



Etiologic heterogeneity of clear-cell and papillary renal cell carcinoma in the Netherlands Cohort Study

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Abstract

At present, mostly case-control and retrospective studies have investigated the association between etiologic risk factors and the development of histologic subtypes of renal cell carcinoma (RCC). Therefore, we assessed the heterogeneity between body mass index (BMI), cigarette smoking, alcohol consumption and hypertension across clear-cell RCC (ccRCC) and papillary RCC (pRCC) risk in the prospective Netherlands Cohort Study on diet and cancer. In 1986, 120 852 participants aged 55 to 69 completed a self-administered questionnaire on diet and other risk factors for cancer. Participants were followed up for cancer through record linkage. Tumor histology was assessed through centralized revision by two experienced uropathologists. After 20.3 years of follow-up, 384 histologically verified RCC cases, including 315 ccRCC and 46 pRCC cases and 4144 subcohort members were eligible for case-cohort analysis. Hazard ratios and 95% confidence intervals were estimated by multivariable-adjusted proportional hazards models. Overall, BMI was associated positively with ccRCC risk, but inversely with pRCC risk. Cigarette smoking was associated with an increased ccRCC, but a decreased pRCC risk. Alcohol consumption was inversely associated with both ccRCC and pRCC risk. Hypertension was associated with an increased risk of both ccRCC and pRCC. Statistically significant etiologic heterogeneity was observed for BMI, BMI change since age 20, and smoking duration in current smokers across ccRCC and pRCC risk. In conclusion, we observed potential heterogeneity for BMI, BMI change and smoking duration across ccRCC and pRCC risk.

KEYWORDS

heterogeneity, prospective cohort study, renal cell carcinoma, risk factors, tumor histology

1 | BACKGROUND

Kidney cancer consists primarily of adenocarcinomas that arise in the renal parenchyma, commonly referred to as renal cell carcinomas (RCC).¹ RCC is comprised of various entities defined by a distinct tumor histology, chromosomal alterations and molecular pathways.²

Abbreviations: BMI, body mass index (kg/m²); CBS, Statistics Netherlands; ccRCC, clear-cell renal cell carcinoma; CI, confidence interval; FFPE tissue, formalin-fixed paraffin-embedded tumor tissue; HR, hazard ratio; NCR, Netherlands Cancer Registry; NLCS, Netherlands Cohort Study on diet and cancer; PALGA, The Netherlands Pathology Registry; pRCC, papillary renal cell carcinoma; RCC, renal cell carcinoma.

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The most common subtypes are clear cell (approximately 70% of all RCC) and papillary RCC (10%-15%).²

Established modifiable risk factors for RCC include cigarette smoking, excess body weight and hypertension.³⁻⁸ Furthermore, alcohol consumption has been associated with a decreased RCC risk in multiple prospective epidemiological studies.^{9,10} Even though histological subtypes of RCC have been formally recognized for more than two decades,¹¹ data on etiologic risk factors linked to these subtypes remains sparse.¹ Previous studies have found evidence for a potential heterogeneity between the risk of ccRCC and pRCC for body mass index,¹²⁻¹⁵ and antihypertensive medication.¹⁶ At present, no histological heterogeneity has been found in relation to cigarette smoking or hypertension status.^{12,14} Lastly, to our knowledge, no studies have directly assessed the etiologic risk heterogeneity between alcohol consumption and histologic RCC subtypes yet. The current available evidence on the heterogeneity between histologic RCC subtypes for these modifiable risk factors is solely based on information from (nested) case-control studies^{12-14,16} and three retrospective studies.^{15,17,18} Additional evidence from large-scale prospective cohort studies may aid in uncovering potential heterogeneity between these established risk factors and ccRCC and pRCC development.

In the Netherlands Cohort Study (NLCS) on diet and cancer, a large nationwide prospective cohort study, we were able to assess tumor histology through a centralized revision by two experienced pathologists. With this information, we aimed to investigate the heterogeneity of associations between ccRCC and pRCC for the main established etiologic risk factors of RCC, namely BMI, cigarette smoking, alcohol consumption and hypertension.

2 | METHODS

2.1 | Study population

The NLCS is a nation-wide prospective cohort study initiated in September 1986 with the inclusion of 58 279 men and 62 573 women between the ages of 55 and 69 years. The study design has been described in detail elsewhere.¹⁹ In short, the study is a prospective cohort study initiated to investigate the association between diet and cancer risk. A case-cohort design was used for efficiency in follow-up for vital status and data processing. A subcohort of 5000 participants, of which 2411 men and 2589 women, was randomly sampled from the full cohort at baseline to estimate person-time at risk for the entire cohort. All participants were followed up by computerized record linkage with the Netherlands Cancer Registry (NCR), the Netherlands Pathology Registry (PALGA) and cause of death from Statistics Netherlands (CBS). In addition, participants were regularly followed up for migration and vital status. Follow-up for vital status of the subcohort was nearly 100% complete after 20.3 years and the completeness of cancer follow-up through record linkage is estimated to be over 96%.²⁰ The institutional review boards of Maastricht University (Maastricht) and the Netherlands Organization for Applied Scientific Research TNO

What's New?

Etiologic risk factors for clear cell renal cell carcinoma (ccRCC) and papillary renal cell carcinoma (pRCC) include alcohol consumption, body mass index (BMI), cigarette smoking, and hypertension. Little is known, however, about variability in how these factors affect the development of RCC histologic subtypes. In this population-based prospective cohort study, examination of variability in associations between established etiologic factors and RCC histologic subtypes revealed significant heterogeneity between BMI and ccRCC and pRCC risk and between risk of these subtypes and smoking duration in current smokers. The findings provide novel insight into relationships between etiologic heterogeneity and mechanisms of RCC development.

(Zeist) approved the NLCS. The NLCS was conducted in accordance with the Declaration of Helsinki. By completing and returning the baseline questionnaire, participants agreed to participate in the NLCS.

In total, 608 RCC cases were identified within the NLCS between 1986 and 2006. Histologically confirmed RCC cases were eligible for the collection of formalin-fixed paraffin-embedded (FFPE) tumor tissues. Overall, FFPE tumor tissues were collected for 454 (79.8%) of the 568 eligible cases.²¹ Tumor histology was revised by two experienced pathologists according to the WHO-classification of RCC tumors.² Of the 454 RCC cases, 366 (80.6%) were clear-cell (cc)RCC cases, 60 (13.2%) papillary (p)RCC cases, 15 (3.3%) chromophobe RCC cases and 13 (2.9%) other or undefined RCC cases. Further classification of pRCC cases resulted in 35 (7.7%) type 1 pRCC, 24 (5.3%) type 2 pRCC and 1 (0.2%) undefined pRCC. To maintain sufficient power in the analyses, type 1 and type 2 pRCC were combined into one category. Chromophobe RCC and other or undefined RCC cases were not assessed due to the insufficient number of cases.

Cohort members with prevalent cancer at baseline, except skin cancer, and incomplete or inconsistent information on exposure variables and a priori selected confounders were excluded from analyses. In total, 515 RCC cases (International Classification for Oncology 3: C64.9) and 4144 subcohort members were included in the analyses. Of the 384 included RCC cases with confirmed tumor histology 315 (82.0%) were ccRCC cases and 46 (12.0%) were pRCC cases.

2.2 | Exposure assessment

All participants completed a mailed, self-administered questionnaire at baseline on dietary habits and other risk factors for cancer. By completing and returning the baseline questionnaire, individuals agreed to participate in the NLCS. From this questionnaire information was derived on anthropometric measures, smoking habits, dietary habits and medical conditions.

Baseline BMI (kg/m^2) was calculated using weight at baseline and the self-reported height squared. To calculate the BMI at age 20, the self-reported weight at age 20 was used in combination with the self-reported height at baseline. Change in BMI since age 20 was calculated by subtracting the BMI at age 20 from the BMI at baseline. In addition, men reported their trouser size and women reported their skirt size as a proxy for body composition.²² Questions on cigarette, cigar and pipe smoking were used to assess smoking status, smoking quantity and smoking duration. Questions on beer, red wine, white wine, sherry, fortified wines, liqueur and liquor were used to assess the consumption of alcohol. Participants who consumed alcoholic beverages less than once a month were considered nonusers. Standard glass sizes were defined as 200 mL for beer, 105 mL for wine, 80 mL for sherry and 45 mL for both liqueur and liquor.²³ These values corresponded to 8, 10, 11, 7 and 13 g of alcohol, respectively. Mean daily alcohol consumption was calculated by multiplying the consumption frequency and the standardized item unit of each alcoholic beverage. Information from the questionnaire was also used to define stable abstainers and stable users of alcohol. Stable abstainers were defined as participants that reported no alcohol consumption 5 years before baseline. Stable users were defined as participants who reported that they drank equal amounts of alcoholic beverages 5 years before baseline. The diagnosis of hypertension was derived from a question on whether the participant was diagnosed with hypertension preceding baseline by a physician. In addition, participants were asked to report the use of any drugs for a period longer than 6 months. From this information, the use of antihypertensive medication was extracted.

2.3 | Statistical analyses

Cox proportional hazard models were used to estimate sex-adjusted and multivariable-adjusted hazard ratio's (HRs) and 95% confidence intervals (CIs). Stata statistical software: release 15 (StataCorp., 2017, College Station, Texas) was used for all analyses. Analyses were adjusted for smoking status (never/former/current), smoking duration (y, continuous, centered), smoking frequency (cig/d, continuous, centered), pipe and/or cigar smoking (never/former/current), alcohol consumption (g/d, continuous), body mass index (kg/m^2 , continuous), diabetes status (no/yes) when applicable. Analyses on BMI change were additionally adjusted for BMI at age 20. As proposed by Leffondré et al,²⁴ smoking duration and smoking frequency were centered to avoid multicollinearity with smoking status. Analyses on smoking cessation were additionally adjusted for cigarette-years, calculated by multiplying smoking frequency with smoking duration, to resolve multicollinearity between smoking duration and smoking cessation. Fruit consumption, vegetable consumption and use of antihypertensive medication were included in models as potential confounders if they altered HRs for RCC risk by more than 10%. None of these potential confounders satisfied this condition, and were, therefore, not included in models as a confounding factor. The use of

antihypertensive medication was studied as a potential risk factor based on findings from previous studies.^{5,25}

Person-years at risk were calculated from baseline until registration of RCC or until date of censoring by death, emigration, loss to follow-up or end of follow-up, whichever occurred first. The proportional hazards assumption was tested with scaled Schoenfeld residuals and log-log curves. The proportional hazard assumption was violated for age, BMI and smoking frequency when using time-on-study as timescale. To resolve this issue, age-on-study was used as timescale with smoking frequency as a time-varying covariate. Standard errors were calculated using the robust Huber-White sandwich estimator, similar to the variance-covariance estimator by Barlow,²⁶ to account for additional variance introduced by sampling a subcohort from the full cohort.

Test for heterogeneity of associations were performed to evaluate differences between ccRCC and pRCC risk for all etiologic risk factors using the competing risks procedure in Stata. *P*-values were calculated with a method developed for the case-cohort design based on bootstrapping. This procedure has been described in more detail elsewhere.^{27,28}

All tests were performed two-sided and *P*-values $<.05$ were considered statistically significant.

3 | RESULTS

The age at baseline of RCC cases was slightly lower, compared to the subcohort (Table 1). In addition, RCC cases were predominantly men, had a slightly increased mean BMI at baseline, BMI at age 20 and trouser and skirt size, were more often current and former smokers, consumed more alcohol and more often reported a diagnosis of hypertension and antihypertensive medication use, compared to the subcohort. Compared to ccRCC cases, papillary RCC cases, were more often men, had a lower BMI at baseline, had a lower trouser and skirt size, were more often former cigarette smokers and pipe or cigar smokers, had a higher cigarette smoking duration and frequency, and consumed less alcohol.

Overall, results between sex-adjusted and multivariable-adjusted Cox-regression models did not indicate large differences. Therefore, sex-adjusted analyses are presented in the supplements (Supplementary Tables 1.1-1.4).

3.1 | Body mass index

In multivariable-adjusted analyses, a positive association was observed between BMI and RCC risk (Table 2). Furthermore, we observed an U-shaped association between BMI at age 20 and RCC risk. BMI change per 1 kg/m^2 increment since age 20 was associated with a nonstatistically significantly increased RCC risk. Trouser and skirt size were associated with an increased risk of RCC across increasing size categories (*p trend*: .02, .005 for trouser and skirt size, respectively).

Baseline characteristics	Subcohort	Renal cell carcinoma		
		Overall	ccRCC	pRCC
Total (n)	4144	515	315	46
Age at baseline (y)	61.3 (4.2)	60.9 (3.9)	60.7 (3.9)	61.1 (3.9)
Male sex (n, %)	2039 (49.2)	337 (65.4)	200 (63.5)	40 (87.0)
Body mass index at baseline (kg/m ²)	25.0 (3.1)	25.4 (3.0)	25.5 (3.0)	24.6 (2.2)
Body mass index at age 20 (kg/m ²)	21.5 (2.6)	21.7 (2.6)	21.9 (2.7)	21.7 (2.1)
Trouser size in men at baseline (size)	51.5 (4.3)	52.1 (3.1)	52.2 (3.4)	51.6 (2.7)
Skirt size in women at baseline (size)	43.5 (3.0)	44.3 (3.0)	44.2 (2.7)	42.8 (1.8)
Cigarette smoking status (n, %)				
Never smokers	1524 (36.8)	136 (26.4)	85 (27.0)	10 (21.7)
Former smokers	1466 (35.4)	219 (42.5)	136 (43.2)	22 (47.8)
Current smokers	1154 (27.9)	160 (31.1)	94 (29.8)	14 (30.4)
Ever cigarette smokers only				
Smoking duration (y)	31.8 (12.2)	32.1 (12.0)	31.7 (11.9)	36.5 (10.6)
Smoking frequency (cig/d)	15.4 (10.3)	17.1 (12.2)	16.5 (11.5)	18.0 (12.0)
Pipe and/or cigar smoking				
Never pipe or cigar smoker (n, %)	3559 (85.9)	414 (80.4)	248 (78.7)	32 (69.6)
Former pipe or cigar smoker (n, %)	308 (7.4)	66 (12.8)	43 (13.7)	10 (21.7)
Current pipe or cigar smoker (n, %)	277 (6.7)	35 (6.8)	24 (7.6)	4 (8.7)
Alcohol intake (g/d) ^a	13.5 (15.1)	15.2 (15.3)	15.0 (15.0)	13.8 (12.3)
Diagnosis of hypertension (n, %)	1093 (26.4)	161 (31.3)	99 (31.4)	16 (34.8)
Use of antihypertensive medication (n, %)	856 (20.7)	124 (24.1)	80 (25.4)	11 (23.9)

Abbreviations: ccRCC, clear cell renal cell carcinoma; pRCC, papillary renal cell carcinoma.

^aIn consumers only.

In general, an increasing ccRCC risk was observed across increasing BMI categories. The strength of the associations was slightly elevated compared to associations observed for overall RCC risk. In addition, a statistically significantly increased risk was found per 1 kg/m² increase (HR 1.04, 95% CI 1.01-1.08). For pRCC risk, associations became increasingly inverse across increasing BMI categories. A borderline significant inverse association was found for pRCC per kg/m² increase (HR 0.91, 95% CI 0.82-1.00). We observed statistically significant heterogeneity across ccRCC and pRCC for baseline BMI (per kg/m²; $p_{\text{heterogeneity}}$: .02). Furthermore, an U-shaped association was found between BMI at age 20 and ccRCC, while no clear association was found for pRCC. Furthermore, an increase in change in BMI since age 20 was associated with an increase in risk for ccRCC, and a decrease in pRCC risk. These differences in BMI change since 20 were statistically significant in tests for heterogeneity ($p_{\text{heterogeneity}}$: .03). Trouser size in men was associated with a statistically significantly increased ccRCC risk per size increase, while no association was found with pRCC risk. However, no heterogeneity of associations was observed ($p_{\text{heterogeneity}}$: .18). No analyses were performed for skirt size in pRCC, because of the limited number of female pRCC cases (n = 5).

3.2 | Cigarette smoking

In multivariable-adjusted models, cigarette smoking status was associated with an increased risk of RCC (Table 3). Associations persisted

TABLE 1 Baseline characteristics of the subcohort and renal cell carcinoma cases in the Netherlands Cohort Study on diet and cancer, 1986-2006

after adjustment for smoking frequency and duration. Restricting analyses to exclusively cigarette smokers strengthened associations in current cigarette smokers. No clear association was found with smoking duration and smoking frequency. Smoking cessation was associated with a decreased RCC risk in categorized analyses.

Similar to RCC overall, an increased ccRCC risk was found in both former (HR 1.26, 95% CI 0.91-1.74) and current smokers (HR 1.41, 95% CI 1.01-1.97). Associations remained similar after adjusting for smoking frequency and duration, and when restricting analyses to exclusively cigarette smokers. No clear association was found between smoking status and pRCC risk. However, when restricting analyses to exclusively cigarette smokers, an inverse association with pRCC risk was found in former (HR 0.66; 95% CI 0.22-1.98) and current smokers (HR 0.46, 95% CI 0.11-1.90). Heterogeneity tests between ccRCC and pRCC risk were not able to provide reliable estimations for analyses on smoking status. No clear association was found between smoking frequency and smoking duration and ccRCC risk. An increased pRCC risk was observed in cases with increasing smoking frequency and duration, although not statistically significant. Statistically significant heterogeneity was observed for smoking duration in current smokers per 5-year increment ($p_{\text{heterogeneity}}$: .04), but not in former smokers ($p_{\text{heterogeneity}}$: .17). While there were indications for a decreased ccRCC and pRCC risk with increasing categories of duration of smoking cessation, solely analyses on pRCC risk suggested a potential inverse association per

TABLE 2 Multivariable-adjusted Cox proportional hazard models with age as timescale for the association between body mass index (BMI) and risk of clear-cell renal cell carcinoma and papillary renal cell carcinoma in the Netherlands Cohort Study on diet and cancer, 1986-2006

Characteristics	Subcohort person-years	Clear-cell renal cell carcinoma			Papillary renal cell carcinoma			P for heterogeneity ^b
		Cases No.	Multivariable-adjusted ^a		Cases No.	Multivariable-adjusted ^a		
			HR	95% CI		HR	95% CI	
BMI at baseline (kg/m ²)								
<23	16 723	55	1	Ref.	11	1	Ref.	
23 to <25	21 298	90	1.14	(0.81-1.63)	18	0.92	(0.42-2.04)	
25 to <27	16 372	81	1.30	(0.90-1.86)	10	0.60	(0.24-1.48)	
≥27	15 477	89	1.61	(1.13-2.30)	7	0.50	(0.19-1.33)	.62 ^c
<i>p trend</i>			.005			.09		
Cont. (per kg/m ²)	69 871	315	1.04	(1.01-1.08)	46	0.91	(0.82-1.00)	.02
BMI at age 20 (kg/m ²) ^d								
<20.0	15 384	61	1.39	(0.93-2.09)	6	0.75	(0.26-2.17)	
20.0 to <21.5	14 576	45	1	Ref.	9	1	Ref.	
21.5 to <23	14 558	67	1.50	(1.01-2.23)	10	1.08	(0.42-2.83)	
≥23	15 549	85	1.76	(1.21-2.57)	8	0.77	(0.29-2.04)	.56
<i>p trend</i>			.05			.98		
Cont. (per kg/m ²)	60 067	258	1.05	(1.00-1.10)	33	1.01	(0.90-1.13)	.70
BMI change since age 20 (kg/m ²) ^e								
<1.5	14 892	60	1	Ref.	8	1	Ref.	
1.5 to <3.5	16 693	73	1.08	(0.75-1.57)	16	1.31	(0.50-3.43)	
3.5 to <5.5	13 659	58	1.15	(0.77-1.72)	7	0.69	(0.22-2.14)	
≥5.5	14 823	67	1.34	(0.89-2.02)	2	0.16	(0.03-0.82)	.80
<i>p trend</i>			.15			.005		
Cont. (per kg/m ²)	60 067	258	1.03	(0.99-1.08)	33	0.89	(0.75-0.98)	.03
Trouser size—Men								
<50	4745	26	1.16	(0.68-1.99)	8	1.86	(0.62-5.59)	
50 to <52	6736	32	1	Ref.	6	1	Ref.	
52 to <54	10 137	63	1.31	(0.84-2.04)	12	1.13	(0.42-3.07)	
54 to <56	5553	41	1.54	(0.95-2.51)	8	1.46	(0.51-4.17)	
≥56	2756	24	1.90	(1.09-3.33)	3	0.98	(0.23-4.11)	.94
<i>p trend</i>			.03			.57		
Cont. (per size)	29 928	186	1.06	(1.01-1.12)	37	1.00	(0.95-1.05)	.18
Skirt size—women ^f								
<42	7012	15	0.87	(0.45-1.69)	1	-		
42 to <44	9372	24	1	Ref.	1	1		
44 to <46	10 272	31	1.16	(0.67-2.01)	3	-		
46 to <48	6529	27	1.52	(0.87-2.67)	0	-		
≥48	3774	17	1.55	(0.81-2.98)	0	-		-
<i>p trend</i>			.04			-		
Cont. (per size)	36 958	114	1.07	(1.01-1.13)	5	-		-

^aAdditionally adjusted for: smoking status (never/former/current), smoking duration (continuous, centered), smoking frequency (continuous, centered), pipe and/or cigar smoking (never/former/current), hypertension status (no/yes), alcohol consumption (g/d, continuous), diabetes (no/yes), models included a time-varying covariate for smoking frequency because of a potential violation of the proportional hazards assumption.

^bBased on multivariable-adjusted models.

^cModels failed to converge more than 10 times during heterogeneity analyses (1000 replications). Models and intrinsic standard errors are based solely on successful bootstraps.

^dAnalysis with BMI at age 20 have a restricted number of cases due to missing values.

^eAdditionally adjusted for BMI at age 20.

^fNot adjusted for pipe and/or cigar smoking due to unstable estimates for these confounding factors.

TABLE 3 Multivariable-adjusted Cox proportional hazard models with age as timescale for the association between cigarette smoking and risk of clear-cell renal cell carcinoma and papillary renal cell carcinoma in the Netherlands Cohort Study on diet and cancer, 1986-2006

Characteristics	Subcohort person-years	Clear-cell renal cell carcinoma			Papillary renal cell carcinoma			P for heterogeneity ^b
		Cases No.	Multivariable-adjusted ^a		Cases No.	Multivariable-adjusted ^a		
			HR	95% CI		HR	95% CI	
<i>Unadjusted for cigarette smoking frequency and duration</i>								
Cigarette smoking status								
Never	27 409	85	1	Ref.	10	1	Ref.	
Former	24 499	136	1.26	(0.91-1.74)	22	0.84	(0.35-2.02)	
Current	17 963	94	1.41	(1.01-1.97)	14	1.08	(0.47-2.51)	.73 ^c
<i>p trend</i>			.05			.78		
Never	27 409	85	1	Ref.	10	1	Ref.	
Former	24 499	136	1.26	(0.90-1.78)	22	0.97	(0.39-2.46)	
Current	17 963	94	1.39	(0.98-1.97)	14	0.65	(0.24-1.77)	.75 ^c
<i>p trend</i>			.06			.39		
<i>Adjusted for cigarette smoking frequency and duration^d</i>								
Cigarette smoking status								
Never	26 090	73	1	Ref.	9	1	Ref.	
Former	19 102	93	1.37	(0.95-1.97)	10	0.66	(0.22-1.98)	
Current	15 348	82	1.54	(1.07-2.22)	13	0.46	(0.11-1.90)	.71 ^c
<i>p trend</i>			.02			.28		
<i>Solely in exclusive cigarette smokers</i>								
Smoking frequency ^e								
>0 to <20 cig/d	21 689	102	1	Ref.	10	1	Ref.	
≥20 cig/d	12 761	73	1.01	(0.72-1.42)	13	1.67	(0.68-4.10)	.18
Cont. (per 5 cig/d), former smoker	19 102	93	1.03	(0.92-1.16)	10	1.10	(0.83-1.47)	.42
Cont. (per 5 cig/d), current smoker	15 348	82	1.03	(0.93-1.14)	13	1.22	(0.91-1.64)	.27
Smoking duration ^f								
>0 to <30 y	13 701	65	1	Ref.	2	1	Ref.	
≥30 y	20 749	110	0.90	(0.62-1.32)	21	4.96	(1.19-20.7)	– ^g
Cont. (per 5 y), former smoker	19 102	93	1.03	(0.92-1.14)	10	1.67	(1.04-2.67)	.17
Cont. (per 5 y), current smoker	15 348	82	0.96	(0.85-1.08)	13	1.26	(0.63-2.51)	.04
Number of years of smoking cessation ^h								
Current smoker	15 348	82	1	Ref.	13	1	Ref.	
>0 to <15	10 444	53	0.91	(0.65-1.29)	7	0.76	(0.30-1.94)	
≥15	8657	40	0.88	(0.59-1.33)	3	0.44	(0.12-1.64)	
Never smoker	26 090	73	0.65	(0.46-0.92)	9	1.62	(0.52-5.06)	.95
<i>p trend, excl. never smokers</i>			.49			.22		
Cont. (per 5 y), former smokers	19 102	93	0.98	(0.86-1.11)	10	0.87	(0.58-1.31)	.98

^aAdditionally adjusted for: pipe and/or cigar smoking (never/former/current), body mass index (continuous), hypertension status (no/yes), alcohol consumption (g/d, continuous), diabetes (no/yes), models included a time-varying covariate for smoking frequency because of a potential violation of the proportional hazards assumption.

^bBased on multivariable-adjusted models.

^cModels failed to converge more than 10 times during heterogeneity analyses (1000 replications). Models and intrinsic standard errors are based solely on successful bootstraps.

^dAdditionally adjusted for cigarette smoking duration (years, centered) and cigarette smoking frequency (cig/d, centered).

^eAdditionally adjusted for smoking duration (years, centered).

^fAdditionally adjusted for smoking frequency (cig/d, centered).

^gEstimates were unstable due to limited sample sizes in subcategories.

^hAdditionally adjusted for cigarette-years.

5 years increase. Tests for heterogeneity did not show statistically significant differences across ccRCC and pRCC for smoking cessation ($p_{\text{heterogeneity}}$: .98).

3.3 | Alcohol

In multivariable-analyses, alcohol consumption was associated with a seemingly nonlinear decreased risk of RCC, although not statistically significant (Table 4). In stable users and abstainers, associations were mostly inverse. The inverse association with RCC risk was the strongest in the category 5 to <15 g/d, when compared to abstainers, in both analyses with all alcohol users and analyses with stable users and abstainers. HRs attenuated in categories above 15 g/d.

Associations were slightly stronger in analyses on ccRCC risk, compared to associations found for RCC overall. A nonlinear association with ccRCC risk was found for alcohol consumption in stable alcohol users and abstainers. In analyses on pRCC risk, a seemingly nonlinear association was observed with an increased pRCC risk at alcohol consumptions <15 g/d and a decreased pRCC risk at higher alcohol consumptions, when compared to abstainers. In stable alcohol

users and abstainers, an inverse association was observed between alcohol consumption and pRCC risk. However, these analyses were performed on a very limited number of participants. Tests for heterogeneity of associations between ccRCC and pRCC were not able to provide reliable estimations for categorical analyses on alcohol consumption. No heterogeneity was observed between ccRCC and pRCC risk in continuous analyses ($p_{\text{heterogeneity}}$ range: .85-.86).

3.4 | Hypertension

In multivariable analyses, self-reported hypertension and the self-reported use of antihypertensive medication were associated with an increased RCC risk (Table 5). Risk estimates were elevated in participants who reported both hypertension and the use of antihypertensive medication.

Similar to analyses on RCC overall, hypertension and the use of antihypertensive medication risks were consistently associated with an increased risk for both ccRCC and pRCC. The observed associations were the strongest with pRCC. Participants who reported both hypertension and the use of antihypertensive medication had a

TABLE 4 Multivariable-adjusted Cox proportional hazard models with age as timescale for the association between alcohol and risk of clear-cell renal cell carcinoma and papillary renal cell carcinoma in the Netherlands Cohort Study on diet and cancer, 1986-2006

Characteristics	Subcohort person-years	Clear-cell renal cell carcinoma			Papillary renal cell carcinoma			P for heterogeneity ^b
		Cases No.	Multivariable-adjusted ^a		Cases No.	Multivariable-adjusted ^a		
			HR	95% CI		HR	95% CI	
Alcohol consumption (g/d)								
Abstainer	16 613	76	1	Ref.	7	1	Ref.	
>0 to <5	20 731	79	0.77	(0.56-1.07)	13	1.42	(0.55-3.66)	
≥5 to <15	15 589	64	0.71	(0.50-1.00)	14	1.48	(0.57-3.84)	
≥15 to <30	10 810	63	0.86	(0.59-1.25)	8	0.89	(0.32-2.46)	
≥30	6127	33	0.77	(0.49-1.23)	4	0.67	(0.19-2.36)	.62 ^c
<i>p trend</i>			.37			.32		
Cont. (per 5 g/d)	69 871	315	0.98	(0.94-1.03)	46	0.94	(0.86-1.04)	.85
Alcohol consumption among stable abstainers/users (g/d) ^d								
Abstainer	12 986	57	1	Ref.	7	1	Ref.	
>0 to <5	11 867	46	0.86	(0.57-1.28)	6	0.81	(0.27-2.42)	
≥5 to <15	9435	42	0.87	(0.57-1.34)	6	0.86	(0.27-2.73)	
≥15 to <30	5832	38	1.09	(0.67-1.77)	3	0.58	(0.15-2.30)	
≥30	3287	20	1.00	(0.55-1.83)	2	0.75	(0.14-3.93)	– ^c
<i>p trend</i>			.82			.57		
Cont. (per 5 g/d)	43 407	203	1.00	(0.94-1.05)	24	0.99	(0.85-1.15)	.86

^aAdditionally adjusted for: smoking status (never/former/current), smoking duration (continuous, centered), smoking frequency (continuous, centered), pipe and/or cigar smoking (never/former/current), hypertension status (no/yes), body mass index (kg/m², continuous), diabetes (no/yes), models included a time-varying covariate for smoking frequency because of a potential violation of the proportional hazards assumption.

^bBased on multivariable-adjusted models.

^cModels failed to converge more than 10 times during heterogeneity analyses (1000 replications). Models and intrinsic standard errors are based solely on successful bootstraps.

^dStable abstainers were defined as participants that reported no alcohol consumption 5 y before baseline. Stable users were defined as participants who reported that they drank equal amounts of beer or other alcoholic beverages 5 y before baseline.

TABLE 5 Multivariable-adjusted Cox proportional hazard models with age as timescale for the association between hypertension and risk of clear-cell renal cell carcinoma and papillary renal cell carcinoma in the Netherlands Cohort Study on diet and cancer, 1986-2006

Characteristics	Subcohort person-years	Clear-cell renal cell carcinoma			Papillary renal cell carcinoma			P for heterogeneity ^b
		Cases No.	Multivariable-adjusted ^a		Cases No.	Multivariable-adjusted ^a		
			HR	95% CI		HR	95% CI	
Self-reported hypertension diagnosis								
No	51 868	216	1	Ref.	30	1	Ref.	
Yes	18 002	99	1.32	(1.02-1.69)	16	1.95	(1.03-3.67)	.67
Use of antihypertensive medication								
No	56 463	235	1	Ref.	35	1	Ref.	
Yes	13 408	80	1.45	(1.10-1.91)	11	1.47	(0.70-3.08)	.82
Hypertension status and antihypertensive use								
No hyp. or no med.	59 848	251	1	Ref.	35	1	Ref.	
Hyp. and med.	10 023	64	1.56	(1.16-2.09)	11	2.41	(1.15-5.01)	.62

^aAdditionally adjusted for: smoking status (never/former/current), smoking duration (continuous, centered), smoking frequency (continuous, centered), pipe and/or cigar smoking (never/former/current), alcohol consumption (g/d, continuous), body mass index (kg/m², continuous), diabetes (no/yes), models included a time-varying covariate for smoking frequency because of a potential violation of the proportional hazards assumption.

^bBased on multivariable-adjusted models.

strongly elevated risk of both ccRCC and pRCC. Overall, tests for heterogeneity indicated no differences between ccRCC and pRCC risk regarding the self-reported hypertension and use of antihypertensive medication ($p_{\text{heterogeneity}}$ range: .62-.82).

4 | DISCUSSION

In this large-scale prospective cohort study, we investigated the etiologic heterogeneity between BMI, smoking, alcohol consumption and hypertension across ccRCC and pRCC risk. We observed statistically significant heterogeneity of associations across ccRCC and pRCC for BMI, BMI change since age 20 and smoking duration in current smokers. We observed no heterogeneity across histologic subtypes for alcohol consumption and hypertension.

There is a growing body of evidence regarding a potential subtype-specific association between BMI and RCC risk. In multiple studies, an association with obesity was observed with ccRCC, and not with pRCC risk.^{12,14,29} In contrast, one study found no difference in BMI across the development of ccRCC and pRCC.¹⁵ Other studies, which only reported differences between the occurrence of clear-cell RCC vs other histologic RCC subtypes combined, also reported potential histologic differences related to obesity.^{13,30,31} In our study, we found evidence for heterogeneity across ccRCC and pRCC risk in continuous analyses for BMI at baseline, as well as for BMI change since age 20. Even though we did not observe statistically significant heterogeneity in categorical analyses, large differences in estimates were observed for BMI categories across ccRCC and pRCC risk. We report a similar association, compared to previous studies, between BMI and ccRCC risk. For pRCC risk, however, we observed consistent inverse associations regarding BMI, while previous studies found no association.^{12,14,29} This may be due to the limited power of our pRCC analyses, as we report results with wide CIs for pRCC. The consistent report of

heterogeneity across multiple studies, does provide an indication of etiologic differences across RCC subtypes regarding BMI.

Several plausible mechanisms may explain the observed association between BMI and ccRCC risk specifically. Clear-cell RCC commonly harbors somatic mutations in the *von Hippel-Lindau* (*VHL*) tumor-suppressor gene.³² Inactivation of *VHL* leads to upregulation of the type 1 insulin-like growth factor receptor (IGF1R) in RCC cells.³³ Obesity has been related to hormonal changes in the body, including an increase in circulating levels of insulin-like growth factor-1 (IGF-I).³⁴ IGF-I strongly stimulates cell proliferation, inhibits apoptosis and can enhance angiogenesis.³⁵ Therefore, the inactivation of *VHL* in ccRCC and the obesity-related increase in IGF-I may amplify the process of tumorigenesis. Another hypothesized mechanism may be the relationship between hypoxia and the development of ccRCC.³⁶ Physiologically, the kidney is sensitive to perturbations in oxygen levels due to the activation of the *VHL-HIF1A* pathway.³⁷ Somatic mutations in this pathway are known to lead to carcinogenesis due to defects in the hypoxia sensing mechanism, which is characteristic of ccRCC development.³⁷ Therefore, it is hypothesized that chronic hypoxia may exert similar effects due to the repeated activation of the hypoxia sensing mechanisms.³⁶ Obesity may achieve this due to the link to obstructive sleep apnea, which causes a state of hypoxia during sleep.³⁸ Therefore, the presence of hypoxia due to obstructive sleep apnea could, in part, explain the observed relationship between obesity and ccRCC in particular.³⁹ However, verification of the association between obstructive sleep apnea and ccRCC risk should still be addressed in future studies.

To our knowledge, three studies have investigated the potential for heterogeneity between cigarette smoking and the risk of histologic subtypes of RCC.^{12,14,17} In these studies, no heterogeneity of associations was found across ccRCC and pRCC for tobacco smoking status.^{12,14,17} In our study, a positive association was observed between cigarette smoking status and ccRCC risk, but no clear association was

found with pRCC risk. Patel et al¹⁷ investigated the heterogeneity between smoking frequency, duration and pack-years across ccRCC and pRCC in detail and found no evidence for heterogeneity. Similarly, we found no heterogeneity of associations for cigarette smoking frequency and smoking cessation. We observed a statistically significant heterogeneity for smoking duration in current smokers ($p_{\text{heterogeneity}}: .04$). However, this may be a chance finding as we observed a very skewed distribution of cigarette-smoking patterns in pRCC cases, which may have affected the heterogeneity estimates between ccRCC and pRCC.

The current evidence suggests that alcohol consumption is inversely associated with the risk of RCC.^{9,10,40,41} As of yet, the potential for histologic heterogeneity regarding alcohol consumption has remained unexplored. In our study, we observed inverse associations between alcohol consumption and both ccRCC and pRCC risk. No heterogeneity was found across ccRCC and pRCC in either overall alcohol consumers or stable users and abstainers. However, these findings need to be validated in future studies.

Previous research has indicated that patients with hypertension more often present with nonclear cell histology.⁴² Even though slightly stronger associations were found between hypertension and pRCC, when compared to ccRCC, we observed no statistically significant heterogeneity of associations, which is in line with findings from Purdue et al.¹² A previous study by Colt et al¹⁶ has indicated potential drug- and histology-specific associations between hypertension and RCC. In their study pRCC, but not ccRCC, was associated with long-term use of diuretics and calcium channel blockers.¹⁶ In our study, we observed similar point estimates between antihypertensive medication use and ccRCC risk and pRCC risk. Unfortunately, due to the limited number of pRCC cases, we were unable to assess the risk related to different types of antihypertensive medication.

The present study had several strengths, including the prospective design, the detailed assessment of exposures and confounders at baseline, and the long duration of cancer follow-up. Our results for overall RCC, as detailed in the supplementary materials (Supplementary Tables 2.1-2.4), were in line with evidence from large-scale meta-analyses on obesity,⁴³ smoking,^{3,8} alcohol consumption^{9,41} and hypertension,⁷ which strengthens the credibility of our results. Furthermore, the differentiation between histological subtypes was based on the centralized revision by two experienced uropathologists, which improved the accuracy of the information on histologic RCC subtypes. However, our study also was subject to some limitations. First, information on anthropometry and exposure status was self-reported by the participants at one single time point. Consequentially, there may have been measurement error due to self-report. Moreover, changes in exposure status during follow-up were not recorded. Second, we had a limited number of cases with a tumor histology other than ccRCC. As a result, we were unable to assess the etiologic heterogeneity in more detail for exposures (eg, antihypertensive medication subtypes), histologic subtypes (eg, chromophobe RCC) and to further categorize the pRCC subtypes (eg, type 1 and type 2 pRCC). In particular, the inability to further stratify pRCC may have influenced results as these were classified as pRCC overall, while type 1 and type 2 pRCC subtypes are known to possess molecular and clinicopathologically distinct characteristics.^{2,44} It may be possible that type 1 and type 2 pRCC are distinctly associated to the risk factors included in our

analyses. Lastly, due to the low number of pRCC cases, we were not able to obtain reliable estimates in all heterogeneity tests.

In conclusion, the results of our study are suggestive of the presence of an etiologic heterogeneity regarding RCC subtypes. In particular, we observed that the association between BMI and ccRCC and pRCC differs. These results highlight the need for more detailed subtype-specific analyses when investigating risk factors for RCC. Evidence from studies on specific tumor histologies may help uncover mechanisms that play a role in the process of tumorigenesis for RCC by uncovering etiologic similarities and differences between tumor subtypes.

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CONFLICT OF INTEREST

The authors declare no potential conflict of interests.

ETHICAL APPROVAL AND CONSENT TO PARTICIPATE

The institutional review boards of the Netherlands Organization for Applied Scientific Research TNO (Zeist) and Maastricht University (Maastricht) approved the NLCS. The NLCS was conducted in accordance with the Declaration of Helsinki. By completing and returning the baseline questionnaire, participants agreed to participate in the NLCS.

DATA AVAILABILITY STATEMENT

The datasets generated and/or analyzed during the current study are not publicly available because the informed consent does not allow for that. However, anonymous data that are minimally required to replicate the outcomes of the study will be made available upon reasonable request and approval by the institutional review boards.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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