, 1-2 days/week, 3-4 days/week, 5-6 days/week, or every day. Participants who drank at least 1 day/week subsequently also reported the average number of drinks per occasion and beverage types. In contrast, participants in Cohort II first reported their alcohol consumption status in terms of being a never, former, or current drinker. Subsequently, participants who were former or current drinkers also answered about their average frequency of alcohol consumption, categorized as 1-3 days/month, 1-2 days/week, 3-4 days/week, or almost every day. Finally, they reported the average amount of drink per occasion and beverage types. The amount of alcohol consumed by each participant in the two cohorts was calculated into grams of ethanol per week. In this study, we categorized participants by alcohol consumption as follows: nondrinker (<1 day/month in Cohort I and II or former drinker in Cohort II), occasional drinker (1-3 days/month), and regular drinker (all excluding those above). Participants among regular drinkers were additionally classified as follows: ethanol 0-149 g/week, 150-299 g/week, 300-449 g/week, and 450 g/week or more. If regular drinkers with missing value of grams of ethanol per week, we classified them as 0-149 g/week. For women, in contrast, we categorized participants as "nondrinkers", "occasional drinkers", and "regular drinkers" because of the small proportion of regular female drinkers.

The baseline questionnaire about tobacco smoking habits included smoking status (never, former, or current smoker), age at initiation, age at cessation (former smokers only), and average number of cigarettes smoked per day. We calculated pack-years, a known indicator of smoking intensity, by multiplying the number of packs of cigarettes (20 per pack) smoked per day by the number of years of smoking. We categorized participants in terms of tobacco smoking as follows: "never smoker", "former smoker", "current smoker with <20 pack-years", "current smoker with ≥20 and <40 pack-years", and "current smoker with ≥40 pack-years". Current smokers who did not respond about the average number of cigarettes smoked per day were categorized as "current smoker with <20 pack-years". For women, we categorized participants as "never smoker", "former

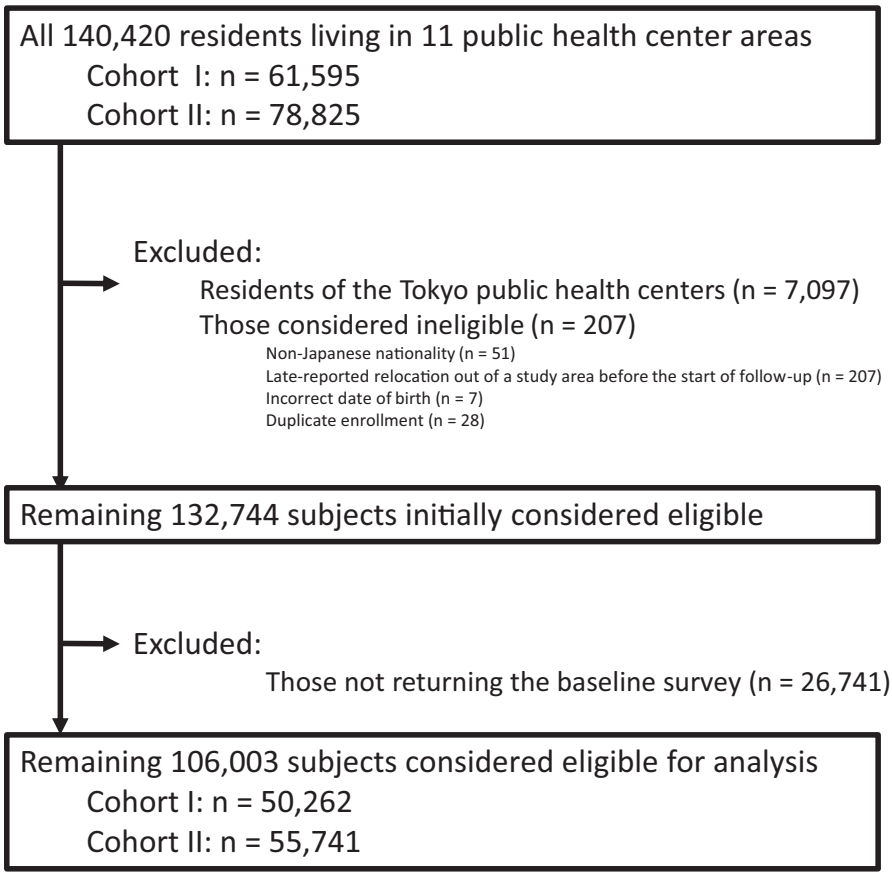

FIGURE 1 Flowchart of selection of study participants, recruited from the Japan Public Health Center-based Prospective Study, to determine risk of renal cell carcinoma according to alcohol consumption and tobacco smoking [Correction added on 2 December 2021, after first online publication: In Figure 1, the value of the resident in the first box was corrected from '146,420' to '140,420' in this version.]

smoker", and "current smoker" because of the small proportion of currently smoking females.

2.5 | Case ascertainment

We collected RCC incidence by active patient notification from major local hospitals in each of the PHC areas and from data linkage with population-based cancer registries, with permission from each of the local governments responsible for the cancer registries. Death certificates were collected as a supplemental information source to capture incident cases primarily notified by death certificate. Renal cell carcinoma incidence was coded as "C64" according to the International Classification of Diseases for Oncology, 3rd edition. [27] In this study, 5.9% and 4.4% of RCC cases had information from death certificate notification and death certificate only, respectively, which suggests that the cancer registries were of reasonable quality.

2.6 | Follow-up

Changes in residence status and survival were identified annually through the residential registry in each municipality in each of the study areas or, for those who had moved out of the study area, through the municipal office of the area to which they had moved. Information on the cause of death was obtained by examining death certificates provided by the Ministry of Health, Labour and Welfare of Japan, with permission. [28] Residency registration and death registration are required by law, and the registries are believed to be complete. During the follow-up period in the present study, 11 596 (10.9%) subjects died, 12 052 (11.4%) moved out of a study area, and 930 (0.9%) were lost to follow-up.

2.7 | Statistical analyses

Person-years of follow-up were calculated for each subject from the date of questionnaire completion until the date of RCC incidence, moving out of the baseline study area, death, or the end of follow-up (31 December 2012 for Osaka, 31 December 2013 for Kochi, 31 December 2014 for Nagasaki, and 31 December 2015 for the others), whichever occurred first. Those who were lost to follow-up were censored at the last confirmed date of presence in the study area.

We used multivariable-adjusted Cox proportional hazards regression to calculate hazard ratios (HRs) and corresponding 95% confidence intervals (CIs) of RCC incidence according to alcohol consumption and tobacco smoking. We fitted two models adjusted for potential confounding factors to ascertain the robustness of the results. Model 1 was adjusted for age at baseline and PHC area, and model 2 for body mass index (calculated by dividing the weight in kilograms by the squared height in meters, with categories of ≤18.5, 18.5-24.9,

25.0-29.9, and ≥30 kg/m^2), medical history (diabetes, hypertension, chronic renal disease; yes, no), and alcohol consumption and tobacco smoking, in addition to the exposures in model 1. In addition, for sensitivity analyses, model 3 and model 4 were the same analyses as model 2 with the exclusion of diabetes participants at baseline and RCC cases diagnosed within 2 years of baseline, respectively. Linear trends in the effect of alcohol consumption and tobacco smoking were assessed by assignment of ordinal categories of alcohol drinking (never, occasional, regular drinkers) and tobacco smoking (never, past, current smokers), respectively. All statistical analyses were carried out using STATA version 14 (STATA Corporation). *P* values of less than .05 were considered significant for all statistical analyses.

3 | RESULTS

We identified 340 cases (230 men and 110 women) among 106 003 eligible participants (50 262 men and 55 741 women), who were followed for an average of 19.1 years for a cumulative total of 2 020 364 person-years. Of those, mean age and BMI were 51.7 years and 23.5 in men, and 52.0 years and 23.4 in women, respectively. Proportions of regular drinkers and current smokers were 66.8% and 52.2% in men and 12.8% and 6.7% in women, respectively.

Table 1 shows the baseline characteristics of participants according to alcohol consumption and smoking status. Regular drinkers tended to include a higher proportion of current smokers and were younger than nondrinkers, whereas current smokers tended to include a higher proportion of regular drinkers than never smokers.

Table 2 shows age- and PHC area-adjusted (model 1) and multivariate-adjusted (model 2) HRs and 95% CIs for the association between alcohol consumption and RCC incidence. In general, a slightly inverse association was observed for risk of RCC and alcohol drinking in several categories for both sexes combined and for men's categories, namely occasional drinkers, overall regular drinkers, and regular drinkers of more than 150 g/week of ethanol; however, this association was not significant with regard to either frequency or amount. Similar results were obtained for the sensitivity analyses (model 3 and model 4).

Table 3 shows age- and PHC area-adjusted (model 1) and multivariate-adjusted (model 2) HRs and 95% CIs for the association between tobacco smoking and RCC incidence. No significant association was found for tobacco smoking and RCC risk in general. In contrast, heavy smoking (≥40 pack-years) significantly increased the risk of RCC in men and women combined (HR 1.50; 95% CI, 1.01-2.30). Although model 3 showed the same result as model 2, model 4 showed no significant increase in HR among heavy smoking (≥40 pack-years) men and women combined (HR 1.41; 95% CI, 0.93-2.14).

4 | DISCUSSION

Here, we evaluated the effect of alcohol consumption and tobacco smoking on RCC incidence in a large Japanese prospective cohort. To our knowledge, this study involves the largest population size and number of cases in an Asian population to date. The results showed a slightly inverse but nonsignificant association between alcohol consumption and risk of RCC incidence. In contrast, heavy smoking (≥40 pack-years) was associated with a significant increase in RCC incidence in men and women combined. However, when RCC cases diagnosed within 2 years after baseline were excluded, the effect of heavy smoking on RCC incidence was marginal.

Previous prospective studies were carried out in large European and North American populations with sufficient RCC cases. Indeed, European and North American populations are more strongly affected by RCC than Asian populations. Although these previous studies indicated a marginally protective effect of alcohol consumption and a positive dose-dependent effect of tobacco smoking, our present findings were not comparable, despite a sufficiently long follow-up period. In terms of tobacco smoking, although European and North American population-based cohort studies, had a comparable or smaller number of RCC cases (range, 249-463) than the JPHC study,[11,13,16] these studies showed a significantly increased risk of RCC incidence, particularly among heavy smokers (HR 1.58-2.26). This in turn suggests that the differences in RCC incidence associated with alcohol consumption and tobacco smoking result from ethnic differences in genetic susceptibility.

The mechanism of the protective effect of alcohol consumption on RCC incidence has not been explicitly identified. One possibility is the role of diabetes, namely the reported effect of light to moderate alcohol consumption in enhancing insulin sensitivity. [29-31] In particular, a meta-analysis showed a significant positive association between diabetes and RCC incidence,[32] suggesting that this effect on diabetes serves as an indirect protective factor against RCC incidence. Our sensitivity analysis, which excluded participants with diabetes, was consistent with the multivariate-adjusted analysis (model 2). In other words, a direct protective effect of alcohol consumption on RCC incidence was not observed in the present study. As noted in previous studies, our results indicate that the indirect effect could be mediated by diabetes.

To account for the inconsistent results between Asian and non Asian populations, we hypothesized that insulin secretion, rather than insulin resistance, might affect RCC incidence. A number of plausible explanations support this hypothesis. First, basal insulin secretion is lower in Japanese than African or Caucasian populations,[33,34] in parallel with a lower RCC incidence than in these populations. Second, diabetes in Japanese tends to be attributable to impaired insulin secretion rather than insulin resistance. [33,35] Accordingly, alcohol consumption might have little effect on diabetes and subsequent RCC incidence, even while it enhances insulin sensitivity. Finally, insulin and insulin-like growth factor 1 likely play a role in cancer incidence through an oncogenic potential mechanism arising from abnormal stimulation of several cellular signaling cascades.[36] Indeed, some cohort studies have shown that hyperinsulinemia is significantly associated with cancer mortality[37,38] and some kinds of cancer incidence, including prostate, lung, breast, and pancreas.[39-41] Taken together, the inconsistent effect of alcohol

TABLE 1 Baseline characteristic of study participants according to alcohol consumption and tobacco smoking status

	Alcohol consumption						
				Weekly ethanol intake in regular drinkers (g/wk)			
	Nondrinker	Occasional drinker	Regular drinker	<150	150-299	300-449	≥450
Men							
Person-years	195 711	84 961	612 211	208 863	180 683	117 559	105 106
Number of subjects	11 196	4376	33 556	11 509	9894	6402	5750
Age at baseline (y), mean (SD)	53.7 (8.5)	50.2 (7.4)	51 (7.7)	51 (8.0)	51.5 (7.8)	51.2 (7.4)	50.3 (7.0)
Body mass index (kg/m^2), mean (SD)	23.3 (3.0)	24 (3.0)	23.5 (2.8)	23.4 (2.7)	23.4 (2.7)	23.5 (2.8)	23.6 (2.9)
Medical history, n (%)							
Diabetes	881 (7.9)	271 (6.2)	2072 (6.2)	674 (5.9)	589 (6.0)	378 (5.9)	431 (7.5)
Hypertension	1687 (15.1)	524 (12.0)	6315 (18.8)	1854 (16.1)	1911 (19.3)	1376 (21.5)	1174 (20.4)
Chronic renal failure	295 (2.6)	78 (1.8)	634 (1.9)	216 (1.9)	186 (1.9)	110 (1.7)	122 (2.1)
Current smoker, n (%)	5286 (47.2)	2066 (47.2)	18 338 (54.7)	5302 (46.1)	5514 (55.7)	3905 (61.0)	3630 (63.1)
Regular drinker, n (%)							
Women							
Person-years	850 905	111 267	135 966	109 961	16 221	4733	5051
Number of subjects	42 497	5536	7144	5742	872	264	266
Age at baseline (y), mean (SD)	48.6 (6.8)	49.3 (7.4)	49.1 (7.3)	49.3 (7.4)	48.8 (7.1)	48.5 (6.7)	47.9 (6.3)
Body mass index (kg/m^2), mean (SD)	23.3 (3.0)	22.8 (2.9)	22.9 (3.0)	22.8 (2.9)	22.9 (3.2)	23.1 (3.3)	23.6 (3.3)
Medical history, n (%)							
Diabetes	1401 (3.3)	103 (1.9)	150 (2.1)	115 (2.0)	16 (1.8)	7 (2.7)	12 (4.5)
Hypertension	7121 (16.8)	633 (11.4)	946 (13.2)	723 (12.6)	134 (15.4)	49 (18.6)	40 (15.0)
Chronic renal failure	848 (2.0)	125 (2.3)	160 (2.2)	122 (2.1)	13 (1.5)	8 (3.0)	17 (6.4)
Current smoker, n (%)	1911 (4.5)	468 (8.5)	1258 (17.6)	750 (13.1)	283 (32.5)	107 (40.5)	128 (48.1)
Regular drinker, n (%)							
	Tobacco smoking						
				Pack-years in current smokers			
	Never smoker	Past smoker	Current smoker	<20	20-39	≥40	
Men							
Person-years	227 955	213 151	466 371	87 216	238 099	140 717	
Number of subjects	11 894	11 856	26 256	4619	13 112	8504	

(Continues)

TABLE 1 (Continued)

	Tobacco smoking					
				Pack-years in current smokers		
	Never smoker	Past smoker	Current smoker	<20	20-39	≥40
Age at baseline (y), mean (SD)	52 (7.6)	54 (8.3)	51 (7.8)	48.7 (7.4)	49.9 (7.5)	53.3 (7.9)
Body mass index (kg/m^2), mean (SD)	24 (2.9)	24 (2.8)	23 (2.8)	23.1 (2.8)	23.0 (2.8)	23.3 (2.9)
Medical history, n (%)						
Diabetes	679 (5.7)	864 (7.3)	1723 (6.6)	268 (5.8)	774 (5.9)	681 (8.0)
Hypertension	2167 (18.2)	2628 (22.2)	3890 (14.8)	660 (14.3)	1827 (13.9)	1403 (16.5)
Chronic renal failure	236 (2.0)	286 (2.4)	504 (1.9)	82 (1.8)	235 (1.8)	187 (2.2)
Current smoker, n (%)						
Regular drinker, n (%)	7102 (61.3)	7960 (68.4)	18 338 (69.9)	3227 (70.9)	9278 (72.1)	5833 (70.7)
Women						
Person-years	1 021 269	16 314	65 766	42 803	15 582	6736
Number of subjects	50 836	894	3712	2368	923	388
Age at baseline (y), mean (SD)	52 (8.0)	51 (8.6)	50 (7.9)	51 (8.6)	51 (7.7)	52 (8.6)
Body mass index (kg/m^2), mean (SD)	23 (3.1)	24 (3.5)	23 (3.5)	24 (3.5)	23 (3.7)	23 (3.7)
Medical history, n (%)						
Diabetes	1481 (2.9)	50 (5.6)	127 (3.5)	66 (2.8)	45 (4.9)	16 (4.1)
Hypertension	8049 (15.8)	180 (20.1)	483 (13.1)	288 (12.2)	136 (14.7)	59 (15.2)
Chronic renal failure	1015 (2.0)	36 (4.0)	89 (2.4)	51 (2.2)	25 (2.7)	13 (3.4)
Current smoker, n (%)						
Regular drinker, n (%)	5574 (11.1)	279 (31.4)	1258 (34.2)	768 (33.0)	358 (39.5)	132 (34.7)

TABLE 2 Hazard ratios (HRs) and 95% confidence intervals (CIs) of renal cell carcinoma according to alcohol drinking status

	Alcohol consumption							
				Weekly ethanol intake in regular drinkers (g/wk)				
	Nondrinkers	Occasional drinkers	Regular drinkers	<150	150-299	300-449	≥450	*P* trend
Total								
Person-years	1 046 615	196 228	748 177	318 825	196 904	122 291	110 157	
Number of cases	147	28	158	68	39	29	22	
Model 1 HR (95% CI)	1 (Reference)	0.82 (0.54-1.25)	0.97 (0.73-1.27)	1.09 (0.79-1.50)	0.83 (0.56-1.23)	0.99 (0.64-1.54)	0.81 (0.50-1.32)	.51
Model 2 HR (95% CI)	1 (Reference)	0.82 (0.54-1.25)	0.93 (0.70-1.23)	1.08 (0.78-1.50)	0.79 (0.53-1.18)	0.92 (0.59-1.43)	0.74 (0.46-1.22)	.28
Model 3 HR (95% CI)	1 (Reference)	0.83 (0.54-1.27)	0.89 (0.66-1.19)	1.03 (0.74-1.44)	0.74 (0.49-1.13)	0.92 (0.58-1.45)	0.70 (0.41-1.17)	.20
Model 4 HR (95% CI)	1 (Reference)	0.87 (0.57-1.32)	0.93 (0.69-1.25)	1.08 (0.77-1.51)	0.81 (0.54-1.22)	0.92 (0.58-1.47)	0.73 (0.44-1.22)	.28
Men								
Person-years	195 711	84 961	612 211	208 863	180 683	117 559	105 106	
Number of cases	61	16	145	57	38	29	21	
Model 1 HR (95% CI)	1 (Reference)	0.61 (0.35-1.06)	0.87 (0.64-1.18)	0.99 (0.68-1.43)	0.77 (0.51-1.16)	0.92 (0.59-1.45)	0.72 (0.44-1.20)	.35
Model 2 HR (95% CI)	1 (Reference)	0.6 (0.34-1.04)	0.83 (0.61-1.13)	0.97 (0.67-1.40)	0.73 (0.49-1.11)	0.86 (0.55-1.36)	0.67 (0.40-1.12)	.38
Model 3 HR (95% CI)	1 (Reference)	0.56 (0.32-1.002)	0.76 (0.56-1.05)	0.88 (0.060-1.29)	0.67 (0.43-1.02)	0.83 (0.52-1.33)	0.60 (0.35-1.03)	.10
Model 4 HR (95% CI)	1 (Reference)	0.61 (0.35-1.07)	0.80 (0.58-1.10)	0.92 (0.62-1.35)	0.73 (0.47-1.11)	0.84 (0.52-1.34)	0.63 (0.37-1.08)	.15
Women								
Person-years	850 905	111 267	135 966					
Number of cases	86	12	13					
Model 1 HR (95% CI)	1 (Reference)	1.29 (0.70-2.40)	1.20 (0.66-2.19)					.46
Model 2 HR (95% CI)	1 (Reference)	1.31 (0.70-2.43)	1.20 (0.65-2.21)					.54
Model 3 HR (95% CI)	1 (Reference)	1.46 (0.78-2.72)	1.22 (0.65-2.30)					.36
Model 4 HR (95% CI)	1 (Reference)	1.39 (0.75-2.61)	1.31 (0.71-2.42)					.27

Note: Model 1, adjusted for age and public health center area.

Model 2, adjusted for age, public health center area, body mass index (≤18.5, 18.5-24.9, 25.0-29.9, and ≥30 kg/m^2), medical history (diabetes, hypertension, and chronic renal disease), and tobacco smoking (never, former, <20 pack-years, ≥20 and <40 pack-years, and ≥40 pack-years).

Model 3, excluding diabetes participants at baseline, in addition to the adjustments in model 2.

Model 4, excluding cases within 2 y from baseline, in addition to the adjustments in model 2.

TABLE 3 Hazard ratios (HRs) and 95% confidence intervals (CIs) of renal cell carcinoma according to tobacco smoking status

	Smoking status						
				Pack-years in current smokers			
	Never smokers	Past smokers	Current smokers	<20	20-39	≥40	*P* trend
Total							
Person-years	1 249 224	229 465		130 020	253 681	147 453	
Number of cases	158	63		25	49	45	
Model 1 HR (95% CI)	1 (Reference)	1.23 (0.87-1.75)		1.2 (0.77-1.89)	1.02 (0.70-1.48)	1.45 (0.98-2.14)	.24
Model 2 HR (95% CI)	1 (Reference)	1.18 (0.83-1.69)		1.25 (0.79-1.98)	1.1 (0.75-1.61)	1.5 (1.01-2.25)	.12
Model 3 HR (95% CI)	1 (Reference)	1.24 (0.80-1.67)		1.24 (0.78-1.99)	0.97 (0.65-1.45)	1.43 (0.95-2.18)	.30
Model 4 HR (95% CI)	1 (Reference)	1.09 (0.75-1.58)		1.14 (0.71-1.85)	1.01 (0.68-1.50)	1.41 (0.93-2.14)	.25
Men							
Person-years	227 955	213 151		87 217	238 099	140 717	
Number of cases	57	62		19	47	43	
Model 1 HR (95% CI)	1 (Reference)	1.2 (0.83-1.73)		1.05 (0.62-1.78)	0.96 (0.65-1.42)	1.36 (0.90-2.03)	.49
Model 2 HR (95% CI)	1 (Reference)	1.16 (0.80-1.69)		1.16 (0.68-1.96)	1.05 (0.70-1.56)	1.40 (0.92-2.13)	.28
Model 3 HR (95% CI)	1 (Reference)	1.14 (0.78-1.66)		1.13 (0.66-1.95)	0.93 (0.61-1.42)	1.33 (0.86-2.05)	.54
Model 4 HR (95% CI)	1 (Reference)	1.11 (0.75-1.63)		1.12 (0.65-1.93)	1.01 (0.67-1.53)	1.39 (0.90-2.14)	.31
Women							
Person-years	1 021 269	16 314	65 121				
Number of cases	101	1	10				
Model 1 HR (95% CI)	1 (Reference)	0.66 (0.09-4.77)	1.82 (0.95-3.52)				.10
Model 2 HR (95% CI)	1 (Reference)	0.61 (0.08-4.40)	1.72 (0.84-3.49)				.18
Model 3 HR (95% CI)	1 (Reference)	0.67 (0.09-4.81)	1.60 (0.76-3.39)				.20
Model 4 HR (95% CI)	1 (Reference)	0.64 (0.09-4.60)	1.16 (0.50-2.73)				.67

Note: Model 1, adjusted for age and public health center area.

Model 2, adjusted for age, public health center area, body mass index (≤18.5, 18.5-24.9, 25.0-29.9, and ≥30 kg/m^2), medical history (diabetes, hypertension, and chronic renal disease), and alcohol drinking (non, occasional, 0-149, 150-299, 300-449, and 450 g/wk or more).

Model 3, excluding diabetes participants at baseline, in addition to the adjustments in model 2.

Model 4, excluding cases within 2 y from baseline, in addition to the adjustments in model 2.

consumption on RCC incidence and the variation in RCC incidence by country could be attributable to ethnic and genetic differences in the mechanisms of diabetes development.

A meta-analysis study showed that male ever smokers, even those with lifetime smoking of only a few cigarettes, had a significantly increased risk of RCC over male never smokers, and a strong dose-dependent increase in RCC risk was seen among both sexes.[42] Although our present results showed that heavy tobacco smoking increased RCC incidence, producing a significant increase in HR required a larger number of pack-years than in previous prospective studies.[11,13,16] One possible explanation for the effect on RCC incidence among heavy smoking participants only is an ethnic disparity in tobacco-associated genetic susceptibility.

Glutathione S-transferase (GST) and N-acetyltransferase 2 (NAT2) are representative polymorphisms associated with tobacco smoking and RCC incidence. With respect to carcinogenesis, GST is involved in protecting against DNA damage through catalysis of the conjugation of glutathione and metabolization of carcinogenic substances in tobacco smoking.[43,44] Although the incidence of the GST null genotype, with high risk of several cancer incidences,[45,46] is higher among Asian than Caucasian populations,[47] meta-analyses of case-control studies showed inconsistent results between GST

genotype and RCC incidence stratified by ethnicity. [48,49] Moreover, a case-control study showed a marginal association with cruciferous vegetables and tobacco smoking stratified by GST genotype.[50] Further studies of RCC incidence should elucidate the association between tobacco smoking and GST polymorphism.

N-acetyltransferase 2 plays a role in the human physiological response to arylamine, a known carcinogen from tobacco smoking, and serves as a trigger for the development of RCC. A case-control study showed that tobacco smoking contributed to a two-fold increase in risk of developing RCC in participants with the slow acetylator genotype of NAT2 than in those with the rapid acetylator genotype.[45] In addition, among smokers, participants with the slow acetylator genotype develop RCC with three-fold greater risk than rapid acetylators.[20] A worldwide population study showed that the slow acetylator genotype of NAT2 accounted for a larger proportion in European than Japanese populations.[51] N-acetyltransferase 2 polymorphism would consequently help explain the significant but marginal association between RCC incidence and tobacco smoking among the Japanese population.

The JPHC study has several strengths. Its large prospective design, high response rate, and negligible proportion of losses to follow-up help avoid possible selection bias and recall bias. Moreover, the participants were representative of the broader Japanese population.[26]

In contrast, several limitations should also be acknowledged. First, statistical power was low due to the small number of RCC cases, especially in women. This could have contributed to the relatively wide confidence intervals with our results and might have also undermined our conclusions due to random error. A pooled analysis of Asian cohorts is warranted. Second, because we did not assess changes in alcohol drinking or tobacco smoking during the follow-up period, a degree of misclassification of exposure was likely not identified. This misclassification would be not differential, however, and would tend to underestimate the effect on RCC incidence. Finally, potentially unmeasured confounders we could not exclude in this prospective study might also be present.

In conclusion, this population-based prospective cohort study identified a slightly inverse but nonsignificant association between alcohol consumption and RCC incidence. In contrast, heavy smoking (≥40 pack-years) was associated with a significant increase in incidence, albeit only when data for men and women were combined. The inconsistency of these results from those in European and North American populations warrants further research into mechanism, with a particular focus on the contribution of insulin secretion and NAT2 polymorphism to the development of RCC.

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DISCLOSURE

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of our study are available from the corresponding author upon reasonable request.

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