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Long-term dietary sodium, potassium and fluid intake; exploring potential novel risk factors for renal cell cancer in the Netherlands Cohort Study on diet and cancer

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Background: As sodium, potassium and fluid intake are related to hypertension, an established risk factor for renal cell cancer (RCC), they may be independent risk factors for RCC.

Methods: The Netherlands Cohort Study (NLCS) with case-cohort design included 120 852 participants aged 55–69 years. At baseline, diet and lifestyle were assessed with questionnaires. After 17.3 years of follow-up, 485 RCC cases and 4438 subcohort members were available for analyses.

Results: Sodium intake increased RCC risk (P-trend = 0.03), whereas fluid and potassium intake did not. For high sodium and low fluid intake, the RCC risk additionally increased (P-interaction = 0.02).

Conclusion: Sodium intake is a potential risk factor for RCC, particularly if fluid consumption is low.

The suggested risk factor pattern for renal cell cancer (RCC), including an increased risk with hypertension, smoking and obesity and a decreased risk with moderate alcohol consumption (Chow *et al*, 2010) also determines cardiovascular disease risk. In addition, evidence clearly suggests that high sodium intake may cause a rise in blood pressure, the development of hypertension (De Wardener and Macgregor, 2002) and affects renal function (Macgregor, 1997; De Wardener *et al*, 2004; Susic and Frohlich, 2012). Furthermore, prolonged sodium excess may contribute directly to kidney damage (Kotchen *et al*, 2013). Therefore, high sodium intake may be a risk factor for RCC, potentially through hypertension.

The effect of sodium on blood pressure may, however, be modified by potassium intake or fluid intake, given their influence on blood pressure regulation and sodium homeostasis, which are both key functions of the kidney (Whelton *et al*, 1997; Rose and Post, 2001). That considered, potassium intake and fluid intake may individually influence RCC risk, or modify potential effects of sodium intake on RCC risk. Until now, only few studies investigated the potential association between RCC risk and sodium intake, potassium intake (Mellemgaard *et al*, 1996) or fluid intake (Lee *et al*, 2006; Hu *et al*, 2009; Allen *et al*, 2011). In these studies, no attention has been given to their joint effects on renal function or on the potential influence of hypertension. In this study, we investigate whether sodium, potassium and fluid intake and their potential interactions are associated with RCC risk in a prospective study.

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MATERIALS AND METHODS

The present study is conducted within the Netherlands Cohort Study (NLCS), a prospective cohort study including 120 852 participants aged 55–69 years at baseline (Van Den Brandt *et al*, 1990). The case-cohort design was used for efficiency in questionnaire processing and follow-up (Prentice, 1986). All cohort members were followed up for cancer occurrence, whereas the subcohort was followed up for vital status to estimate person years at risk for the entire cohort. All participants completed a baseline questionnaire on dietary habits and lifestyle. Details on the dietary assessment in the NLCS are available online (Supplementary Information). In brief, a 150-item, food frequency questionnaire (FFQ) represented the dietary part of the questionnaire (Goldbohm *et al*, 1994, 1995). Intakes of sodium, potassium and fluid were calculated using the computerised Dutch food composition table (Nevo tabel, 1986). Sodium and potassium intake were adjusted for total energy intake using the residual method (Willett and Stampfer, 1986). Sodium intake did not include sodium from added salt, yet the baseline questionnaire included specific questions on salt added during home-preparation or before consumption (Van Den Brandt *et al*, 2003), from which discretionary salt intake was calculated (Supplementary Information). In addition, information on salt preference was available (Supplementary Information).

After 17.3 years of follow-up, 485 histological confirmed, epithelial RCC cases and 4438 subcohort members with complete dietary information were included in Cox proportional hazards analyses adjusted for the case-cohort design (Barlow, 1994). Associations between sodium, potassium and fluid intake and RCC risk were analysed in the total population, by hypertension status and when participants with a low-salt diet were excluded, as these subpopulations may differ in dietary behaviours, so influencing the associations under study. Confounders were selected *a priori* and included age, energy intake and RCC risk factors (i.e. sex, BMI, hypertension, smoking, alcohol consumption). Robustness of data was investigated by excluding the first two years of follow-up and by reanalysing data separately for the first and second half of follow-up. Interactions with sodium and discretionary salt intake were investigated for potassium and fluid intake and for RCC risk factors. A P-value < 0.05 was considered significant. Data were analysed with STATA (version 12).

RESULTS

Energy-adjusted sodium intake was lower in subcohort members than in RCC cases (Table 1). Discretionary salt intake, perceived

Table 1. Characteristics of renal cell cancer cases, subcohort members, and per quintile of sodium intake in the subcohort, NLCS 1986–2003

			Quintiles of sodium intake[a,b,c]					
Baseline characteristics (Mean ± s.d.)	**Cases**	**Subcohort**	**1 (low)**	**2**	**3**	**4**	**5 (high)**	***P*-value[d]**
Total (*N*)	485	4438	889	887	888	887	887	
Exposures (in g per day)								
Sodium intake[c]	2.5 ± 0.7	2.3 ± 0.6	1.6 ± 0.3	2.0 ± 0.2	2.3 ± 0.3	2.6 ± 0.3	3.2 ± 0.5	—
Discretionary salt intake[e,f]	2.9 ± 3.1	2.8 ± 2.7	3.0 ± 2.9	2.7 ± 2.7	2.8 ± 2.6	2.8 ± 2.8	2.7 ± 2.7	0.27
Perceived saltiness (%)[f,g]								
Not salty enough	1.3	1.9	2.7	1.4	1.7	1.8	2.1	
Good	38.4	41.9	41.5	40.8	41.3	43.3	42.7	
A little too salty	42.5	41.2	42.0	42.2	42.3	40.0	39.8	
Much too salty	17.9	14.9	13.9	15.7	14.8	15.0	15.4	0.86
Fluid intake (ml per day)	2081 ± 463	2081 ± 486	2055 ± 467	2025 ± 439	2050 ± 512	2068 ± 459	2206 ± 528	<0.001
Potassium intake (mg per day)[c]	3519 ± 569	3524 ± 572	3406 ± 551	3494 ± 516	3529 ± 561	3580 ± 565	3611 ± 637	<0.001
Potential confounders								
Age (years)	61.4 ± 3.9	61.4 ± 4.2	61.6 ± 4.4	61.6 ± 4.3	61.3 ± 4.3	61.2 ± 4.1	61.2 ± 4.1	0.10
Male sex (%)	64.5	49.4	—[b]	—[b]	—[b]	—[b]	—[b]	—[b]
Total energy intake (kcal per day)	1971 ± 490	1923 ± 516	—[c]	—[c]	—[c]	—[c]	—[c]	—[c]
Alcohol consumption (g ethanol per day)[h]	14.8 ± 14.8	13.6 ± 15.1	18.9 ± 19.2	13.1 ± 13.8	12.5 ± 14.7	11.3 ± 11.6	11.9 ± 13.5	<0.001
BMI (kg m^{-2})[f]	25.5 ± 3.0	25.0 ± 3.1	24.6 ± 3.1	24.7 ± 3.0	25.2 ± 3.1	25.2 ± 3.1	25.4 ± 3.3	<0.001
Cigarette smoking[f]								
Status: current (%)	32.4	28.3	33.6	28.1	27.0	24.9	27.7	0.001
Duration in current smokers (years)	39.8 ± 9.1	38.6 ± 9.9	39.0 ± 10.4	38.6 ± 9.4	38.7 ± 9.7	38.8 ± 9.4	38.0 ± 10.2	0.68
Intensity in current smokers (cigarettes per day)	16.0 ± 8.5	15.0 ± 8.7	16.5 ± 9.6	14.1 ± 8.7	14.8 ± 8.6	15.2 ± 8.3	14.4 ± 7.9	0.02
Prescribed low-salt diet—yes (%)	8.0	7.5	7.2	8.7	7.8	5.5	8.1	0.11
Hypertension—yes (%)	36.1	32.0	26.3	36.5	31.4	33.7	31.8	<0.001

Abbreviations: BMI = body mass index; s.d. = standard deviation.
[a]Quintile boundaries are based on subcohort members.
[b]Quintile boundaries are specific for sex.
[c]Intakes are energy-adjusted.
[d]*P*-value for difference tested with Kruskal–Wallis test (continuous) or Chi-square test (categorical).
[e]Salt intake refers to sodium chloride intake.
[f]*N* does not correspond with the overall *N*, due to missing values.
[g]Saltiness of soups and restaurant food.
[h]In consumers only.

saltiness, potassium intake and fluid intake were similar among RCC cases, subcohort members and quintiles of sodium intake.

Sodium intake was associated with an increased RCC risk (Table 2). In multivariable-adjusted analyses, we observed a significantly increasing trend across quintiles (P-trend = 0.03) to a maximum in the highest quintile (HR(95% CI): 1.40(0.99–1.97)) and a significant increase in RCC risk per increment of 1 g per day (HR(95% CI): 1.07(1.00–1.15)). For discretionary salt intake, the RCC risk was u-shaped, with a significantly increased HR for non-users and a non-significantly increased HR for users in quartile 4 (*vs* 1) (HR(95% CI): 2.36(1.56–3.56) and 1.16(0.85–1.58), respectively). Only after excluding non-users, there was a significant increase in RCC risk per increment of 1 g per day (HR(95% CI): 1.04(1.00–1.08)). Furthermore, participants who indicated soups and restaurant food as being 'much too salty' (*vs* 'good') had the highest RCC risk (HR(95% CI): 1.70(1.24–2.33)). Fluid and potassium intake were not associated with RCC risk.

Table 2. Renal cell cancer risk according to indicators of sodium intake, fluid intake and potassium intake, NLCS 1986–2003

			Age- and sex-adjusted model[a]		Multivariable-adjusted model[b]	
Exposures in g per day (median in subcohort (men/women))	**Cases**	**Person years**	**HR**	**95% CI**	**HR**	**95% CI**
Sodium intake						
Quintile 1 (1.9/1.5)	70	11 842	1.00	(ref)	1.00	(ref)
Quintile 2 (2.2/1.8)	76	11 803	1.10	(0.78–1.55)	1.07	(0.75–1.52)
Quintile 3 (2.5/2.0)	81	11 833	1.17	(0.83–1.63)	1.11	(0.78–1.57)
Quintile 4 (2.8/2.3)	89	11 553	1.35	(0.97–1.88)	1.28	(0.91–1.79)
Quintile 5 (3.4/2.8)	93	11 370	1.41	(1.01–1.95)	1.40	(0.99–1.97)
P for trend				0.02		0.03
Increment per 1 g per day			1.07	(1.00–1.14)	1.07	(1.00–1.15)
Discretionary salt intake[c]						
No salt	45	3033	2.51	(1.69–3.74)	2.36	(1.56–3.56)
Quartile 1 (0.7/0.7)	91	14 392	1.00	(ref)	1.00	(ref)
Quartile 2 (2.0/1.7)	79	13 981	0.89	(0.65–1.23)	0.92	(0.66–1.26)
Quartile 3 (3.4/2.9)	100	13 985	1.12	(0.83–1.51)	1.14	(0.84–1.55)
Quartile 4 (5.5./5.1)	94	13 009	1.16	(0.85–1.57)	1.16	(0.85–1.58)
P for trend				0.27		0.39
Increment per 1 g per day			1.01	(0.97–1.06)	1.02	(0.98–1.06)
Perceived saltiness[d]						
Not salty enough	4	1084	0.52	(0.19–1.45)	0.48	(0.17–1.35)
Good	148	22 589	1.00	(ref)	1.00	(ref)
A little too salty	167	23 599	1.14	(0.90–1.44)	1.17	(0.92–1.48)
Much too salty	77	8101	1.62	(1.20–2.18)	1.70	(1.24–2.33)
P for trend				0.001		0.001
Fluid intake (l per day)						
Quintile 1 (1.6/1.5)	83	11 084	1.00	(ref)	1.00	(ref)
Quintile 2 (1.9/1.8)	76	11 599	0.88	(0.63–1.22)	0.88	(0.62–1.24)
Quintile 3 (2.1/2.0)	90	12 066	1.00	(0.73–1.37)	1.01	(0.72–1.42)
Quintile 4 (2.4/2.2)	89	11 686	1.02	(0.75–1.41)	1.01	(0.69–1.47)
Quintile 5 (2.8/2.6)	71	11 966	0.81	(0.58–1.14)	0.78	(0.49–1.23)
P for trend				0.49		0.62
Increment per 1 l per day			0.89	(0.72–1.10)	0.83	(0.60–1.16)
Potassium intake						
Quintile 1 (2.8/2.9)	71	11 228	1.00	(ref)	1.00	(ref)
Quintile 2 (3.1/3.2)	83	11 582	1.15	(0.82–1.60)	1.16	(0.83–1.62)
Quintile 3 (3.4/3.6)	91	12 195	1.20	(0.87–1.67)	1.21	(0.85–1.71)
Quintile 4 (3.7/3.8)	74	11 680	1.01	(0.72–1.42)	1.04	(0.72–1.50)
Quintile 5 (4.2/4.3)	90	11 716	1.24	(0.89–1.72)	1.28	(0.87–1.90)
P for trend				0.42		0.41
Increment per 1 g per day			1.06	(0.89–1.27)	1.10	(0.87–1.39)

[a]HR adjusted for age (years) and sex (male/female).
[b]HR adjusted for age (years), sex (male/female), energy intake (kcal per day), alcohol consumption (g ethanol per day), BMI (kg m^{-2}), smoking [status (non-current/current), duration (years) and intensity (cigarettes per day)] and, if applicable, for sodium intake (g per day), discretionary salt intake (g per day), fluid intake (l per day), potassium intake (g per day) and hypertension (yes/no).
[c]Salt intake refers to sodium chloride intake.
[d]Saltiness of soups and restaurant food.

We observed no difference between multivariable-adjusted models with and without hypertension as confounder, indicating that mediation was not present (data not shown). In addition, no significant interactions between hypertension and any of the exposures under study regarding RCC risk were observed (Supplementary Table). In participants without hypertension, the RCC risk for discretionary salt intake ('no' *vs* quartile 1) was no longer significant (HR(95% CI): 1.74(0.84–3.63)). Excluding the first two years of follow-up or excluding participants with a low-salt diet did not change results (data not shown). However, the association between sodium intake and RCC risk clearly attenuated over time. We observed a higher HR for quintile 5 (*vs* 1) of sodium intake during the first nine years of follow-up and a lower HR during the second nine years of follow-up (HR(95% CI): 1.71(1.08–2.71) and 1.12(0.69–1.82), respectively).

There was a significant interaction between sodium and fluid intake, but not between sodium and potassium intake regarding RCC risk (*P*-interaction = 0.02 and 0.73, respectively; Table 3). Participants with high sodium and low fluid intake compared to those with low sodium and low fluid intake had a higher RCC risk (HR(95% CI): 1.91(1.10–3.32)). Other interactions between sodium or discretionary salt intake and RCC risk factors were not significant (data not shown).

DISCUSSION

To our knowledge, this is the first prospective study to investigate sodium, potassium and fluid intake and their interactions as potential risk factors for RCC. For sodium intake, the association with RCC risk has been reported in a case-control study, showing a decreased risk for higher sodium intake in men, but not in women (Mellemgaard *et al*, 1996). In the present study, we observed an increased RCC risk for higher sodium intake and no interaction between sex and sodium intake for RCC risk. In addition, we found no indications for mediation or effect-modification by hypertension, suggesting that sodium intake may be associated with RCC risk independently of hypertension. Fluid intake was not associated with RCC risk, which is in line with previous prospective cohort studies (Lee *et al*, 2006; Allen *et al*, 2011), but not with a case-control study showing an increased RCC risk for higher fluid intake (Hu *et al*, 2009). All studies, however, ignored potential confounding by or effect-modification through sodium intake. Yet, we observed an interaction between sodium and fluid intake for RCC risk, which supports our hypothesis that the balance between sodium and fluid intake is important in RCC aetiology. Potassium intake was not associated with RCC risk, which is similar to previous research (Mellemgaard *et al*, 1996).

We recognise that salt (sodium chloride) intake is a difficult concept to measure accurately, particularly with questionnaires. However, our baseline questionnaire was specifically designed to study salt intake as it additionally included specific questions on discretionary salt intake. Although the FFQ was able to rank individuals adequately according to sodium intake when compared to nine-day dietary records (Goldbohm *et al*, 1994; Van Den Brandt *et al*, 2003), information on the validity of discretionary salt intake was not available. Nevertheless, the mean salt intake (sodium from ready-to-eat foods plus discretionary salt) in our population (8.7 g per day) is comparable to that of the Dutch population in 1986 (Nederlandse Voedingsraad, 1986).

Exposures were only assessed at baseline. Although nutrient intakes were rather stable during the first five years follow-up (Goldbohm *et al*, 1995), they may have changed during later follow-up, possibly explaining the attenuation in risk estimate over time.

Compared to sodium intake, which is calculated using standardised measurement units of the FFQ, the inter-individual range of discretionary salt intake is very large (up to factor 10). To capture all variability, it might be desirable to combine both indicators of sodium intake into one overall intake variable. However, discretionary salt intake is highly influenced by habits, attitudes and beliefs (Shepherd and Farleigh, 1986). In fact, those who wish to reduce salt intake may particularly reduce discretionary salt intake. The observed u-shape in RCC risk for discretionary salt intake may perhaps reflect one's ability to reduce discretionary salt intake to prevent or control hypertension. Indeed, participants with hypertension were overrepresented in the lowest category of discretionary salt intake (data not shown). Therefore, an overall intake variable was less informative than both

Table 3. Renal cell cancer risk for sodium intake by fluid intake and potassium intake, NLCS 1986–2003

	Tertile of sodium intake[a,b]									
	1 (low)			2			3 (high)			
Exposures	**Cases/py**	**HR[c]**	**95% CI**	**Cases/py**	**HR[c]**	**95% CI**	**Cases/py**	**HR[d]**	**95% CI**	***P*-value[d]**
Fluid intake										
Low[e]	22/4902	0.78	(0.43–1.43)	33/5106	1.03	(0.60–1.76)	42/3653	1.91	(1.10–3.32)	
Moderate[e]	57/8994	1.00	(0.63–1.56)	56/9042	0.96	(0.60–1.54)	64/7872	1.31	(0.83–2.06)	
High[e]	39/5803	1.00	(ref)	48/5463	1.28	(0.81–2.02)	48/7567	0.93	(0.59–1.46)	0.02
Potassium intake[b]										
Tertile 1 (low)	42/7421	1.03	(0.62–1.70)	43/6232	1.23	(0.74–2.03)	38/5164	1.35	(0.81–2.24)	
Tertile 2	47/6659	1.32	(0.81–2.15)	47/6718	1.27	(0.78–2.07)	52/6621	1.47	(0.92–2.37)	
Tertile 3 (high)	29/5619	1.00	(ref)	47/6661	1.32	(0.80–2.17)	64/7306	1.72	(1.07–2.77)	0.73

Abbreviation: py = person years.
[a]Tertile boundaries are based on subcohort members and are specific for sex.
[b]Intakes are energy-adjusted.
[c]HR adjusted for age (years), sex (male/female), energy intake (kcal per day), discretionary salt intake (g per day), alcohol consumption (g ethanol per day), BMI ($kg\,m^{-2}$), smoking (status (non-current/current), duration (years) and intensity (cigarettes per day)), hypertension (yes/no) and, if applicable, for fluid intake (ml per day) or potassium intake (mg per day).
[d]*P*-value for interaction tested with Wald χ^2 test.
[e]Categories low, moderate and high fluid intake correspond to, respectively, ≤1750; 1750–2250 and >2250 ml per day.

individual indicators of sodium intake separately, as HRs for this overall variable fully reflected the arbitrary combination of a linear and u-shaped trend (data not shown).

We used high-perceived saltiness as an indicator of low-salt preference. Salt preference may indicate actual sodium intake, although no consensus has been reached (Mattes, 1997). Indeed, we observed an inverse relation with perceived saltiness for discretionary salt intake ($P<0.001$), but not for sodium intake ($P=0.86$). The association between high-perceived saltiness and RCC risk was, however, in opposite direction as expected, as previously observed for stomach cancer (Van Den Brandt *et al*, 2003). Perhaps, this association may be explained by the hedonic shift, in which the taste of reduced-sodium products becomes more acceptable over time (Mattes, 1997).

The mechanism through which sodium intake may influence RCC risk is unknown. Perhaps, high renal sodium load constitutes to RCC carcinogenesis through inflammation, as sodium is suggested to have inflammatory properties, which can have tumour-promoting consequences (Fiore *et al*, 2011; Hanahan and Weinberg, 2011).

In conclusion, sodium intake is a potential risk factor for RCC, particularly if fluid consumption is low, but potassium and fluid intake are not associated with RCC risk. However, these findings await confirmation in other prospective studies and for specific RCC subtypes. Special attention should be given to the role of hypertension and other related diseases, such as end-stage renal disease, in the association between sodium intake and RCC risk.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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