HHS Public Access

Author manuscript

J Urol. Author manuscript; available in PMC 2015 May 05.

Published in final edited form as:

J Urol. 2013 November ; 190(5): 1657–1661. doi:10.1016/j.juro.2013.04.130.

Risk Factors for Renal Cell Carcinoma in the Vitamin and Lifefstyle (VITAL) Study

Liam C. Macleod, MD MPH[1], **James M. Hotaling, MD MS**[2], **Jonathan L. Wright, MD MS**[1,2], **Michael T. Davenport, MD**[1], **John L. Gore, MD**[1], **Jonathan Harper, MD**[1], and **Emily White, PhD**[1,2,3]

[1]University of Washington Medical Center, Department of Urology, 1959 NE Pacific St., BB-1121, Seattle WA 98195, phone 206.535.5886 or 206.685.1982, fax 206.543.3272

[2]Fred Hutchinson Cancer Research Center, 1100 Fairview Ave. N., Mailstop M4-B402, Seattle, WA 98109, phone 206.667.4685, fax 206.667.5977

[3]University of Washington, Department of Epidemiology, 1959 NE Pacific St., Health Sciences Building F-262, Box 357236, Seattle, WA 98195, phone 206.543.1065, fax 206.543.8525

Abstract

PURPOSE—The incidence of renal cell carcinoma (RCC) is increasing worldwide. Cited risk factors include obesity, smoking and hypertension, but few others have been confirmed by prospective studies. We used a prospective cohort to validate established RCC risk factors and to evaluate more controversial risk factors for incident RCC.

MATERIALS/METHODS—77,260 residents of Washington aged 50-76 years completed a questionnaire between 2000-2002 on demographic, lifestyle and health data. Incident RCC cases were determined through linkage to the regional cancer registry through Dec 31, 2009. Multivariate methods using covariates and cut offs selected ***a priori*** analyzed the association between RCC and previously studied factors related to lifestyle (body mass index [BMI], smoking, alcohol/fruit/vegetable consumption) and health (hypertension, diabetes, kidney disease, viral hepatitis).

RESULTS—There were 249 incident cases of RCC. Independent RCC risk factors in the fully adjusted model with HR and 95% CIs were: BMI (HR 1.71, CI 1.06, 2.79, for >=35 kg/m^2 vs. <25 kg/m^2), smoking (HR 1.67, CI 1.16, 2.42, for >=37.5 pack-years vs. none), hypertension (HR 1.70, CI 1.30, 2.22), kidney disease (HR 2.58, CI 1.21, 5.50), viral hepatitis (HR 1.80, CI 1.03, 3.14). Diabetes was associated with RCC (HR 1.83, CI 1.26, 2.65) in a base model adjusting for age and gender, but not in the multivariate model. We found no association between alcohol, fruit, or vegetable intake and RCC.

CONCLUSIONS—We identified significant association between RCC and obesity, smoking, hypertension, renal disease and viral hepatitis. Identification of risk factors offers an opportunity for targeted education and intervention.

Keywords

risk factors; renal cell carcinoma; obesity; smoking; kidney cancer

Background/Introduction

The lifetime risk of renal cell carcinoma (RCC) is 1.56% for US residents.[1] Based on data from the Surveillance Epidemiology and End Results cancer registry (SEER), the incidence of RCC increased significantly since 1975 with an annual percent increase of 2.4% through 2009[1]. Globally, geographic variation in RCC demonstrates higher age standardized incidence rates (11.9 per 100,000) in more developed regions compared to less developed areas (2.5 per 100,000).[2]

The reasons for regional and historical variations in RCC are unknown. Increased use of diagnostic imaging (magnetic resonance imaging, computed tomography and ultrasound) may detect more RCC. However, non-homogeneity of RCC incidence rates suggests existence of modifiable risk factors. Obesity, smoking and hypertension have each demonstrated strong associations with RCC[3,4]. Hypertension is a significant RCC risk factor in a variety of large prospective cohorts in a dose-dependent manner[5, 6]. The association between smoking and RCC is noted in a large meta-analysis, and was further supported by studies showing an association in those exposed to second hand inhalation[7, 8]. Obesity, central obesity and weight gain are associated with RCC[9, 10]. Several other risk factors have been evaluated (including diet, diabetes, liver disease, kidney disease, alcohol, among others) that have either conflicting results or have not been studied prospectively[3, 4]. Due to discrepancies in the literature, our objective was to use a large community cohort in which presence of RCC was ascertained prospectively to evaluate associations between known and suspected risk factors and RCC. These risk factors included demographic factors (gender, age, race), lifestyle factors (obesity, smoking, alcohol use and fruit and vegetable intake) and health-related factors (hypertension, diabetes, renal disease, viral hepatitis).

Materials and Methods

Selection of Study Participants

We included members of the VITamin And Lifestyle (VITAL) cohort of 77,719 individuals aged 50 to 76 living in a 13-county area of western Washington State. Our study was approved by the Institutional Review Board of the Fred Hutchinson Cancer Research Center. Detailed descriptions of recruitment, data collection and follow up have been previously published [11]. The cohort was recruited October 2000 through December 2002 via a commercial mailing list. Survey data was collected **via one 24-page questionnaire at study entry**. A total of 79,300 surveys were returned of which 77,719 passed quality control checks for internal coherence and completeness. For this analysis we excluded an additional 459 individuals: 242 who had a diagnosis of RCC prior to baseline, 212 who did not answer

the question regarding personal history of RCC, and 5 individuals who were diagnosed over follow-up with RCC of unusual histology (collecting duct carcinoma) or non-RCC renal tumors (spindle cell sarcoma, dedifferentiated liposarcoma, leiomyosarcoma and diffuse large B-cell tumor). Benign pathology (angiomyolipoma, oncocytoma) were not considered RCC for this analysis. This resulted in a total cohort of 77,260.

Baseline Data Collection

We performed literature review to select established risk factors and potential risk factors for study and cross referenced these with the VITAL database. Baseline data were obtained from a 24-page self-administered, validated questionnaire profiling dietary supplement consumption, dietary intake, personal attributes, cancer risk factors and medical history. Risk factors selected for this study included self-report of four medical conditions: hypertension, diabetes, kidney disease (excluding kidney stones) and viral hepatitis. Hypertension and diabetes were defined as self-report of medications for these conditions. We also evaluated smoking history. Self-reported weight and height were used to calculate body mass index (BMI). Intake of alcohol, fruit and vegetables were based on a 120-item food frequency questionnaire; estimated intake was adjusted for portion size of each food item reported. Intake of fruit and vegetables was also adjusted for summary questions on frequency of total fruit intake and of total vegetable intake and categorized into tertiles. Vegetable intake excluded potatoes due to their high starch and low fiber content compared to other vegetables. Missing data is reported in table 1 when numbers were significant (≥5 individuals).

Follow-up of Subjects for RCC and Censored Data

Incident cases of RCC were identified by linkage to the Seattle-Puget Sound SEER cancer registry through December 31, 2009. For each participant the end of follow-up was the earliest of the date of RCC diagnosis (n = 249), the date of withdrawal from the study (n = 22), the date of relocation out of the designated 13-county area of Washington covered by Seattle-Puget Sound SEER (n = 5,345), the date of death (n=6,238), or the date of last cohort follow-up (December 31, 2009, n = 65,406). Participants who died were identified via linkage to Washington State death files. Moves out-of-area were monitored through the US Postal Service (USPS) National Change of Address system and follow-up contact with participants.

Statistical Analyses

In univariate analysis, the statistical significance of the association between each risk factor and incident RCC was tested using Pearson's chi-squared for each variable in ordinal form, or Student's t-test for continuous variables, comparing cases and non-cases. For multivariate analyses, Cox proportional hazards regression was performed, using age as the time variable. Because age is the time variable, it does not appear in the tables. Participants were considered at risk for RCC from their age at completion of the questionnaire through age at the end of follow-up. A base model was created that adjusted for age and gender. A fully-adjusted model included age, gender, race and all nine risk factors, which were selected a priori. All cut-points were also selected prior to analysis and either used established criteria (for example BMI) or with natural tertiles, quartiles or quintiles if no established criteria was

available. For medical diagnoses, the presence or absence of the condition was used as criteria. The proportional hazards assumption for the Cox model was evaluated with Schoenfeld goodness of fit testing. All analyses were performed using Stata® v11.

Results

After median follow-up of 8 years (range 0 to 9) 249 incident cases of RCC were identified among 77,260 eligible subjects. Based on unadjusted comparisons among VITAL participants (Table 1), those with RCC were more likely to be male, older, obese, smokers, heavier drinkers, have hypertension, have diabetes, have a history of renal disease and have a history of viral hepatitis.

In the fully adjusted model, male gender, obesity, smoking, hypertension, history of kidney disease and viral hepatitis demonstrated significant associations with RCC (Table 2). Female gender and non-black/non-white race (designated as “other”) were associated with decreased risk of RCC. However, only 13 cases of RCC were in non-white participants. Diabetes was independently associated with RCC in the base model; but not in the multivariate model. Finally, alcohol, fruit and vegetable consumption were not associated with RCC.

Discussion

This analysis of VITAL confirms several previously identified risk factors for RCC including the modifiable risk factors of obesity, smoking and hypertension. Further, we found male gender, renal disease and viral hepatitis to be associated with risk of RCC.

Obesity and smoking have commonly been linked with several cancers including RCC. In this study, morbidly obese individuals (BMI >= 35) had a 71% increased risk of RCC compared with normal weight individuals (BMI < 25). Future study of the hormonal or metabolic differences in adipose tissue may help further define the relationship.[12, 13] Similarly to obesity, we observed a threshold effect for smoking and risk of RCC. Smokers with more than 22.5 pack-years of exposure had a greater than 50% increased risk of RCC compared with never smokers. These results add to public health and clinical efforts to address the obesity epidemic and to continue reducing smoking use.

Other studies have found associations between RCC risk and alcohol, fruit and vegetable intake. Several studies have reported a reduction in risk of RCC with alcohol consumption.[14, 15] Conversely, in the present analysis, we found no association between alcohol intake and RCC risk. Intake of fruits and vegetables have also been reported from other studies to be associated with a reduction in RCC risk including the Nurses Health Study (NHS) and the Health Professionals Followup Study (HPFS). [16] However, the European Prospective Investigation into Cancer and Nutrition (EPIC) database represented over 300,000 Europeans and detected over 300 cases of RCC in follow up, and found no association between RCC and fruit or vegetable consumption[17]. The VITAL data is consistent with the EPIC study. The lack of an observed protective association between fruit, vegetable and alcohol intake in our study could be due in part to different regional dietary practices. Further, as VITAL was a study on supplements and health-related behaviors, it may have attracted a larger health conscious group with lower drinking habits and avid fruit

and vegetable consumption. Data on alcohol should be interpreted cautiously given other deleterious health effects of heavy consumption, including risk of other cancers.

Prior data link risk of RCC with chronic medical conditions such as diabetes, hypertension, hepatitis C (HCV) and acquired cystic or polycystic diseases of the kidney. The most consistently observed association in the literature for chronic medical conditions is with hypertension and the present analysis similarly found a positive association. In this study, a statistically increased risk of RCC with viral hepatitis infection was detected. However, VITAL does not contain data on the specific viral hepatitis infection. In a cohort study of 67,000 individuals, hepatitis C infection was associated with an 80% greater risk of RCC (adjusted risk ratio of 1.8 (95% CI 1.05 to 2.98); however, the authors did not control for obesity, smoking or hypertension[18]. One mechanistic explanation involves expression of hepatitis C virus core protein by mammalian cells, as in transgenic mouse models this was associated with hepatic oncogenesis[19]. Hepatitis C virus core protein RNA has been isolated in renal tubules and glomeruli of infected patients undergoing renal biopsy[20]. Another group suggests a potential link between HCV and RCC in the NY-REN-54 protein which is involved in the autophagic response in regulation of abnormal renal cells and to which HCV co-localizes prior to internalization by the infected host cell[21]. Our findings are based on self-reported ‘viral hepatitis’, and thus misclassification with non-hepatitis C hepatitides cannot be ruled out. Patients with hepatitis C have a higher incidence of renal disease, thus, the observed association between renal disease and RCC could also play a role[22].

In addition to hypertension and HCV, researchers have investigated renal disease at diabetes in relation to RCC. Acquired cystic disease of the kidney and adult polycystic kidney disease have been studied in small prospective case series and case-control studies with evidence for independent association with RCC.[23-27] A specific question on renal cystic disease was not available in the VITAL questionnaire; however, including responses to “has a doctor ever told you that you had kidney disease (not kidney stones)?” resulted in a significant association. The effect size is large, but it is unclear what type of renal disease was captured, as even those reporting renal failure may have had a variety of etiologies. In the VITAL study, renal disease is self-reported *prior* to the diagnosis of RCC in these individuals and those with pre-existing RCC were excluded. This association has been described in smaller case series, but is novel in a large prospective cohort such as VITAL. Finally, we observed association with diabetes and RCC in the base model however it was not significant in the multivariate model. In the Nurses Health Study, an increased risk of RCC was seen among those with type 2 diabetes, but this study was limited to women.[28] In the present analysis a sub-group analyses of diabetes by gender was not performed due to a limited number of RCC cases. Further research is indicated to evaluate the associated between RCC and these chronic conditions.

This analysis of the VITAL data has several limitations. We detected 249 cases, which may have limited the power of the analysis to detect differences compared to studies with a larger number of cases. The VITAL cohort had poor representation of non-whites. Findings may differ among non-whites but this cannot be assessed with the VITAL data. The question on renal disease was a single question and it was not possible to define which types of renal disease were prevalent among the VITAL cohort. The same is true for ascertainment of viral

hepatitis. Similarly, all reported variables may suffer from bias due to self-reporting and also may vary over time for given individuals. For renal disease and viral hepatitis a confounder may be that these individuals are subjected to more contact with health care, which could result in detection bias for RCC. Although it was possible to confirm a history of hypertension and diabetes through reported use of medications, it was not possible to determine the severity of hypertension or the degree of glycemic control among diabetics. Finally, the VITAL study study was focused on use of vitamins and other supplements, and therefore may have induced responses among a more health-conscious group of eligible individuals. Despite these limitations, this analysis was strengthened by the prospective ascertainment of RCC cases, the high RCC event rate, the large sample size within VITAL, diligent follow-up through SEER linkage, and the ability to control for potentially confounding variables.

Conclusions

In the VITAL cohort, RCC is significantly associated with male gender, obesity, smoking, hypertension, history of renal disease and history of viral hepatitis. The association of RCC and renal disease is novel in such a large cohort. Similarly, the association with hepatitis has only been reported in one other study. Finally, smoking follows a threshold effect curve with increased risk beginning at 22.5 pack years; whereas, obesity follows a dose-response pattern with increasing magnitude of risk by increasing level of obesity. These findings are important as they offer the potential for public health intervention and clinically based education and intervention in high risk individuals.

References

1. Howlander, N. e. a. SEER Stat Fact Sheets: Kidney and Renal Pelvis. Vol. 2012. Bethesda, MD: 2011.
2. Ferlay, J,SH.; Bray, F.; Forman, D.; Mathers, C.; Parkin, DM. GLOBOCAN 2008 v1.2 Cancer Incidence and Mortality Worldwide: IARC CancerBase No. 10. Vol. 2012. Internation Agency for Research on Cancer; Lyon, France: 2008.
3. Navai N, Wood CG. Environmental and modifiable risk factors in renal cell carcinoma. Urol Oncol. 2012; 30:220. [PubMed: 22385993]
4. Weikert S, Ljungberg B. Contemporary epidemiology of renal cell carcinoma: perspectives of primary prevention. World J Urol. 2010; 28:247. [PubMed: 20390283]
5. Chow WH, Gridley G, Fraumeni JF Jr. et al. Obesity, hypertension, and the risk of kidney cancer in men. N Engl J Med. 2000; 343:1305. [PubMed: 11058675]
6. Weikert S, Boeing H, Pischon T, et al. Blood pressure and risk of renal cell carcinoma in the European prospective investigation into cancer and nutrition. Am J Epidemiol. 2008; 167:438. [PubMed: 18048375]
7. Theis RP, Dolwick Grieb SM, Burr D, et al. Smoking, environmental tobacco smoke, and risk of renal cell cancer: a population-based case-control study. BMC Cancer. 2008; 8:387. [PubMed: 19108730]
8. Hunt JD, van der Hel OL, McMillan GP, et al. Renal cell carcinoma in relation to cigarette smoking: meta-analysis of 24 studies. Int J Cancer. 2005; 114:101. [PubMed: 15523697]
9. Adams KF, Leitzmann MF, Albanes D, et al. Body size and renal cell cancer incidence in a large US cohort study. Am J Epidemiol. 2008; 168:268. [PubMed: 18544571]
10. Pischon T, Lahmann PH, Boeing H, et al. Body size and risk of renal cell carcinoma in the European Prospective Investigation into Cancer and Nutrition (EPIC). Int J Cancer. 2006; 118:728. [PubMed: 16094628]

11. White E, Patterson RE, Kristal AR, et al. VITamins And Lifestyle cohort study: study design and characteristics of supplement users. Am J Epidemiol. 2004; 159:83. [PubMed: 14693663]
12. Modesitt SC, Hsu JY, Chowbina SR, et al. Not all fat is equal: differential gene expression and potential therapeutic targets in subcutaneous adipose, visceral adipose, and endometrium of obese women with and without endometrial cancer. Int J Gynecol Cancer. 2012; 22:732. [PubMed: 22635025]
13. Linder K, Arner P, Flores-Morales A, et al. Differentially expressed genes in visceral or subcutaneous adipose tissue of obese men and women. J Lipid Res. 2004; 45:148. [PubMed: 14563828]
14. Setiawan VW, Stram DO, Nomura AM, et al. Risk factors for renal cell cancer: the multiethnic cohort. Am J Epidemiol. 2007; 166:932. [PubMed: 17656615]
15. Mahabir S, Leitzmann MF, Virtanen MJ, et al. Prospective study of alcohol drinking and renal cell cancer risk in a cohort of finnish male smokers. Cancer Epidemiol Biomarkers Prev. 2005; 14:170. [PubMed: 15668492]
16. Lee JE, Giovannucci E, Smith-Warner SA, et al. Intakes of fruits, vegetables, vitamins A, C, and E, and carotenoids and risk of renal cell cancer. Cancer Epidemiol Biomarkers Prev. 2006; 15:2445. [PubMed: 17164369]
17. Weikert S, Boeing H, Pischon T, et al. Fruits and vegetables and renal cell carcinoma: findings from the European prospective investigation into cancer and nutrition (EPIC). Int J Cancer. 2006; 118:3133. [PubMed: 16425278]
18. Gordon SC, Moonka D, Brown KA, et al. Risk for renal cell carcinoma in chronic hepatitis C infection. Cancer Epidemiol Biomarkers Prev. 2010; 19:1066. [PubMed: 20332260]
19. Moriya K, Fujie H, Shintani Y, et al. The core protein of hepatitis C virus induces hepatocellular carcinoma in transgenic mice. Nat Med. 1998; 4:1065. [PubMed: 9734402]
20. Sansonno D, Lauletta G, Montrone M, et al. Hepatitis C virus RNA and core protein in kidney glomerular and tubular structures isolated with laser capture microdissection. Clin Exp Immunol. 2005; 140:498. [PubMed: 15932511]
21. Wiwanitkit V. Renal cell carcinoma and hepatitis C virus infection: is there any cause-outcome relationship? J Cancer Res Ther. 2011; 7:226. [PubMed: 21768723]
22. Tsui JI, Vittinghoff E, Shlipak MG, et al. Association of hepatitis C seropositivity with increased risk for developing end-stage renal disease. Arch Intern Med. 2007; 167:1271. [PubMed: 17592100]
23. Heinz-Peer G, Schoder M, Rand T, et al. Prevalence of acquired cystic kidney disease and tumors in native kidneys of renal transplant recipients: a prospective US study. Radiology. 1995; 195:667. [PubMed: 7753991]
24. Lee HH, Choi KH, Yang SC, et al. Renal cell carcinoma in kidney transplant recipients and dialysis patients. Korean J Urol. 2012; 53:229. [PubMed: 22536464]
25. Bonsib SM. Renal cystic diseases and renal neoplasms: a mini-review. Clin J Am Soc Nephrol. 2009; 4:1998. [PubMed: 19875768]
26. Hajj P, Ferlicot S, Massoud W, et al. Prevalence of renal cell carcinoma in patients with autosomal dominant polycystic kidney disease and chronic renal failure. Urology. 2009; 74:631. [PubMed: 19616833]
27. Keith DS, Torres VE, King BF, et al. Renal cell carcinoma in autosomal dominant polycystic kidney disease. J Am Soc Nephrol. 1994; 4:1661. [PubMed: 8011975]
28. Joh HK, Willett WC, Cho E. Type 2 diabetes and the risk of renal cell cancer in women. Diabetes Care. 2011; 34:1552. [PubMed: 21602426]

Table 1

Distribution of risk factors among renal cell carcinoma (RCC) cases and non-cases in the VITAL cohort

	Raw, unadjusted data for RCC cases and non-cases		
	RCC Cases* N (%)	Non-cases* N (%)	P-value†
Race			0.188
White	236 (94.8)	70,509 (91.6)	
Black	2 (0.8)	975 (1.3)	
Other	11 (4.4)	5,521 (7.1)	
Gender			<0.000
Male	160 (64.4)	36,935(48.0)	
Female	89 (35.7)	40,076 (52.0)	
Age (years)			<0.000
50-54	36 (14.5)	27,836 (23.2)	
55-59	36 (14.5)	17,470 (22.7)	
60-64	65 (26.0)	13,993 (18.2)	
65-69	53 (21.3)	12,683 (16.4)	
70+	59 (23.7)	15,002 (19.5)	
BMI (kg/m^2)			0.011
<25	59 (23.7)	25,279 (32.8)	
25-29	104 (41.8)	29,984 (38.9)	
30-34	47 (18.9)	12,115 (15.7)	
35+	28 (11.2)	5,824 (7.6)	
Missing	11 (4.4)	3,809 (5)	
Smoking (pack-years)			<0.000
Never	88 (35.4)	36,307 (47.2)	
>0 to <7.5	34 (13.7)	12,010 (15.6)	
≥7.5 to 22.5	45 (12.1)	9,405 (12.2)	
≥22.5 to 37.5	45 (18.1)	9,119 (11.8)	
37.5+	47 (18.8)	9,254 (12.0)	
Missing	5 (2.0)	916 (1.2)	
Alcohol consumption (drinks/day)			0.269
0	97(39.0)	27,799 (36.1)	
1	95 (38.2)	30,864 (40.1)	
2	23 (9.2)	8,547 (11.1)	
3+	23 (9.2)	7,839 (10.1)	
Missing	11 (4.4)	1,962 (2.6)	
Fruit Intake (servings/day)			0.115
Tertile 1	80 (32.1)	23,303 (30.3)	
Tertile 2	77 (30.9)	23,306 (30.3)	
Tertile 3	61 (24.5)	23,321 (30.3)	
Missing	31 (12.5)	7,081 (9.1)	

	Raw, unadjusted data for RCC cases and non-cases		
	RCC Cases* N (%)	Non-cases* N (%)	P-value†
Vegetable Intake (servings/day)			0.021
Tertile 1	85 (34.1)	23,298 (30.3)	
Tertile 2	78 (31.3)	23,305 (30.3)	
Tertile 3	55 (22.1)	23,327 (30.3)	
Missing	31 (12.5)	7,081 (9.1)	
Hypertension			<0.000
Yes	127 (51.0)	25,347 (32.9)	
No	122 (49.0)	51,664 (67.1)	
Diabetes			<0.000
Yes	32 (13.0)	5,369 (7.0)	
No	215 (87.0)	71,642 (93.0)	
Kidney Disease			0.003
Yes	7(2.8)	752 (1.0)	
No	240 (97.2)	76,241 (99.0)	
Viral Hepatitis			0.045
Yes	13 (5.3)	2,357 (3.1)	
No	234 (94.7)	74,636 (96.9)	

*Fruit and vegetable intake were on a separate page of the questionnaire and had more missing values than other variables in the study. Missing data not reported if affecting <5 individuals).

†Pearson's chi-squared for categorical variables, Student's T-test for continuous variables.

Table 2

Base model and multivariate model results for risk of RCC by risk factor in the VITAL cohort.

	Cox Proportional Hazards Regression on RCC	
	Base Model*	**Multivariate Model†**
	HR (CI)	HR (CI)
Female	0.51 (0.39, 0.66)	0.55 (0.41, 0.72)
Race		
White	1.00 (referent)	1.00 (referent)
Black	0.62 (0.15, 2.50)	0.49 (0.12, 1.99)
Other Race	0.62 (0.34, 1.13)	0.51 (0.27, 0.96)
BMI (kg/m^2)		
<25	1.00 (referent)	1.00 (referent)
25-29	1.31 (0.95, 1.81)	1.23 (0.88, 1.72)
30-34	1.51 (1.06, 1.81)	1.20 (0.81, 1.78)
>35	2.32 (1.48, 3.65)	1.71 (1.06, 2.79)
Smoking (pack-years)		
Never	1.00 (referent)	1.00 (referent)
>0 to <7.5	1.11 (0.75, 1.65)	1.15 (0.77, 1.71)
≥7.5 to 22.5	1.17 (0.77, 1.78)	1.16 (0.76, 1.77)
≥22.5 to 37.5	1.80 (1.25, 2.59)	1.67 (1.16, 2.42)
≥37.5	1.76 (1.23, 2.52)	1.58 (1.09, 2.29)
Alcohol consumption (drinks/day)		
0	1.00 (referent)	1.00 (referent)
1	1.17 (0.43, 3.14)	0.94 (0.71, 1.26)
2	1.01 (0.35, 2.92)	0.76 (0.47, 1.20)
3+	0.85 (0.29, 2.51)	0.69 (0.43, 1.11)
Fruit Intake (servings/day)		
Tert 1	1.00 (referent)	1.00 (referent)
Tert 2	0.96 (0.74, 1.32)	1.07 (0.78, 1.50)
Tert 3	0.82 (0.59, 1.15)	1.02 (0.71, 1.46)
Vegetable Intake (servings/day)		
Tert 1	1.00 (referent)	1.00 (referent)
Tert 2	0.92 (0.68, 1.26)	0.97 (0.71, 1.33)
Tert 3	0.71 (0.50, 1.01)	0.76 (0.52, 1.11)
Hypertension	1.91 (1.48, 2.47)	1.70 (1.30, 2.22)
Diabetes	1.83 (1.26, 2.65)	1.39 (0.92, 2.09)
Kidney disease	3.13 (1.47, 6.63)	2.58 (1.21, 5.50)
Viral hepatitis	1.81 (1.04, 3.17)	1.80 (1.03, 3.14)

*Adjusting for age and gender only.

†Adjusting for all variables in the table, variables selected a priori.