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Dietary acid load and risk of head and neck and oral cavity cancers: An epidemiologic study

Alvaro L. Ronco[1,2,3] | Wilner Martínez-López[4,5] | Juan M. Calderón[3] | Maximilian A. Storz[6]

[1]Unit of Oncology and Radiotherapy, Pereira Rossell Women's Hospital, Montevideo, Uruguay

[2]Department of Oncology, School of Medicine, CLAEH University, Maldonado, Uruguay

[3]Biomedical Sciences Center, University of Montevideo, Montevideo, Uruguay

[4]Academic Unit on Radiation Protection, Faculty of Medicine, University of the Republic, Montevideo, Uruguay

[5]Genetics Deparment and Biodosimetry Service, Instituto de Investigaciones Biológicas Clemente Estable, Montevideo, Uruguay

[6]Department of Internal Medicine II, Center for Complementary Medicine, Freiburg Medical Center, Faculty of Medicine, University of Freiburg, Freiburg, Germany

Correspondence
Maximilian Andreas Storz, Department of Internal Medicine II, Centre for Complementary Medicine, University of Freiburg, Freiburg, Germany.
Email: maximilian.storz@uniklinik-freiburg.de

Abstract

Aim: Metabolic acidosis subsequent to a high dietary acid load (DAL) leads to inflammation and cell transformation, which are common features of cancer development. Because the epidemiologic evidence associating DAL and cancer risk is still limited, we sought to explore the potential role of DAL as a risk factor for head and neck and oral cavity tumors.

Methods: A case–control study was performed on 1126 men (563 cases and 563 age frequency and residence matched controls), drawn from the major public hospitals in Montevideo, Uruguay. Participants were interviewed through a multitopic questionnaire, including a food frequency questionnaire. Food-derived nutrients were calculated from available databases. DAL was calculated based on validated measures including potential renal acid load (PRAL) and net endogenous acid production (NEAP) scores. Odds ratios (OR) were estimated by logistic regression, adjusting for potential confounders.

Results: We found significant and direct associations between dietary acid load and risk of head and neck and oral cavity cancers (OR = 2.10 and OR = 1.95 for highest PRAL and NEAP, respectively). In addition, stratified analyses by subsites displayed the highest estimates for pharyngeal cancer (OR = 2.40 and OR = 2.28 for highest PRAL and NEAP, respectively). No association was found for oral cavity cancers.

Conclusions: An acidogenic diet may increase the risk of head and neck cancers. Our findings align well with our previous studies focused on other anatomic sites. Studies conducted on food groups and nutritional patterns align with our results. Further studies are needed to confirm these findings.

KEYWORDS
cancer, dietary acid load, epidemiology, larynx, oral cavity, pharynx

1 | INTRODUCTION

Cancers of the upper aero-digestive tract, which comprise cancers of the oral cavity, larynx, pharynx, and esophagus, have high incidence rates worldwide and represent the fourth most common cause of mortality from cancer globally.[1–3] Upper aerodigestive cancer is a chronic disease of complex multifactorial origin[1] with a poor survival rate in untreated patients.[4]

The disease is more common in males than in females[5] and more prevalent in certain demographic groups, for example, rural populations.[6] The most common predisposing risk factor include alcohol,[5,7] smoking (including secondhand smoking),[1,8] and chewing tobacco.[8,9] Moreover, dental risk factors such as periodontitis, infrequent tooth brushing, tooth loss, poor oral hygiene, and mechanical irritation from dentures and faulty prosthetic devices, as well as human papillomavirus infection appear to play an important role.[10,11]

Historically, there has always been a high interest in the relationship between dietary risk factors and upper aerodigestive cancers.[12–14] Kasum et al.[14] reported inverse associations for certain foods (including whole grains, yellow and orange vegetables, and fiber) and upper aerodigestive cancer risk. In contrast, red chili powder,[15] eggs,[16] and dietary patterns rich in animal products were shown to increase upper aerodigestive cancer risk.[17–19]

Several research groups also analyzed potential associations of upper aerodigestive cancers and pro-inflammatory dietary patterns.[20,21] In addition, a meta-analysis by Zhu and colleagues demonstrated that a mere one-unit increment in the widely used dietary inflammatory index was associated with an 18% increased upper aerodigestive cancer risk.[21]

Pro-inflammatory diets may cause systemic inflammation and subsequently increase cancer risk.[21] Another vital factor in this context is dietary acid load (DAL).[22] A high DAL, caused by a frequent intake of acidogenic foods (including meat, dairy, and eggs) and by a low intake of alkaline foods (as vegetables and fruits),[23] leads to metabolic acidosis that promotes tissue damage which can further initiate inflammation.[24] Cancer patients have a reduced capacity to adjust their acid–base balance.[24,25] Therefore, they may be particularly vulnerable to a high DAL.

DAL has recently been shown to increase the risk for various cancer types,[26–31] and no associations were reported for some tumors.[32,33] However, it has never been investigated in the context of head and neck and oral cavity cancers. Therefore, we sought to change this and investigated potential associations between otorhinolaryngologic tumors (including cancers of the oral cavity, larynx, and pharynx) and DAL in a case–control study in Uruguay.

2 | METHODS

This study is part of a large multi-site case–control study investigating associations between a series of environmental factors and the risk of cancer in Montevideo, Uruguay. The methods have been described elsewhere in detail.[27–31] A brief description of the methodology is given below.

2.1 | Cases and controls selection

Between 1996 and 2004, all newly diagnosed and microscopically confirmed male cases of head and neck, including oral cancers registered in Uruguay's capital were considered eligible for this study. The sample included $n = 1126$ individuals. Trained social workers (blinded with regard to research goals) worked at the hospitals in two phases: First, they performed routine screenings, working with Medical Records personnel's collaboration to identify potentially eligible participants at the four major hospitals of Montevideo. The study team contacted potential study participants (suffering from newly diagnosed head and neck and oral cavity cancers). Esophagus cancers were not analyzed as part of this analysis. We identified a total of $n = 563$ head and neck and oral cancer cases, whose main subsites were: oral cavity ($n = 103$), pharynx ($n = 185$), and larynx ($n = 275$). A complete classification is given in Table 1.

As in other reports proceeding from the same multisite database, TNM staging was not requested. Clinical diagnoses were usual methods of identification of cases, which were afterwards microscopically confirmed: 558 (99.1%) were squamous cell carcinomas; the remaining 5 (0.9%) comprised lymphoepiteliomas and adenocarcinomas.

Second, they contacted during the same period and at the same institutions a similar number ($n = 563$) of patients afflicted with non-neoplastic diseases, who were eligible to be matched by the age-frequencies of the cases, as well as their urban/rural residence, and their region. After providing verbal and written consent to participate in the study, all eligible participants were interviewed face-to-face. Proxy interviews were not accepted.

All controls were admitted for medical conditions unrelated to stimulants (drink and tobacco). We excluded controls with a recent history of dietary modifications (within the past 5 years) that may have caused an additional bias. Controls suffered from the following medical conditions: abdominal hernia (108, 19.2%), eye disorders (106, 18.9%), bone diseases (104, 18.4%), skin diseases (61, 10.8%), injuries and trauma (56, 9.9%), appendicitis (36, 6.5%), varicose veins (32, 5.7%), hydatid cyst (17, 3.0%), blood disorders (10, 1.8%), and other medical disorders (33, 5.8%).

2.2 | Questionnaire

We administered a questionnaire that included both socio-demographic and anthropometric variables. Moreover, the questionnaire inquired about the history of substance usage (including tobacco and alcohol), cancer history in 1st-2nd degree relatives, and potential occupational hazards and exposures. In addition to that, the questionnaire also included a detailed food frequency questionnaire (FFQ) with $n = 64$ items. The employed FFQ was representative of the Uruguayan diet, focused on food consumption 5 years before the interview, and all dietary questions were open-ended. We tested the FFQ for reproducibility with good results (see previous study[34] for details). In addition, local tables of food composition were used to estimate nutrient and energy intake.

2.3 | Dietary acid load estimation

We explained the employed methods for DAL estimation elsewhere in detail.[27–31] Two validated formulas were used to calculate dietary

TABLE 1 Distribution of cancer cases, according to the anatomic site and subsites, classified following the International Code of Diseases for Oncology (ICD-9)

Anatomic site	*N* = 563	Subsite	ICD-9 code	*N* by subsite
Oral cavity	103			
Tongue	73	Base	141.0	35
		Lateral	141.2	3
		2/3 Anterior	141.4	1
		Unspecified part	141.9	34
Mouth floor	11	Unspecified part	144.9	11
Mouth	19	Cheek mucosa	145.0	1
		Hard palate	145.2	3
		Soft palate	145.3	5
		Uvula	145.4	2
		Palate unspecified	145.5	7
		Retromolar	145.6	1
Pharynx	185			
Oropharynx	73	Tonsil	146.0	47
		Tonsil pillars	146.2	1
		Vallecula	146.3	6
		Epiglottis	146.4	1
		More than one part	146.8	1
		Unspecified part	146.9	17
Nasopharynx	14	Unspecified part	147.9	14
Hypopharynx	95	Pyriform sinus	148.1	72
		Aryepiglottic fold	148.2	7
		Posterior	148.3	1
		Unspecified part	148.9	15
Pharynx	3	Unspecified part	149.0	3
Larynx	275			
		Glottis	161.0	53
		Supraglottis	161.1	83
		Subglottis	161.2	5
		More than one part	161.8	1
		Unspecified part	161.9	133

Note: The ICD-9 (World Health Organization) was the Coding system used by the National Cancer Registry of Uruguay during the years of the study.

acid load.[35,36] We calculated the potential renal acid load (PRAL) of diet as follows:

$$\begin{aligned}\text{PRAL}\,(\text{mEq/day}) = {} & (0.49 \times \text{total protein}\,[\text{g/day}]) \\ & + (0.037 \times \text{phosphorus}[\text{mg/day}]) \\ & - (0.021 \times \text{potassium}[\text{mg/day}]) \\ & - (0.026 \times \text{magnesium}[\text{mg/day}]) \\ & - (0.013 \times \text{calcium}[\text{mg/day}])\end{aligned}$$

This calculation method considers intestinal absorption rates for various micronutrients and protein; it has been validated versus urinary pH in healthy individuals with good results.[35]

Net endogenous acid production (NEAP) was estimated using Frasetto's formula[36]:

$$\begin{aligned}\text{NEAP}(\text{mEq/day}) = {} & (54.5 \times \text{protein}[\text{g/day}])/(0.0256 \\ & \times \text{potassium}[\text{mg/day}]) - 10.2\end{aligned}$$

This method considers sulfuric acid production (subsequent to protein metabolism) and the rate of bicarbonate production (subsequent to the metabolization of intestinally absorbed potassium salts of organic acids).[36] In particular, a negative PRAL score reflects an alkaline-forming potential, whereas positive scores indicate an acid-forming potential.[23]

2.4 | Statistical analysis

STATA software (Release 10, Stata Corp LP, College Station, TX, 2007) was used for all statistical analyses. We treated almost all questionnaire variables as continuous variables. Categorization was done for analysis purposes only. Descriptive statistics included frequencies for categorical variables and means (standard error in parenthesis) for continuous, normally-distributed variables.

We calculated odds ratios (ORs) and their corresponding 95% confidence intervals (95% CI) by unconditional logistic regression. Terms for potential observable confounders were included in the multivariate analyses. They included age, residence, family history of cancer in 1st and 2nd-degree relatives, body mass index, total energy intake, smoking history, mate intake, ethanol intake, and iron intake (see Tables 4 and 5). No participants were excluded as outliers for any dietary component. Heterogeneities in the stratified analyses were explored through likelihood-ratio tests.

3 | RESULTS

Table 1 displays the classification of cancer cases, by anatomic site and by subsites. The main cancer sites were: oral cavity ($n = 103$), pharynx ($n = 185$), and larynx $n = 275$). Of them, unspecified larynx, supraglottis, and pyriform sinus were the most frequent cancer subsites.

TABLE 2 Selected socio-demographic characteristics and habits of the population under study ($n = 1126$)

Variables	Categories	Controls (n = 563) %		Cases (n = 563) %		p-value
Age groups	<50	70	12.5	70	12.5	
	50–69	377	67.0	377	67.0	
	≥70	116	20.5	116	20.5	1.00
Urban/rural status	Urban	481	85.4	461	81.9	
	Rural	82	14.6	102	18.1	0.11
Education years	<5	258	45.8	305	54.2	
	≥5	305	54.2	258	45.8	0.005
Body mass index (kg/m^2)	NW ≤ 24.99	241	44.0	396	72.6	
	OW-OB ≥ 25.00	315	56.0	154	27.4	<0.001
FH of cancer in	No	412	73.9	402	71.4	
1st & 2nd degree	Yes	286	26.8	67	28.6	0.51
"Mate" intensity (liters-years)	Non drinkers	81	14.4	48	8.5	
	1.0–43.9	158	28.1	169	30.0	
	44.0–72.1	204	36.2	181	32.2	
	≥72.2	120	21.3	165	29.3	0.001
Mate temperature	Warm	24	5.0	20	3.9	
	Hot	419	86.9	452	87.8	
	Very hot	39	8.1	43	8.3	0.70
Dietary energy (kcal/day)	≤2109	227	40.3	149	26.5	
	2110–2595	186	33.0	190	33.7	
	≥2596	150	26.6	224	39.8	<0.001
Alcohol status	Never	203	36.1	69	12.3	
	Ex drinker	67	11.9	85	15.1	
	Current	293	52.0	409	72.6	<0.001
Smoking status	Non smoker	132	23.4	13	2.3	
	Ex-smoker	139	24.7	114	20.3	
	Ever smoker	292	51.9	436	77.4	<0.001
Smoking intensity (pack-years)	Non smoker	132	23.4	13	2.3	
	0.1–34.0	216	38.4	114	20.2	
	34.1–50.0	102	18.1	134	23.8	
	≥50.1	113	20.1	302	53.6	<0.001

Note: Distribution of cases and controls.
Abbreviations: FH of Cancer, family history of cancer; NW, normal weight; OW, overweight; OB, obesity.

Table 2 shows the general features of the studied population. Controls were more educated and displayed higher BMI than cases. Alcohol drinking, "mate" drinking, and energy intake were higher among cancer cases. Cases included more smokers than controls, and also with a higher smoking intensity. The family cancer history was not relevant in this sample.

Table 3 shows a detailed comparison of mean iron types and selected nutrients between head and neck and oral cavity cancer cases and controls. Although there were no significant differences in total iron intake, cancer cases displayed higher animal and heme iron intakes. In contrast, controls had higher intakes of plant and non-heme iron. Both iron ratios, Animal/Plant iron ratio and Heme/Non-heme iron ratio, were significantly different between cases and controls, prevailing higher ratios among cases. Finally, controls showed significantly higher vitamin C, carotenoids, and fiber intakes.

The mean values of DAL scores and their components are displayed in Table 4. Both PRAL and NEAP scores were significantly higher among cancer cases. The same applied for daily protein, phosphorus, potassium, and magnesium intakes. Results demonstrated a significantly higher intake of animal-sourced components. All five components with plant sources were not statistically different. On the

TABLE 3 Mean daily values ± standard deviation (SD) of selected nutrients and bioactive substances adjusted by energy

Variable	Units	Controls ($n = 563$) Mean ± SD	Cases ($n = 563$) Mean ± SD	*p*-value
Energy	kcal	2256 ± 573	2499 ± 682	<0.0001
Total iron	mg/10^3 kcal	7.73 ± 1.40	7.82 ± 1.43	0.29
Animal iron	mg/10^3 kcal	2.98 ± 0.96	3.27 ± 1.03	<0.0001
Plant iron	mg/10^3 kcal	4.75 ± 1.55	4.54 ± 1.50	0.02
A/P iron	Ratio	0.76 ± 0.55	0.86 ± 0.58	0.004
Heme iron	mg/10^3 kcal	1.76 ± 0.67	1.97 ± 0.70	<0.0001
NHeme iron	mg/10^3 kcal	5.97 ± 1.41	5.84 ± 1.38	0.13
H/NH	Ratio	0.32 ± 0.17	0.36 ± 0.18	<0.0001
Vitamin C	mg/10^3 kcal	59.6 ± 39.8	51.8 ± 32.1	0.0003
Carotenoids	mg/10^3 kcal	10.51 ± 7.18	10.22 ± 6.99	0.48
Total fiber	g/10^3 kcal	5.16 ± 2.07	4.41 ± 2.65	<0.0001

Note: Comparison between cases and controls.
Abbreviations: g, grams; mg, milligrams; kcal, kilocalories; A/P, animal/plant; H/NH, heme/non-heme.

TABLE 4 Mean daily values ± standard errors of the acid load scores and their components

Variable	Units	Controls (mean ± SE)	Cases (mean ± SE)	*p*-value
Total proteins	g/day	57.9 ± 0.7	66.0 ± 0.9	<0.001
Animal proteins	g/day	53.1 ± 0.7	61.1 ± 0.9	<0.001
Plant proteins	g/day	4.8 ± 0.1	4.9 ± 0.1	0.66
Total phosphorus	mg/day	837.6 ± 10.4	922.5 ± 11.2	<0.001
Animal phosphorus	mg/day	510.2 ± 7.5	584.4 ± 8.7	<0.001
Plant phosphorus	mg/day	327.5 ± 5.5	338.1 ± 6.0	0.19
Total potassium	mg/day	1976.3 ± 25.9	2074.9 ± 26.6	0.008
Animal potassium	mg/day	724.3 ± 11.5	835.6 ± 13.2	<0.001
Plant potassium	mg/day	1252.0 ± 20.7	1239.3 ± 20.9	0.67
Total magnesium	mg/day	186.2 ± 2.5	196.2 ± 2.6	0.006
Animal magnesium	mg/day	56.6 ± 0.9	65.1 ± 1.0	<0.001
Plant magnesium	mg/day	129.6 ± 2.2	131.1 ± 2.2	0.63
Total calcium	mg/day	602.3 ± 9.3	621.2 ± 8.9	0.14
Animal calcium	mg/day	343.7 ± 7.9	357.3 ± 7.7	0.22
Plant calcium	mg/day	258.6 ± 4.1	263.9 ± 4.2	0.37
PRAL score	mEq/day	5.21 ± 0.45	9.72 ± 0.48	<0.001
NEAP score	mEq/day	54.07 ± 0.72	59.19 ± 0.75	<0.001

other hand, global calcium intake was slightly higher but not statistically significant.

Table 5 displays the crude and adjusted risk estimates for both DAL scores. The crude ORs were higher than the adjusted ones for PRAL and NEAP scores, and their p-values for linear trends were also significant. The best regression models derived an OR = 2.10 for the highest PRAL tertile and an OR = 1.95 for the highest NEAP tertile. Both estimates and linear trends were statistically significant.

Finally, Table 6 shows the results of analyses performed by strata of anatomic subsites (oral cavity, pharynx, and larynx). Whereas PRAL and NEAP scores were not associated with the risk of oral cavity cancer, the association with pharyngeal cancer was statistically significant and the strongest one. Larynx cancer also showed significant risk associations for PRAL and for NEAP scores.

4 | DISCUSSION

The main aim of our study was to explore whether a high dietary acid load was associated with an increased risk for selected upper aerodigestive cancers in a Uruguayan population. Our results confirmed this hypothesis and revealed that higher acid load scores (NEAP and PRAL) significantly increased our sample's odds for the studied cancers (Table 5).

After adjusting for various covariates, we found significantly higher odds for otorhinolaryngologic cancers in those individuals with the highest PRAL (OR: 2.10, CI: 1.46–3.03) and NEAP scores (OR: 1.95, CI: 1.37–2.78). This phenomenon was observed for both larynx and pharynx cancers in a separate analysis stratified by anatomic site (Table 6), which in addition revealed heterogeneity from a statistical point of view, suggesting no association of DAL for oral cavity

TABLE 5 Crude and adjusted odds ratios (OR) of head and neck and oral cavity cancers for acid load scores (PRAL and NEAP)

		I		II		III		
Acid load scores	**Regression models**	**OR**	**95% CI**	**OR**	**95% CI**	**OR**	**95% CI**	**Trend (*p*-value)**
PRAL (mEq/day)		**≤3.35**		**3.36–12.08**		**≥12.09**		
	Model 1	1.00	---	**1.34**	1.00–2.79	**2.48**	1.85–3.32	<0.001
	Model 2	1.00	---	1.11	0.79–1.57	**2.10**	1.46–3.03	<0.0001
NEAP (mEq/day)		**≤48.7**		**48.8–62.7**		**≥62.8**		
	Model 1	1.00	---	**1.55**	1.16–2.07	**2.25**	1.68–3.02	<0.001
	Model 2	1.00	---	1.27	0.89–1.79	**1.95**	1.37–2.78	0.002

Note: *p*-values for their linear trends. Regression models: Model 1 = Adjusted by age (continuous), and residence (urban/rural). Model 2 = Model 1 + family history of cancer in 1st and 2nd degree (binary No/Yes) + body mass index (continuous) + energy (categorical, 3) + smoking status (categorical, 3) + smoking intensity (continuous) + "mate" intensity (continuous) + ethanol g/day (continuous) + total iron (continuous). Total iron = dietary iron/1000 kcal/day (in mg).

TABLE 6 Crude and adjusted odds ratios (OR) of UADT for acid load scores (PRAL and NEAP), stratified by anatomic sites

		I		II		III		
Acid load scores	**Anatomic sites**	**OR**	**95% CI**	**OR**	**95% CI**	**OR**	**95% CI**	**Trend (*p*-value)**
PRAL (mEq/day)		**≤3.35**		**3.36–12.08**		**≥12.09**		
	All sites	1.00	---	1.11	0.79–1.57	**2.10**	1.46–3.03	<0.0001
	Oral cavity	1.00	---	0.84	0.46–1.55	1.29	0.69–2.43	0.49
	Pharynx	1.00	---	1.16	0.71–1.91	**2.40**	1.44–4.01	0.005
	Larynx	1.00	---	1.14	0.74–1.77	**2.22**	1.42–3.47	<0.0001
NEAP (mEq/day)		**≤48.7**		**48.8–62.7**		**≥62.8**		
	All sites	1.00	---	1.27	0.89–1.79	**1.95**	1.37–2.78	0.002
	Oral cavity	1.00	---	1.04	0.56–1.91	1.06	0.56–1.98	0.98
	Pharynx	1.00	---	1.21	0.73–1.99	**2.28**	1.40–3.71	0.006
	Larynx	1.00	---	1.37	0.89–2.11	**2.00**	1.29–3.09	0.006

Note: *p*-values for their linear trends. Regression model: Adjusted by age (continuous) + residence (urban/rural) + family history of cancer in 1st and 2nd degree (binary No/Yes) + body mass index (continuous) + energy (categorical, 3) + smoking status (categorical, 3) + smoking intensity (continuous) + "mate" intensity (continuous) + ethanol g/day (continuous) + total iron (continuous). Total iron = total dietary iron/1000 kcal/day (in mg). Likelihood ratio test for heterogeneity of anatomic sites → $p < 0.0001$ (both PRAL and NEAP).

cancers. Such heterogeneity yields a theoretical approach: the oral cavity might not be influenced similarly by the acidogenic dietary style because of more resistant histologic features than the pharynx and larynx.[37,38]

It seems reasonable to hypothesize that the first anatomic area of the upper aerodigestive region (at least at the mucosal lining), which is initially exposed to potential extreme temperatures and several different chemicals, salivation, and chewing, might be more able than the pharynx and larynx to preserve its microstructure from a putative biochemical disruption derived from the diet. We cannot preclude a possible different influence of an acidogenic diet through cellular and extracellular pH changes at these distinct anatomic levels.

For a better risk modeling, we included "mate" intake in our analysis. It is a hot infusion prepared from the *Ilex paraguariensis* herb and a staple in temperate South America. More than 80% of Uruguayans have the habit of drinking "mate," and they are the world's highest "mate" consumers, with approximately 9–10 kg/person/year of the herb and approximately 400 liters/person/year of infusion.[39] The International Agency for Research on Cancer (IARC)[40] included hot "mate" drinking as a possible carcinogenic for humans (a 2A agent) because of the presence of polycyclic aromatic hydrocarbons.[41,42] Later, the IARC revised the "mate" classification in 2016 and changed it from group 2A to group 3 (low risk). Nevertheless, the new assignment was only for "not very hot" mate, based on insufficient animal and human evidence,[43] and establishing >65°C as a lower limit for the "very hot" category. Another study reported 69.5°C as the mean temperature for regional consumers.[44] The infusion was reported last decade as a risk factor for oral cancer among the Uruguayan population,[45] and a recent meta-analysis mentioned "mate" as a risk factor for upper aerodigestive cancers.[46] Therefore, we believe it was justified to include the infusion in our calculations because those consumers labeled as "hot mate" drinkers seem to have a high proportion of "very hot mate" consumers, according to IARC.

The role of DAL as a potential cancer risk factor is a topical area that recently attracted increased interest by several research groups: a high DAL (representing an acidifying diet rich in animal products) has been associated with increased odds for many types of solid cancers, including bladder,[31] prostate,[30] lung,[29] colorectal,[27] and breast cancer.[28,47] In addition, a high DAL may also increase the risk for cancer recurrence in breast cancer survivors.[24] Our current findings confirm the role of DAL as a novel (and most importantly modifiable) risk factor in the field of Oncology and cancer prevention.

One of the hallmarks of current Western dietary patterns is the paucity of fresh fruits, vegetables, and legumes.[48] At the same time, modern Western diets contain excessive amounts of animal protein (mainly from meat, dairy, and eggs) and fat.[49] The consequence of this disequilibrium is an increase in DAL, which has been associated with a series of health problems.[27–31]

A high acid load can decrease blood pH towards the lower end of the normal physiological range resulting in mild metabolic acidosis.[50,51] Chronic low-grade metabolic acidosis can cause tissue damage, further initiating inflammation.[24,51] The latter is of paramount concern in cancer patients, who have a reduced capacity to adjust their acid–base balance.[25]

Both systemic and local inflammation may play a relevant role in patients with head and neck cancers, particularly in laryngeal squamous cell carcinoma.[52,53] Local inflammation derived from an acidic microenvironment may induce genomic instability on normal cells through the activation of cytokines, which may stimulate tumor invasion and metastasis.[54–57] Moreover, it may work as an evolutionary force for aggressive clones of acid-adapted cells.[54]

The mechanical and biochemical actions on the oral tissues at the extracellular matrix (ECM) level imply that the composition and concentration of its specific components are dysregulated. In addition, complex molecules (e.g., integrins) participate in the regulation of cell–cell and cell-ECM metabolism and play a role in modulating intracellular spatial relationships, therefore affecting the entire epithelial architecture.[58] Dysregulation leads to a tissue remodeling associated with inflammation, fibrosis, and stiffness, evolving towards premalignant and further malignant conditions.[59] Past observations indicated more remarkable cell polarity changes in oropharyngeal and laryngeal carcinomas.[58] A deeper analysis of these and other mechanistic features is beyond the scope of this exploratory epidemiological study.

In light of the potential pathomechanisms that may explain our findings, it is conceivable that a reduction in DAL could be a protective measure to reduce the risk of head and neck cancers. Various direct acidity targeting approaches have been postulated, such as oral buffers, targeted but experimental agents to raise tumor pH[60]; yet diet appears probably the most accessible, feasible, and affordable option for most populations.[23]

4.1 | Strengths and limitations

The present study has strengths and limitations that require a thorough discussion. The FFQ used for this study has never been validated due to external factors. However, it showed adequate reproducibility in other studies.[34] Although our nutritional assessment dates back to the year 2004, recent investigations of dietary patterns in Uruguay revealed that few things have changed.[61] As such, we believe that our nutritional assessment still provides sufficient validity.

We tried to minimize selection bias by frequency-matching techniques and matched controls and cases on both age and residence. Of note, potential confounders, such as air pollutants, which play an important role in the development of upper aerodigestive cancers,[62] have not been captured correctly, and we recognize them as a limitation. Other epidemiological items, such as infection with viruses like Epstein–Barr or Human Papilloma and the sexual activity of the study participants, were not included in our questionnaire. Although they could constitute another limitation, we should take into account that the study period was somehow previous to the international rise of pharyngeal cancers beginning around 2002–2004.[63]

Besides, it would have been helpful to have done a similar study on women. However, during the study years, the head and neck and oral cavity cancers were not high-ranked tumors regarding their

incidence or mortality in the female sex. Consequently, we lacked a database on women for the studied cancer sites. Therefore, a comparison of DAL between sexes is welcome for future research.

The large sample size and some key features of the study (e.g., that all study interviews were done face-to-face by the same interviewers at the same hospitals) reducing bias is a significant strength of this study. The same applies to the low attrition rate.

5 | CONCLUSIONS

Results suggest that an acidogenic dietary style could probably increase the risk of head and neck and oral cavity cancers. The findings support our previous findings, which focused on other anatomic sites as breast, lung, colorectum, and prostate. In addition, studies conducted on food groups and nutritional patterns align with the present findings. Results shown here are the first ones reported on head and neck and oral cavity cancers, to the best of our knowledge. Therefore, further studies are warranted to confirm these findings and explore the associations for the female sex.

6 | ETHICAL CONSIDERATIONS

Each hospital Director has allowed the project after receiving approval from the respective Ethical Committee. In Uruguay, during the 1980s and up to the first decade of the current century, it required only oral consent from the patients, assuming their data confidentiality by the research staff. Based on first and last name + ID number, an auto-generated number was built to preserve anonymity. No specific code was formally requested for epidemiologic observational studies. After getting their consent for the study, all the participants underwent an in-person interview in the hospitals.

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CONFLICT OF INTERESTS

The authors report no conflict of interests.

ETHICS STATEMENT

Each hospital Director has consented to the project after receiving approval from the respective Ethical Committee. In past years, up to 2005, it required only oral consent from the patients assuming their data confidentiality; no specific code was formally requested for epidemiologic observational studies. In addition, an auto-generated number was built based on first and last name + ID number to preserve anonymity. All work was conducted in accordance with the Declaration of Helsinki (1964).

AUTHOR CONTRIBUTIONS

ALR worked on the concept, design, literature search, data acquisition and analysis, statistical analysis, manuscript preparation, editing and review; WML and JMC worked on literature search, manuscript editing, and manuscript review; MAS worked on the concept, and performed literature search, manuscript preparation, editing, and review.

PATIENT CONSENT STATEMENT

Consent was obtained as explained above.

CLINICAL TRIAL REGISTRATION

No specific code was formally requested for epidemiologic observational studies during the study period.

DATA AVAILABILITY STATEMENT

All data associated with this paper will be made available upon reasonable request.

ORCID

Alvaro L. Ronco https://orcid.org/0000-0002-6328-1482
Wilner Martínez-López https://orcid.org/0000-0002-9384-4231
Juan M. Calderón https://orcid.org/0000-0002-4083-3686
Maximilian A. Storz https://orcid.org/0000-0003-3277-0301

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