World Cancer Research Journal WCRJ 2021; 8: e2096

DIETARY ACID LOAD AND RISK OF KIDNEY CANCER: AN EPIDEMIOLOGIC CASE-CONTROL STUDY

A. L. RONCO[1-3], M. A. STORZ[4], W. MARTÍNEZ-LÓPEZ[5,6], J. M. CALDERÓN[3], W. GOLOMAR[7]

[1]Unit of Oncology and Radiotherapy, Pereira Rossell Women's Hospital, Montevideo, Uruguay
[2]School of Medicine, CLAEH University, Prado and Salt Lake, Maldonado, Uruguay
[3]Biomedical Sciences Center, University of Montevideo, Puntas de Santiago, Montevideo, Uruguay
[4]Center for Complementary Medicine, Department of Internal Medicine II – Faculty of Medicine, University of Freiburg, Freiburg, Germany
[5]Genetics Department and Biodosimetry Service, Instituto de Investigaciones Biológicas Clemente Estable, Montevideo, Uruguay
[6]Academic Unit on Radiation Protection, Faculty of Medicine, University of the Republic, Montevideo, Uruguay
[7]Department of Medical Oncology, National Cancer Institute, Montevideo, Uruguay

Abstract – *Objective:* *Recent research studies linked the intake of processed meat and fatty foods to an increased risk of renal cell carcinoma. Fruits and vegetables, on the other hand, may convey protective effects. Dietary acid load (DAL) has been proposed as a potential risk factor for various cancer types within the last years. The present study sought to explore potential associations between this novel risk factor and renal cancer.*

Patients and Methods: *A case-control study was performed in 114 cases and 864 age-frequency matched controls (978 patients) through a multi-topic inquiry, including a food frequency questionnaire. DAL was calculated based on two commonly used formulas: Potential Renal Acid Load (PRAL) score and Net Endogenous Acid Production (NEAP) score. Odds ratios (OR) and their 95% confidence intervals were estimated by logistic regression, adjusted for potential confounders.*

Results: *We found no significant statistical associations between DAL and kidney cancer risk. The OR for the highest tertiles of scores were: PRAL (=0.91), NEAP (=1.59), and NEAPr (=0.87). All observed trends were non-significant.*

Conclusions: *Although previous studies showed direct, significant associations between a high DAL and risk of certain cancers, we were unable to observe such an association in the present study. Our results indicate that other dietary components that are not related to alkalizing/acidifying properties might explain the interactions between nutrition and kidney cancer. Since to our knowledge, our study is the first epidemiologic report on DAL and renal cancer risk, and further research is warranted to confirm the present findings.*

KEYWORDS: *Diet, Dietary acid load, Renal cancer, Kidney cancer, Epidemiology, NEAP, PRAL, Nutrition.*

INTRODUCTION

Renal cancer (RC) is a frequently occurring malignancy with approximately 431,000 new cases diagnosed globally in 2020[1]. RC incidence rates have gradually increased over the past decades and are currently two-fold higher in men than in woman[2]. The list of established RC risk factors includes excess body weight, tobacco smoking and a past medical history of chronic kidney disease and hypertension[3,4]. Several studies

Corresponding Author: Alvaro L. Ronco, MD; e-mail: alv.ronco58@gmail.com

also associated certain analgesics and occupational exposure to solvents with an increased risk of RCC; however, data for these associations is limited[2,5].

More recent investigations discussed an unhealthy lifestyle as a possibly contributing risk factor for RC[6]. The consumption of processed meats and high-fat foods has been linked to increase development of renal cell carcinoma[6], whereas fruits and vegetables may protect from it[7,8].

Another potential risk factor for RC has still received brief attention: an increased Dietary Acid Load (DAL). DAL is determined by the balance of base-inducing foods (including vegetables, fruits and legumes) and acid-inducing foods, such as meat, dairy and eggs[9]. A high DAL burden contributes to metabolic acidosis, which, in turn, promotes inflammation, tissue damage, and, potentially, cancer development[10].

Several large-scale epidemiological studies found an association between a high DAL and an increased risk for various cancers, including colorectal[11], lung[12], pancreas [13] and breast cancer[14,15]. By the same token, a high DAL has also been associated with several established RC risk factors, including hypertension[16] and chronic kidney diseases[17,18]. In light of these findings, it is conceivable that a high DAL could also contribute to RC. We, therefore, examined this association in a case-control study in Uruguay - a country that is known for its high consumption of animal-based foods[19,20].

MATERIAL AND METHODS

Selection of cases

We described the methods of our study in detail elsewhere [11]. In brief, we performed a case-control study examining environmental factors and cancer risk in the capital of Uruguay: Montevideo. All newly diagnosed RC cases that were registered in the 4 major hospitals of Montevideo between 1996 and 2004, were considered eligible for this study. We identified 114 cases. Six hundred eighty-four (684) individuals that were hospitalized for non-neoplastic diseases during the same time period and in the same hospitals were considered eligible controls.

These individuals were hospitalized for health conditions unrelated to tobacco smoking or alcohol consumption. Individuals who recently modified their diet were considered ineligible. Controls presented with the following health-related problems: blood disorders (n=40, 4.3%) bone diseases (n=45, 4.9%), hydatid cyst (n=47, 5.1%), varicose veins (n=51, 5.5%), appendicitis (n=62, 6.6%), injuries and trauma (n=66, 7.1%), skin disorders (n= 88, 9.5%), abdominal hernia (n=232 patients, 25.0%), eye disorders (n=254, 27.3%), and other medical disorders (n=44, 4.7%).

Trained social workers that were blinded with regard to the research goals undertook routine screenings with the aim of identifying patients who were recently diagnosed with RC. In parallel, potentially eligible controls were also contacted by the same interviewing staff. We did not accept proxy interviews and interviewed all participants face-to-face.

Questionnaire

We used a questionnaire that contained both anthropometric and socio-demographic variables, a detailed history of substance usage (covering alcohol and tobacco), occupational exposure and, finally, cancer history in 1st-2nd degree relatives. A 64-item food frequency questionnaire (FFQ) that was representative of the Uruguayan diet was also included. We tested the FFQ for reproducibility with good results [21]. All diet-related questions were open-ended. We used local tables of food composition to estimate nutrient and total energy intake.

Dietary Acid Load Estimation

We used three established formulas to estimate DAL, derived from the original studies by Remer et al [22] and Frasetto et al [23]. In a first step, we calculated potential renal acid load (PRAL) of diet:

$$PRAL\ (mEq/day) = (0.49 \times total\ protein\ [g/day]) + (0.037 \times phosphorus[mg/day]) - (0.021 \times potassium[mg/day]) - (0.026 \times magnesium[mg/day]) - (0.013 \times calcium[mg/day])$$

This formula includes intestinal absorption rates for protein, potassium, phosphate, magnesium, and calcium. More than two decades ago, Remer et al[22] validated PRAL scores *vs.* urinary pH in healthy individuals with good results. In a second step, we calculated net endogenous acid production (NEAP) as follows:

$$NEAP\ (mEq/day) = (54.5 \times protein[g/day]) / (0.0256 \times potassium[mg/day]) - 10.2$$

This score considers sulfuric acid production from protein metabolism and the rate of bicarbonate production subsequent to the metabolization of intestinally absorbed potassium salts of organic acids[23]. Both scores were strongly correlated (r=0.84, $p<0.001$) in previous studies. Negative scores (NEAP/PRAL) indicate an alkaline-forming potential, whereas positive scores indicate an acid-form-

ing potential. Both scores were used previously to examine potential associations between DAL and cancer risk[11,12,14,24].

Finally, we included a third DAL score that was also developed by Remer et al[25]: NEAPR. The formula by Remer et al[25] estimates net endogenous acid production based on a combination of the aforementioned PRAL-score and an anthropometry-based estimate for organic acid excretion (OAest):

$$\textit{Estimated NEAPR (mEq/d)} = \textit{PRAL (mEq/d)} + \textit{OAest (mEq/d)}$$

The calculation of OAest was done as follows: Individual body surface area x 41/1.73.

We estimated individual body surface area with a commonly used formula that has been developed by Du Bois and Du Bois[26], which appears to be applicable to a wide range of patients[27]:

$$\textit{Body surface area } (m^2) = [0.007184 \times \textit{height}(cm)^{0.725} \times \textit{weight}(kg)^{0.425}].$$

Statistical Analysis

In statistical analyses, the questionnaire variables were usually treated as continuous variables. Categorization was done for analysis purposes. Together with basic descriptive analyses (frequencies, mean values, chi-square tests), we calculated Odds Ratios (ORs) and 95% confidence intervals (95% CI) by unconditional logistic regression[28]. Terms for potential confounders were included in the multivariate analyses. The equations included age, residence, education, body mass index, family history of cancer, smoking intensity, alcohol status, "mate" intensity, heme iron intake, energy intake, fiber intake, and a series of dietary antioxidants. No participants were excluded as outliers for any dietary component. Heterogeneities in the stratified analyses were explored through likelihood-ratio tests. The analyses were done using STATA software (Release 10, Stata Corp LP, College Station, TX, 2007) and the 3-D graphics were built with STATISTICA software (Release 10, StatSoft Inc., 2011, Tulsa, OK, USA), using the distance weighted least squares option.

RESULTS

Table 1 displays the distribution of both controls and cases based on selective variables. Significant differences appear only in a few items: family history of cancer (p=0.02), total energy intake (p=0.003), and alcohol status (p=0.02). Whereas the cancer history is more frequent among cases, a higher energy intake and the current alcohol status are more frequent among controls.

Table 2 shows the mean daily values of the acid load scores and their components. We categorized protein and micronutrients according to their animal/plant original source. The comparison between cases and controls shows that controls had higher intakes of all studied dietary components, regardless of their animal or plant source.

Table 3 shows the crude and adjusted ORs of renal cancer for acid load scores (PRAL and the two NEAP scores). The estimates for the highest tertile of DAL scores were 0.91, 1.59 and 0.87, for PRAL, NEAP and NEAPR, respectively.

Figure 1 shows two 3-D graphics, analyzing the interrelationships of three key variables of our regression model: the dietary energy (X axis), the body mass index (Y axis), and the PRAL score (Z axis). Each graphic corresponds to the patient status: controls (left) and cases (right). In the control group, the lowest PRAL scores appear on the left side (corresponding to a low energy intake and slightly increase with lower BMI), whereas the highest PRAL scores are shown on the right side. On the other hand, cases display higher scores and these appear concentrated not at the highest energy intake, but closer to the midscale. Surprisingly, cases show a very low PRAL score among high energy consumers, at the very right side of the graph, notably lower among low BMI bearers (close to the front side of the graph).

DISCUSSION

This study sought to explore whether a high dietary acid load was associated with an increased risk of renal cancer in a Uruguayan population. Our findings suggest that higher DAL scores (both NEAP and PRAL) may not increase the risk of RC. To the best of our knowledge, this is the first epidemiological investigation that investigated potential associations between both variables risk. The lack of a potential association, however, comes rather unexpected (particularly with regard to RC risk factors) and warrants further discussion.

The current Western dietary pattern is characterized by a large proportion of processed foods, animal products and excessive sodium[29,30]. At the same time, this dietary pattern is also deficient in fresh fruits, vegetables and legumes[31]. This substantial shortage of plant foods may not compensate for the excessive DAL induced by (processed) meats, cheese, eggs and certain dairy products[29]. The consequence of this disequilibrium is an increase in DAL that has been associated with a series of health problems. In the present study, mean DAL scores

TABLE 1. General features of the studied population.

Variables	Categories	Controls % (n=684)		Cases % (n=114)		Global p-value
Age groups	≤ 39	30	4.4	6	5.3	
	40-49	102	14.9	12	10.5	
	50-59	162	23.7	32	28.1	
	60-69	260	38.0	38	33.3	
	70-79	110	16.1	22	19.3	
	80-89	20	2.9	4	3.5	0.62
Sex	Men	448	65.5	77	67.5	
	Women	236	34.5	37	32.5	0.67
Education years	≤ 5	360	52.6	70	61.4	
	≥ 6	324	47.4	44	32.6	0.08
Residence regions	Montevideo	409	59.8	63	55.3	
	Other counties	275	40.2	51	44.7	0.36
Body Mass Index (kg/m²)	≤ 24.99	306	44.7	45	39.5	
	25.0-29.99	283	41.4	46	40.3	
	≥ 30.0	95	13.9	23	20.2	0.20
FHC in 1st-2nd degree	No	500	73.1	71	62.3	
	Yes	184	26.9	43	37.7	0.02
Tea status	Never	615	89.9	100	87.7	
	Ever drinker	69	10.1	14	12.3	0.48
"Mate" status	Never	100	14.6	8	7.0	
	Ever drinker	584	85.4	106	93.0	0.03
Coffee status	Never	606	88.6	95	83.3	
	Ever drinker	78	11.4	19	16.7	0.11
Red meat intake (serv/year)	≤ 286	221	32.3	48	42.1	
	287-416	244	35.7	36	35.6	
	≥ 417	219	32.0	30	26.3	0.12
Dietary energy (kcal/day)	≤ 1943	213	31.1	54	47.4	
	1944-2450	232	33.9	28	24.6	
	≥ 2451	239	34.9	32	28.1	0.003
Smoking status	Never	245	35.8	34	29.8	
	Ex-smoker	125	18.3	21	18.4	
	Current	314	45.9	59	51.8	0.42
Alcohol status	Never	344	50.3	66	57.9	
	Ex drinker	56	8.2	15	13.2	
	Current	284	41.5	33	28.9	0.02

are exclusively positive in both cases and controls, indicating an acidifying dietary style in both groups (Table 2). Furthermore, the control subgroup had higher mean intakes of all essential DAL contributors, both the acidifying (proteins and phosphorus) as well as the alkalizing ones (magnesium, potassium, and calcium). Hypothetically, this fact might reflect a neutralization of potentially harmful actions of the former group of substances by the latter; however, it requires further research. Lemann et al[32] estimated that an average Western (American) diet generates an acid load of approximately 50 mEq/d. Mean values in our study (see NEAP scores, Table 2) are comparable, indirectly suggesting a lower intake of fruits and vegetables and a higher intake of animal products and dairy. Various epidemiological studies associated this particular dietary pattern with an increased risk for RC[33-35]. A 2014 Japanese study identified beef intake and a fondness for fatty foods as potential risk factors for an increased RC risk[35]. The only preventive factor identified by the authors was the consumption of starchy roots (including sweet potato and potato).

Other studies also emphasized that a diet high in fiber, fruits and vegetables may protect from renal cancer[7,36]. Fruits and vegetables are abundant in polyphenols and antioxidants, which exhibit anticancer effects and were shown to be effective

TABLE 2. Mean daily values ± standard deviation of the acid load scores and their components. Stratification of items according to their animal/plant original source. Comparison between cases and controls.

Variable	*Units*	*CONTROLS Mean ± SD*	*CASES Mean ± SD*	*Diff.(p)*
Total Proteins	g/d	55.5 ± 17.6	50.3 ± 19.7	0.004
Animal proteins	g/d	50.6 ± 16.8	45.9 ± 18.9	0.007
Plant proteins	g/d	4.8 ± 2.2	4.4 ± 2.0	0.04
Total Phosphorus	mg/d	813.8 ± 240.8	720.8 ± 264.9	0.0002
Animal phosphorus	mg/d	494.2 ± 163.8	439.9 ± 184.1	0.001
Plant phosphorus	mg/d	319.6 ± 135.6	280.9 ± 133.1	0.005
Total Potassium	mg/d	1950.2 ± 613.4	1776.6 ± 673.7	0.006
Animal potassium	mg/d	690.7 ± 243.7	622.4 ± 263.8	0.006
Plant potassium	mg/d	1259.5 ± 505.0	1154.2 ± 523.8	0.04
Total Magnesium	mg/d	183.6 ± 61.5	164.0 ± 61.4	0.002
Animal magnesium	mg/d	54.3 ± 18.2	49.1 ± 20.5	0.005
Plant magnesium	mg/d	129.2 ± 53.9	114.9 ± 50.5	0.008
Total Calcium	mg/d	581.3 ± 216.5	546.0 ± 231.8	0.11
Animal calcium	mg/d	335.0 ± 180.2	326.1 ± 182.3	0.63
Plant calcium	mg/d	246.3 ± 99.5	220.0 ± 96.6	0.009
PRAL score	mEq/d	4.00 ± 10.23	2.64 ± 10.17	0.19
NEAP score	mEq/d	52.30 ± 17.34	51.58 ± 16.67	0.68
NEAPr score	mEq/d	46.55 ± 11.11	46.08 ± 11.17	0.68

Abbreviations: g=grams; mg=milligrams; mEq=milliequivalents.

against multiple targets in cancer development and progression[37,38]. In particular, a high intake of vitamin C may reduce the risk of RC[39], although some studies could not confirm this association[40]. In contrast, certain animal-derived foods may increase the risk for RC. Significantly positive associations were found for certain meat products such as beef[41], and dairy products[33,42].

In light of these findings, it appears surprising that a high DAL (which is the consequence of a high intake of animal foods and a deficient intake in plant foods) shows no associations with RC in our study. One would expect opposite findings, particularly when considering that a high DAL is a potential risk factor for hypertension[43,44] and chronic kidney disease[18,45,46] – which are both considered risk factors for RC.

TABLE 3. Crude and Adjusted Odds Ratios (OR) of PC for acid load scores (PRAL and the two NEAP scores). All scores are expressed in mEq/day.

Model	*I*	*II*	*III*	*Continuous OR*	*p trend*
PRAL	**< -0.15**	**-0.15 – 8.51**	**> 8.51**		
I	1.00 ---	0.73 (0.45-1.19)	0.79 (0.49-1.27)	0.987 (0.968-1.007)	0.19
II	1.00 ---	0.64 (0.35-1.14)	0.76 (0.36-1.62)	0.970 (0.932-1.009)	0.13
III	1.00 ---	0.69 (0.38-1.24)	0.91 (0.42-1.96)	0.980 (0.939-1.022)	0.34
NEAP	**< 43.37**	**43.37 – 58.19**	**> 58.19**		
I	1.00 ---	0.74 (0.45-1.23)	1.08 (0.68-1.73)	0.997 (0.986-1.009)	0.65
II	1.00 ---	0.82 (0.45-1.49)	1.26 (0.62-2.53)	0.994 (0.978-1.011)	0.48
III	1.00 ---	0.91 (0.49-1.68)	1.59 (0.77-3.31)	0.999 (0.982-1.016)	0.92
NEAPr	**< 41.91**	**41.91 – 52.00**	**> 52.00**		
I	1.00 ---	0.94 (0.58-1.52)	0.81 (0.50-1.33)	0.997 (0.979-1.014)	0.70
II	1.00 ---	0.78 (0.44-1.38)	0.74 (0.36-1.52)	0.996 (0.962-1.030)	0.79
III	1.00 ---	0.85 (0.48-1.51)	0.87 (0.41-1.83)	1.007 (0.971-1.044)	0.71

Regression models:
I- Basic = age (continuous), residence (binary)
II- Complex = basic + education (continuous), bmi (continuous), af1 (binary), energy (continuous), fibre (continuous), smoking intensity (continuous), alcohol status (categoric), "mate" intensity (continuous), heme iron density (continuous)
III- Full = complex + total carotenoids (continuous), vitamin C (continuous), vitamin E (continuous)

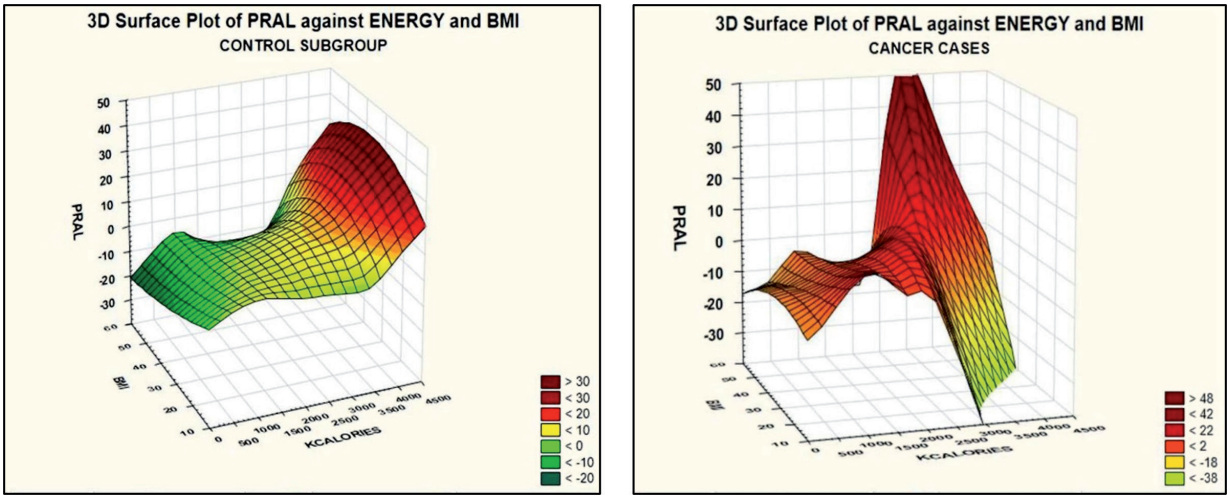

Fig. 1. 3-D graphs showing the interrelationships among PRAL score, body mass index and dietary energy. Comparison between controls (left picture) and renal cancer cases (right picture). Axes correspondence: X = energy (in kcal); Y = BMI (in kg/m^2); and Z = PRAL score (in mEq/d).

Nevertheless, it must be taken into consideration that the main function of normal kidneys is to maintain the systemic acid-base balance, mainly through reclaiming all filtered bicarbonate entering the proximal tubule, decreasing, in this way, the chance to develop an acid environment around the glomerulus and tubule system[47].

We were unable to identify significant risk associations concerning all scores. Yet, complex interplays among the presented variables are potentially hard to be captured with the different regression analyses. What we found might be a chance finding (a negative one, to be accurate), which cannot be precluded. Kidney cancer exhibits some paradoxical findings, apparently, according to the bibliography [48]. The fact that a higher BMI is found among control patients compared to RC cases is not easy to explain either. The small sample size of the case group could play an important role here. Nevertheless, the so-called "obesity paradox", deeply analyzed in a recent systematic review[48], demonstrated favorable kidney cancer outcomes in patients with body mass indices above the normal range compared to non-obese ones, adding a particular complexity to the landscape. In fact, our graphical analyses (Figure 1) revealed that among the control subset, the more alkaline scores are located within an area of high BMI subjects, which is opposite to what occurs among cancer cases, where their lowest PRAL scores fall within low BMI individuals.

Another crucial aspect worth mentioning is that cancer patients with low PRAL values had a high energy intake (Table 1). An average energy intake of 3200-4500 kcal/day is not compatible with a plant-based diet (individuals on a lacto-ovo-vegetarian consume approximately 1800-2000 kcal/day) [49]. We believe that in this particular cohort, individuals with lower PRAL values still consumed a lot of calorie-dense (non-plant-based) foods. Table 2 (indicating % of plant protein) also supports that assumption. It appears paradoxical, but individuals with high PRAL values consumed fewer calories as opposed to some with low PRAL-values.

Finally, our analysis did not support a potential role of iron intake as an RC risk factor (results not shown), different to the usual findings in other specialized studies[50-52]. This point might be important since the kidney is actively involved in systemic iron homeostasis as it reabsorbs filtered iron to prevent loss in the urine. Furthermore, iron is essential for the high metabolic demands of renal cells. As stated by Van Swelm et al[53], the molecular mechanisms involved in renal iron handling may differ from those observed in other tissues (e.g. as the liver and duodenum), because the complex organization of the kidney tissue and differential expression of iron transporters pose a different scene. Importantly, iron regulation and handling occur at both the systemic and the tissue level and may be influenced by multiple processes that can occur in parallel[54], and this complicates the study of the role of iron in renal disease[53].

Strengths and limitations

Our study has limitations and strengths that warrant further discussion. Epidemiological investigations share several common problems, particularly selection bias. However, we tried to reduce this bias by age-frequency matching controls and cases. Moreover, whereas interviewer bias is less likely to have taken place, we may not exclude the chance of having a certain degree of recall bias. Both cases and

controls were drawn from a large cohort (also investigating other cancers and their association with environmental factors), and the involved interviewers were unaware of the study's objectives. Another limitation is the lack of urine analyses: a high DAL may influence urine pH values, yet we cannot investigate this association for missing data. Other potential confounders, such as home or occupational exposure to pollution (e.g., toxic chemicals), were not assessed. Finally, the employed FFQ has not been validated due to external factors; yet it showed reproducibility satisfactorily in other studies[21].

As for the strengths, the interviews were done face-to-face by the same interviewers at the same hospitals. We performed data collection in the same period. Moreover, our sample is characterized by a low attrition rate and limited potential selection bias.

CONCLUSIONS

In conclusion, calculated NEAP and PRAL scores were not significantly associated with RC risk, in all cases supported by adjusted regression models. Our results do not suggest that an acidogenic dietary style could contribute to the RC risk. This risk might involve a complex interplay among several substances, and further investigations are warranted to confirm our findings.

Funding:
The authors report no funding.

Author contributions:
A.L.R. participated in the original idea, design, data processing, statistical analyses, text redaction, graph design, and general supervision; M.S. collaborated in the text redaction, draft supervision, language checking, and general supervision; W.M.L. collaborated in the text supervision, biochemical and molecular supervision, and final draft supervision; J.M.C. collaborated in tables design and the text supervision; W.G. collaborated in the text redaction and supervision.

Ethical considerations:
Each hospital Director has consented the project after receiving approval from the respective Ethical Committee. In past years (1990-2005), only oral consent was required from the patients, assuming the confidentiality about their data by the research staff, and no specific code was formally requested for epidemiologic observational studies.

ORCID ID:
Alvaro L. Ronco 0000-0002-6328-1482

Conflict of Interest:
The authors (ALR, MAS, WML, JMC and WG) declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

REFERENCES

1. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, Bray F. Global Cancer Statistics 2020: GLOBOCAN Estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2021; 71: 209-249.
2. Qayyum T, Oades G, Horgan P, Aitchison M, Edwards J. The epidemiology and risk factors for renal cancer. Curr Urol 2013; 6: 169-174.
3. Scelo G, Larose TL. Epidemiology and risk factors for kidney cancer. J Clin Oncol 2018; 36: 3574-3581.
4. Capitanio U, Bensalah K, Bex A, Boorjian SA, Bray F, Coleman J, Gore JL, Sun M, Wood C, Russo P. Epidemiology of renal cell carcinoma. Eur Urol 2019; 75: 74-84.
5. Kabaria R, Klaassen Z, Terris MK. Renal cell carcinoma: links and risks. Int J Nephrol Renovasc Dis 2016; 9: 45-52.
6. Tahbaz R, Schmid M, Merseburger AS. Prevention of kidney cancer incidence and recurrence: lifestyle, medication and nutrition. Curr Opin Urol 2018; 28: 62-79.
7. Huang T, Ding P, Chen J, Yan Y, Zhang L, Liu H, Liu P, Che J, Zheng J, Yao X. Dietary fiber intake and risk of renal cell carcinoma: evidence from a meta-analysis. Med Oncol 2014; 31: 125.
8. Lee JE, Männistö S, Spiegelman D, Hunter DJ, Bernstein L, Brandt PA van den, Buring JE, Cho E, English DR, Flood A, Freudenheim JL, Giles GG, Giovannucci E, Hakansson N, Horn-Ross PL, Jacobs EJ, Leitzmann MF, Marshall JR, McCullough ML, Miller AB, Rohan TE, Ross JA, Schatzkin A, Schouten LJ, Virtamo J, Wolk A, Zhang SM, Smith-Warner SA. Intakes of fruit, vegetables, and carotenoids and renal cell cancer risk: A pooled analysis of 13 prospective studies. Cancer Epidemiol Biomarkers Prev 2009; 18: 1730-1739.
9. Scialla JJ, Anderson CAM. Dietary acid load: A novel nutritional target in chronic kidney disease? Adv Chronic Kidney Dis 2013; 20: 141-149.
10. Wu T, Seaver P, Lemus H, Hollenbach K, Wang E, Pierce JP. Associations between dietary acid load and biomarkers of inflammation and hyperglycemia in breast cancer survivors. Nutrients 2019; 11: E1913.
11. Ronco AL, Martínez-López W, Calderón JM, Mendoza BA. Dietary acid load and colorectal cancer risk: a case-control study. World Cancer Res J 2020; 7: e1750.
12. Ronco AL, Martínez-López W, Calderón JM, Golomar W. Dietary acid load and lung cancer risk: A case-control study in men. Cancer Treatment Res Commun 2021; 28: 100382.
13. Shi LW, Wu YL, Hu JJ, Yang PF, Sun WP, Gao J, Wang K, Peng Y, Wu JJ, Zhong GC. Dietary acid load and the risk of pancreatic cancer: A prospective cohort study. Cancer Epidemiol Biomarkers Prev 2021; 30: 1009-1019.
14. Park Y-MM, Steck SE, Fung TT, Merchant AT, Hodgson ME, Keller JA, Sandler DP. Higher diet-dependent acid load is associated with risk of breast cancer: Findings from the sister study. Int J Cancer 2019; 144: 1834-1843.
15. Ronco AL, Martínez-López W, Mendoza BA, Calderón JM. Epidemiologic evidence for association between a high dietary acid load and the breast cancer risk. SciMed J 2021; 3: 166-176.
16. Parohan M, Sadeghi A, Nasiri M, Maleki V, Khodadost M, Pirouzi A, Sadeghi O. Dietary acid load and risk of hypertension: A systematic review and dose-response meta-analysis of observational studies. Nutrition, Metabolism and Cardiovascular Diseases 2019; 29: 665-675.

17. Rebholz CM, Coresh J, Grams ME, Steffen LM, Anderson CAM, Appel LJ, Crews DC. Dietary acid load and incident chronic kidney disease: Results from the ARIC Study. Am J Nephrol 2015; 42: 427-435.
18. Angeloco LRN, Arces de Souza GC, Romão EA, Frassetto L, Chiarello PG. Association of dietary acid load with serum bicarbonate in chronic kidney disease (CKD) patients. Eur J Clin Nutr 2020; 74: 69-75.
19. De Stefani E, Deneo-Pellegrini H, Boffetta P, Ronco AL, Aune D, Acosta G, Mendilaharsu M, Brennan P, Ferro G. Dietary patterns and risk of cancer: A factor analysis in Uruguay. Int J Cancer 2009; 124: 1391-1397.
20. Food and Agricultural Organization. http://faostat.fao.org/site/610/ DesktopDefault.aspx? Page ID=610 #ancor. Accessed 30 April 2010.
21. Ronco AL, De Stefani E, Boffetta P, Deneo-Pellegrini H, Acosta G, Mendilaharsu M. Food patterns and risk of breast cancer: A factor analysis study in Uruguay. Int J Cancer 2006; 19: 1672-1678.
22. Remer T, Manz F. Estimation of the renal net acid excretion by adults consuming diets containing variable amounts of protein. Am J Clin Nutr 1994; 59: 1356-1361.
23. Frassetto LA, Todd KM, Morris RC Jr, Sebastian A. Estimation of net endogenous noncarbonic acid production in humans from diet potassium and protein contents. Am J Clin Nutr 1998; 68: 576-583.
24. Safabakhsh M, Imani H, Yaseri M, Omranipour R, Shab-Bidar S. Higher dietary acid load is not associated with risk of breast cancer in Iranian women. Cancer Rep (Hoboken) 2020; 3: e1212.
25. Remer T, Dimitriou T, Manz F. Dietary potential renal acid load and renal net acid excretion in healthy, free-living children and adolescents. Am J Clin Nutr 2003; 77: 1255-1260.
26. DuBois D, DuBois EF. A formula to estimate the approximate surface area if height and weight are known. Arch Intern Med 1916; 17: 863-871.
27. Wang Y, Moss J, Thisted R. Predictors of body surface area. J Clin Anesth 1992; 4: 4-10.
28. Breslow NE, Day NE. Statistical methods in cancer research: Volume 1. The analysis of case-control studies. International Agency for Research on Cancer, Sci Pub 32, Lyon 1980.
29. Adeva MM, Souto G. Diet-induced metabolic acidosis. Clin Nutr 2011; 30: 416-421.
30. Statovci D, Aguilera M, MacSharry J, Melgar S. The impact of western diet and nutrients on the microbiota and immune response at mucosal interfaces. Front Immunol [Internet] 2017 Jul 28 [cited 2021 Jun 18]; 8. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/ PMC5532387/
31. Hariharan D, Vellanki K, Kramer H. The western diet and chronic kidney disease. Curr Hypertens Rep 2015; 17: 16.
32. Lemann J. Relationship between urinary calcium and net acid excretion as determined by dietary protein and potassium: a review. Nephron 1999; 81 Suppl 1: 18-25.
33. Hsu CC, Chow W-H, Boffetta P, Moore L, Zaridze D, Moukeria A, Janout V, Kollarova H, Bencko V, Navratilova M, Szeszenia-Dabrowska N, Mates D, Brennan P. Dietary risk factors for kidney cancer in Eastern and Central Europe. Am J Epidemiol 2007; 166: 62-70.
34. Brock KE, Gridley G, Chiu BC-H, Ershow AG, Lynch CF, Cantor KP. Dietary fat and risk of renal cell carcinoma in the USA: a case-control study. Br J Nutr 2009; 101: 1228-1238.
35. Washio M, Mori M, Mikami K, Miki T, Watanabe Y, Nakao M, Suzuki K, Ozasa K, Wakai K, Tamakoshi A. Risk factors for renal cell carcinoma in a Japanese population. Asian Pac J Cancer Prev 2014; 15: 9065-9070.
36. Rashidkhani B, Lindblad P, Wolk A. Fruits, vegetables and risk of renal cell carcinoma: a prospective study of Swedish women. Int J Cancer 2005; 113: 451-455.
37. Niedzwiecki A, Roomi MW, Kalinovsky T, Rath M. Anticancer efficacy of polyphenols and their combinations. Nutrients 2016; 8: 552.
38. Briguglio G, Costa C, Pollicino M, Giambò F, Catania S, Fenga C. Polyphenols in cancer prevention: New insights (Review). Int J Funct Nutr 2020; 1: 9.
39. Jia L, Jia Q, Shang Y, Dong X, Li L. Vitamin C intake and risk of renal cell carcinoma: a meta-analysis. Sci Rep 2015; 5: 17921.
40. Bertoia M, Albanes D, Mayne ST, Männistö S, Virtamo J, Wright ME. No association between fruit, vegetables, antioxidant nutrients and risk of renal cell carcinoma. Int J Cancer 2010; 126: 1504-1512.
41. Handa K, Kreiger N. Diet patterns and the risk of renal cell carcinoma. Public Health Nutr 2002; 5: 757-767.
42. Mellemgaard A, McLaughlin JK, Overvad K, Olsen JH. Dietary risk factors for renal cell carcinoma in Denmark. Eur J Cancer 1996; 32A: 673-682.
43. Akter S, Eguchi M, Kurotani K, Kochi T, Pham NM, Ito R, Kuwahara K, Tsuruoka H, Mizoue T, Kabe I, Nanri A. High dietary acid load is associated with increased prevalence of hypertension: the Furukawa Nutrition and Health Study. Nutrition 2015; 31: 298-303.
44. Krupp D, Esche J, Mensink GBM, Klenow S, Thamm M, Remer T. Dietary acid load and potassium intake associate with blood pressure and hypertension prevalence in a representative sample of the German adult population. Nutrients 2018; 10: E103.
45. Banerjee T, Crews DC, Wesson DE, Tilea A, Saran R, Rios Burrows N, Williams DE, Powe NR. Dietary acid load and chronic kidney disease among adults in the United States. BMC Nephrol 2014; 15: 137.
46. López M, Moreno G, Lugo G, Marcano G. Dietary acid load in children with chronic kidney disease. Eur J Clin Nutr 2020; 74: 57-62.
48. Kim LH, Doan P, He Y, Lau HM, Pleass H, Patel MI. A systematic review and meta-analysis of the significance of body mass index on kidney cancer outcomes. J Urol Vol 2021; 205: 346-355.
49. Allès B, Baudry J, Méjean C, Touvier M, Péneau S, Hercberg S, Kesse-Guyot E. Comparison of sociodemographic and nutritional characteristics between self-reported vegetarians, vegans, and meat-eaters from the NutriNet-Santé Study. Nutrients 2017; 9: E1023.
50. Ronco AL, Calderón JM, Mendoza BA. Dietary iron, water intake and risk of urinary bladder cancer: a case-control study. World Cancer Res J 2020; 7: e1685.
51. Ronco AL, Calderón JM, Mendoza BA, Espinosa E, Lasalvia-Galante E. Dietary iron sources and colorectal cancer risk: a role for sex. J Cancer Sci Treat 2019; 2: 93-110.
52. Ronco AL, Espinosa E, Calderón JM. A case-control study on heme/non-heme iron and breast cancer risk. Ann Clin Nutr 2018; 3: 1011.
53. van Swelm RPL, Wetzels JFM, Swinkels DW. The multifaceted role of iron in renal health and disease. Nature Rev Nephrol 2020; 16: 77-98.
54. van Raaij SEG, Rennings AJ, Biemond BJ, Schols SEM, Wiegerinck ETG, Roelofs HMJ, Hoorn EJ, Walsh SB, Nijenhuis T, Swinkels DW, van Swelm RPL. Iron handling by the human kidney: glomerular filtration and tubular reabsorption both contribute to urinary iron excretion. Am J Physiol 2019; 316: f606-f614.