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Potencial inflamatorio de la dieta argentina y carcinoma oral de células escamosas

The inflammatory potential of Argentinian diet and oral squamous cell carcinoma

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The inflammatory compounds of Argentinean diet and oral squamous cell carcinoma in adult patients

Los compuestos inflamatorios de la dieta argentina y el carcinoma oral de células escamosas en pacientes adultos

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ABSTRACT

Introduction: the goal of this study was to evaluate if there is an association between dietary components related to inflammation processes and oral squamous cell carcinoma (OSCC) in Argentina.

Methods: case-control study 3:1, both genders, ages 24-80 years attended at External Offices of Facultad Odontología Universidad Nacional de Córdoba between 2012 and 2015. Dietary information was collected using a qualitative-quantitative food frequency questionnaire. The Dietary Inflammatory Index (DII) was applied. Logistic regression was applied in order to assess the association among case/control status and DII.

Results: a significant increase in median intake of macronutrients, such as fat, and protein was observed. In addition, dietary components, such as cholesterol, iron, riboflavin, monounsaturated fatty acids, polyunsaturated fatty acids, omega-6, omega-3, and vitamin B6 among others showed a significant increase in cases compared to controls ($p < 0.05$). It was observed a significant association between the DI index and OSCC by logistic regression (OR 1.69, 95% CI [1.18-2.43]) adjusted by alcohol and tobacco consumption from continuous DII.

Conclusion: this research showed that a relation between the DI indexes, as representative of the inflammatory components of the diet and the risk of OSCC, and it does enable future research regarding diet and its relation to oral cancer to be re-directed.

Key words: Diet. Inflammation. Oral cáncer. Case-control study. Nutritional index. Human.

RESUMEN

Introducción: el objetivo de este estudio fue evaluar la asociación entre los componentes de la dieta relacionados a procesos inflamatorios y el carcinoma oral de células escamosas (COCE) en Argentina.

Métodos: estudio caso-control 1: 3, ambos sexos, de 24 a 80 años de edad, atendidos en los consultorios externos de la Facultad de Odontología de la Universidad Nacional de Córdoba, entre 2012 y 2015. La información dietética se recopiló mediante un cuestionario de frecuencia de alimentos cualitativo-cuantitativo. Se determinó el Índice Inflamatorio Dietético (DII) con la estimación de los valores de nutrientes de la dieta. Se aplicó un modelo de regresión logística para evaluar la asociación entre el estado del caso/control y DII.

Resultados: se observó un aumento significativo de los valores medios (mediana) en la ingesta de macronutrientes, como grasa y proteínas. Además, los componentes dietéticos, como colesterol, hierro, riboflavina, ácidos grasos monoinsaturados, ácidos grasos poliinsaturados, omega-6, omega-3 y vitamina B6, entre otros, mostraron un aumento significativo en los casos en comparación con los controles ($p < 0,05$). Además, por el modelo de regresión logístico, ajustado por el consumo de alcohol y tabaco, se observó una asociación significativa entre el índice DI (variable continua) y COCE (OR 1,69, IC del 95% [1,18-2,43]).

Conclusión: esta investigación mostró una relación entre el índice DI, como representante de los componentes inflamatorios de la dieta, y el riesgo de COCE, sugiriendo la necesidad de continuar con la investigación sobre la relación de la dieta y el riesgo de desarrollar cáncer oral.

Palabras clave: Dieta. Inflamación. Cáncer oral estudio de casos y controles. Índice nutricional. Humano.

INTRODUCTION

Oral cancer (OC) is the sixth most prevalent human cancer, and the majority is oral squamous cell carcinomas (OSCC). OC presents high morbidity and low survival rates. Cancer is a complex pathology and its incidence and survival index are closely related to social, cultural and socio-economic determinants of health (1,2) some of which are epigenetic factors such as diet (3,4). Nowadays, there is controversy in epidemiological studies about the relationship of diet and oral carcinogenesis. Some researches indicates that red meat intake or a diet poor in fruit and vegetables could increase the risk of different cancers such as OSCC (5,6), probably because certain components of diet are related to inflammatory processes. Chronic local inflammation is known to disturb the homeostatic control of cell signaling pathways, which may make normal cells become premalignant or malignant. In some kinds of cancer, the inflammatory environment is present before a malignant change occurs. However, in other kinds of cancer, malignant change induces an inflammatory environment around a primary lesion and promotes tumor development (7). And it is recognized that inflammatory processes play main roles at different stages of tumorigenesis; especially chronic inflammation predisposes to develop cancer (8). There is evidence that various dietary components could lead to acute or chronic inflammation. For this reason it is interesting to measure the degree of inflammation of the diet consumed daily by healthy people in relation to people with OSCC (7,8). The researchers of University of South Carolina’s Cancer Prevention and Control Program have developed an inflammatory index (DII), and this DII has applied in different kind of cancers and other diseases (9-12). However there are scarce studies about DII association with OC; and this relation yet has not been studied in Argentinian people with OSCC. Whence the aim of this study was to evaluate if there is an association between inflammatory components of diet and OSCC in adult patients, the results of this study could be used in preventive programs of OSCC.

MATERIAL AND METHODS

A case-control study 3:1, both genders, was carried out between 2012 and 2015. The filiations and type of nutritional dietary intake data were collected in medical-odonto-stomatological clinical records. Clinical data were registered in a single form by previously calibrated dentists (Kappa coefficient > 0.6). The risk lifestyle habits were assessed using the criteria of Secchi et al. 2015 (5).

All the *cases* (n = 27) were ≤ 80 years old at diagnosis (age range 23-83 years, mean 58.96 years) and were drawn from the Clinical Office of the Stomatology, Faculty of Dentistry, National University of Córdoba, Argentina. A total of 27 patients, newly diagnosed by anatomopathological analysis and classified by the International Classification of Diseases (ICD-10) codes C00 to C14, were considered eligible for the study. The subjects considered controls (n = 86) were enrolled in the same period and at the same place as the cases. They presented at the time of the survey an average age of 59.06 years with an age range between 21-86 years. They did not present neoplastic diseases, and they did not have changes in their dietary habits and / or alteration of habits such as smoking and drinking in a period of no less than 5 years. These were matched by gender and age (± 5-years) with the cases.

The risk factors were assessed according following criteria: *Smoker*: current consumption of at least one cigarette/day over a 1-year minimal period; *Alcohol*: current consumption of 2 drinks/week over a 1-year minimal period. The *workplace* (occupational exposure to carcinogens) is considering of risk if worked in risk industries such as textile, rubber, coal, dyes, leather, herbicides, automotive, plastics and chemicals. The *age* was categorized as < 45 years and ≥ 45 years; considering the major age as risk. *DII score* was considered as continuous variable or categorized into tertiles, based on controls cut points, age as continuous variable), *body mass index* calculated as BMI = weight (kg)/ height $(m)^2$ was categorized into < 25 or ≥ 25 according World Health Organization criteria (https://www.who.int/news-

room/fact-sheets/detail/obesity-and-overweight). *Education* as primary, secondary, terciary and universitary.

Dietary assessment

A food intake frequency questionnaire (quali-quantitative), validated by Navarro et al. 2001 (13), was administered to cases and controls by trained nutritionists at the stomatological clinical office after clinical examination and anatomopathological diagnosis.

This questionnaire includes two sections: a) bio-socio-cultural characteristics, anthropometric measurements and lifestyle; and b) daily food intake, evaluating dietary exposure in the 5 years prior to diagnosis for cases and before interview for controls. Additionally, a photographic food atlas also validated by Navarro et al., 2000 (14), and Nutrio software were used 1.29 for the nutritional composition analysis.

Dietary Inflammatory Index assessment (DII®)

Details of the steps involved in the DII calculation are described elsewhere (15,16). In order to compute the DII score, dietary information for each study participant was first linked to the regionally representative database, which provided a robust estimate of a mean and a standard deviation for each of the 45 parameters (i.e., foods, nutrients, and other food components) considered in the DII definition (15,16). These parameters were then used to derive the subject's exposure relative to the standard global mean as a z-score, by subtracting the mean of the regionally representative database from the amount reported, and dividing this value by the parameter's standard deviation. To minimize the effect of "right skewing", this value was converted to a centred percentile score, which was computed by doubling the raw percentile score and then subtracting 1. This score was then multiplied by the respective food parameter effect score (derived from a literature review of 1943 articles) (16). All of these food parameter-specific DII scores were then summed to create the overall DII score for every subject in the

study. DII was calculated per 1000 kcal. A higher DII score shows a pro-inflammatory dietary rich in nutrients such as saturated fat and total cholesterol; a lower DII score indicates that diet is more anti-inflammatory, enriched in nutrients as vitamins, minerals, among other antioxidant compounds (17).

Ethical aspects

This study was approved by the Research and Ethics Committee of the Ministry of Health of the Province of Córdoba (No. 1378) and all subjects signed informed consent forms. Patients who were under therapeutic medication such as corticosteroids or chemotherapy drugs that modify or alter the clinical behavior of malignant oral lesions were excluded. Patients diagnosed with other cancers, systemic diseases, chronic alcoholism and drug addiction were also excluded.

Statistical analysis

The data were statistically described using average± standard error and median value in quantitative variables or relative/absolute frequencies in qualitative variables. Kruskal-Wallis test for testing Ho: median consumption is equal between cases, and controls were performed because normal distribution of data was not proved. The measure of association (odds ratio (OR) and its 95% confidence interval (CI 95%) were estimated by constructing the logistic regression model between the presence of disease and the DI index (DII). For all tests, $p < 0.05$ was set for statistical significance. The software Stata Statistical Software, version 13 (Stata Corp LP -2014- College Station, TX 77845, USA) was used for all analysis.

RESULTS

Patients with Oral Squamous Cell Carcinoma (OSCC) showed lesions in various oral cavity sites - tongue, palate, lip, oral mucosa, gum and floor of

the mouth. The most of the patients were diagnosed within one year of the first symptoms appearing.

The demographic characteristics of the study population are shown in table I. Cases and controls showed similar distributions of the biodemographic characteristics and the risk factors in the case-controls studied were observed (Table I).

A significant increase of the median intake of fat and protein was observed (Table II). Other dietary components such as cholesterol, iron, monosaturated fatty acid (MUFA), polyunsaturated fatty acid (PUFA), omega-6, omega-3, selenium, vitamin B6, and vitamin E showed a significant increase in cases compared to the control group (Table II). The ratio omega 6/omega 3 of control (average 8.49 ± 3.9) patients was significant lower respect to case patients (average 10.44 ± 4.9) ($p = 0.025$, Mann Whitney test) (Table II).

The median of DII was 0.81, range -2.24 to 3.72 in all population. On the other hand, it was observed a significant association between the DI index and OSCC by logistic regression (OR 1.69, 95% CI [1.18-2.43]) adjusted by alcohol and tobacco consumption from continuous DII (Table III). Similar result was observed with categories of DII based on tertiles (Table III).

DISCUSSION

The results of this study showed a high significant daily intake of *fat, and protein* in patients with OSCC, respect to control subjects. These findings match our own previous studies, which demonstrated an increased intake of macronutrients and daily energy (5). A few years ago, it is suggested that factors as the increase and bioavailability of growth factors, the increase in estrogen and factors that modify metabolism, the adipocytokine levels, low-grade inflammation, cellular oxidative stress, and alterations of the microbiome can be recognized associated to carcinogenesis (18). It has been demonstrated that NFκB signaling, expression of COX-2, TNFα, and IL-1β are all increased in the mammary glands and visceral fat of obese female mice obtained through genetic and diet-induced obesity models; these molecules

participate in chronic inflammation process, which has been linked to various epithelial malignancies (18,19).

A highly significant intake of *iron* was observed in patients with OSCC in this study. This observation matches other studies demonstrating a relationship between this micronutrient and the presence of multiple cancer types, such as lung cancer, breast cancer, prostate cancer, colorectal cancer, hepato-cellular cancer, pancreatic cancer, hematological cancers, renal cell carcinoma and melanoma (5,21). In these studies, abnormal iron contents or deficiency in iron uptake, utilization and storage have been reported. One explanation is that the iron has important functions in mammalian cells, such as cell proliferation, metabolism and growth. The iron- and heme-containing proteins, including enzymes involved in DNA stability and cell cycle progression, mitochondrial enzymes implicated in respiratory complexes, and detoxifying enzymes such as peroxidase and catalase, controlled these processes. For example, the heme-iron can promote endogenous production of nitrous compounds and catalyze free radical formation, leading to oxidative cell damage (21).

We also observed an increase of vitamin B6 intake in patients with OSCC. Vitamin B6 takes part in a plenty of coenzyme reactions; and may influence on one-carbon metabolism-related DNA synthesis and methylation, reducing inflammation, cell proliferation and oxidative stress; in addition it has observed related to the risk of cancers like colorectal (22).

Plus, a high intake of *omega-6* and *PUFA* was observed in this study in patients with OSCC compared with control subjects. Omega-6 metabolism produces arachidonic acid (AA), which makes inflammatory prostaglandins and lipoxins by oxidation. In contrast, sources of omega-3 have anti-inflammatory activities (23). There is evidence that food components as α-linolenic acid, omega-3 and omega-6 PUFAs, conjugated linoleic acid, butyrate, curcumin, resveratrol, genistein, vitamin A, vitamin D, etc., can regulate some points of inflammatory process (24).

Our results showed that the higher value of ratio omega 6/omega 3 in oral cancer patients, probably it was related to major intake of omega-6. Our previous experimental work showed that the tumor of DMBA-induced in mouse fed of chia oil (enriched omega-3) reduced the ω−6/ω−3 ratio and decreased the tumor development. The relationship between omega 6 and omega 3 could modify the action of carcinogenic factors and decrease the risk of oral cancer development (25). In general, western populations the ratio of PUFAs ω-6/ω-3 varies between 10:1 to 20-25:1, while in populations such as Japanese this ratio of 4:1. *In vivo* studies such as *in vitro* in animals have shown that the balance between the ω-6 and ω-3 PUFAs has an impact on the development of cancers such as prostate cancer (25). In human feeding studies with fish or fish oil, EPA and DHA partially replace ω-6 PUFAs, especially AA, probably in the membranes of all cells. In Western diets the amount of ω-6 is greater than in others and therefore the amount of eicosanoids that are obtained from the metabolic pathway of AA, are in greater quantities than those produced by the route of the PUFAs ω-3. It is known that LA and ALA are not exchangeable compounds that compete for Δ6-desaturase, an enzyme that participates in the elongation of the hydrocarbon chains of PUFAs. In addition, it is known that the activity of desaturases Δ6- and Δ5 are the main factor controlling the conversion of LA from diet to AA (25).

Furthermore in our study we observed *selenium* (Se) increased in the intake of patients with OSCC. Experiments *in vivo*, *in vitro*, and in healthy persons have shown that Se is involved in the regulation of epigenetic mechanisms. These studies have determined that high exposure to Se leads to inhibition of DNA methyltransferase activity; affects methylation of specific tumor suppressor genes, among other pathways studied (26).

Several of the dietary components observed in this study participate in epigenetic events such as vitamin B6, PUFA omega 6 and omega 3, Se, among others. The dietary modulation of the epigenome is related to the processes of the role of the metabolism of a one-carbon. Methylation

reactions catalyzed by the enzyme methyltransferases depend on a set of methyl-S-adenosylmethionine (SAM) amino acids in the human body. Methyl-tetrafolate is a methyl donor group and converts homocysteine to methionine. Then this methionine activates SAM by means of methionine adenosyltransferase, adding a methylated cytosine group. This addition of the methyl group is known as the metabolism of a carbon and is a complex process that can be affected by several of the dietary factors among which can be mentioned folate, methionine and several vitamins of group B (B2, B6 and B12). This is why the factors consumed in the diet related to the methyl group can participate in the epigenetic changes (27-30).

Our study showed relationship between the *DII* and risk of OSCC. The other cancers such as gastric, prostate and colorectal show this relationship (31-33). It is known that inflammation is associated with the malignancy development of most cancers; and the inflammatory tumor microenvironment is related to several factors such as microorganism infections, obesity, tobacco smoking, and excessive alcohol consumption, these factors increase cancer risk and encourage malignant progression (18,29,30).

The limits of the present study could be the moderately small number of enrolled patients or the lack of incorporation of specific foods and nutrients of Argentinian cooking culture into the frequency questionnaire applied. Other limitation this study may be the retrospective character of the case-control design, but the information was collected with an instruction to report on exhibit in the last 5 years.

In conclusion our results allow rejects the null hypothesis of no association between the DII, suggesting that the inflammatory components of the daily diet could be involved in development of OSCC, these results are consistent with biological mechanism described in both experimental and observational studies in OSCC and another type of cancers. There is a need for future researches about diet and its relation to oral premalignant and malignant lesions in a large sample.

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Table I. Biodemographic and risk factors characteristics studied

Characteristics		Categories	Control (n = 86) FA (FR %)	Case (n = 27) FA (FR %)	OR	95% CI		p (Fisher test)
						LB	UB	
Bio demographic	Gender	Male	46 (53.5)	15 (55.5)	Reference category			
		Female	40 (46.5)	12 (44.4)	1.32	0.45	3.87	0.6162
	Age	< 45 years	16 (18.6)	4 (14.8)	Reference category			
		≥ 45 years	69 (81.4)	23 (85.2)	1.36	0.32	5.81	0.6743
	Education	Primary	36 (41.8)	13 (48.1)	Reference category			
		Secondary	24 (27.9)	7 (25.9)	0.95	0.27	3.33	0.9332
		Terciary	12 (13.9)	2 (7.4)	0.43	0.06	3.21	0.4074
		University	14 (16.3)	5 (18.5)	0.81	0.21	3.1	0.7555
	BMI[1]	< 25	28 (32.6)	11 (40.7)	Reference category			
		≥ 25	53 (61.6)	16 (59.3)	1.30	0.54	3.14	0.5631
Risk factors	Smoker[2]	Never/ex	56 (65.1)	17 (63.0)	Reference category			
		Current	30 (34.9)	10 (37.0)	0.64	0.19	2.15	0.4676
	Alcohol consumption[3]	Never/ex	56 (65.1)	15 (55.5)	Reference category			
		Current	30 (34.9)	12 (44.4)	1.21	0.37	3.9	0.751

	Work[4]	Never	73 (84.9)	20 (74.1)	Reference category		
		Current and at least more than 5 years	13 (15.1)	7 (25.9)	2.38	0.68	8.35	0.1764

Absolute and relative % frequencies (RF calculated over total of controls or cases). p-values < 0.05 indicates a statistical significance.

[1]*Body mass index*. *BMI = weight (kg)/height (m)²*. [2]*Smoker*: current consumption of at least one cigarette/day over a 1-year minimal period. [3]*Alcohol*: current consumption of 2 drinks/week over a 1-year minimal period. [4]*Work*: one or more years of exposure to carcinogens considered risk as work in industries such as textiles, rubber, leather, herbicides, automotive, plastic, chemicals by IARC.

Table II. Macronutrients and micronutrients including estimation of DI index in both groups

Diet Compounds of DII (n = 113)	Control (n = 86)			Case (n = 27)			P (Mann-Whitney)a
	Average	SE	Median	Average	SE	Median	
Carbohydrate	305.2	133.6	280.9	343.2	109.8	334.4	0.0923

(g/day)	7	9	5	4	7		
Protein (g/day)	*107.87*	*43*	*96.3*	*129.42*	*47.85*	*118.08*	*0.025*
Fat (g/day)	*112.32*	*62.89*	*94.9*	*167.22*	*103.39*	*141.4*	*0.0057*
Energy (Cal/day)	*2766.95*	*1165.92*	*2462.74*	*3476.72*	*1305.84*	*3515.9*	*0.0055*
Colesterol (mg/day)	*415.25*	*207.56*	*376.75*	*529.75*	*235.88*	*520.41*	*0.0171*
Iron (mg/day)	*18.65*	*7.87*	*17.58*	*23.2*	*9.63*	*21.04*	*0.0233*
VitA (µg/day)	1404.81	1043.59	1039.29	1672.03	927.14	1735.57	0.1106
Riboflavin (mg/day)	2.11	0.93	1.94	2.39	1.02	2.04	0.2255
VitB6 (mg/day)	*1.29*	*0.6*	*1.25*	*1.57*	*0.59*	*1.35*	*0.0245*
VitC (mg/day)	187.34	132.91	156.11	197.91	176.32	124.43	0.8769
VitE (mg/day)	*6.21*	*4.14*	*4.85*	*10.66*	*8.06*	*8.43*	*0.0021*
Selenium (µg/day)	*106.59*	*51.88*	*95.87*	*142.98*	*47.34*	*145.72*	*0.0014*
Zinc (mg/day)	11500	6546.94	8849.61	13506.05	6958.74	11616.66	0.0789
Etanol (g/day)	13.13	23.62	1.99	32.32	56.47	0.9	0.9836
Fiber (g/day)	15.41	6.58	15.5	17.53	6.06	16.62	0.0885
Tea (cc/day)	66.28	127.41	0	62.35	115.61	0	0.6721
Omega 3 (g/day)	*1.54*	*0.89*	*1.26*	*2.32*	*1.43*	*1.59*	*0.0095*
Omega 6 (g/day)	*12.11*	*6.51*	*10.51*	*23.91*	*21.47*	*16.85*	*0.0008*
Saturat fat (g/day)	*47.31*	*28.91*	*39.04*	*60.56*	*33.12*	*55.33*	*0.0205*
Garlic (g/day)	0.03	0.14	0	0.04	0.17	0	0.9371
Onion (g/day)	10.7	10.46	7.14	11.23	14	3.57	0.2624
MUFA (g/day)	*42.81*	*25.26*	*35*	*59.99*	*36.61*	*48.33*	*0.0067*

PUFA (g/day)	*13.64*	*7.18*	*12.12*	*26.23*	*22.56*	*17.9*	*0.0007*
Caffeine (mg/day)	162.22	137.06	115.19	154.78	196.53	86.25	0.1881
Omega 6/omega3 ratio	*8.49*	*3.9*	*7.47*	*10.44*	*4.87*	*8.94*	*0.025*

Letters in italic indicate statistical significance at $p < 0.05$. *MUFA: monosaturated fatty acid; PUFA: polyunsaturated fatty acid. [a]Mann Whitney U test for proving Ho: median are equals between cases and controls.*

Table III. The relationship between DII and oral squamous cell carcinoma from Logistic Regression model

DII	Population	Crude OR	(95% CI)	p-value	Adjusted[a] OR	(95% CI)	p-value
Continuous	113	1.68	(1.20-2.35)	0.0027*	1.69	(1.18-2.43)	0.0043*
T1 (< 0.37)	48/113	1 (Ref.)			1 (Ref.)		
T2 (0.37-1.69)	34/113	2.53	(0.92-6.96)	0.0728	2.74	(0.97-3.60)	0.0577
T3 (≥ 1.69)	31/113	19.66	(2.47-156.50)	0.0049*	18.46	(2.28-149.72)	0.0063*

OR: odd ratio; CI: confidence interval. [a] Adjusted by alcohol and tobacco consumption. T1: DII values lower than the first tertile; T2: DII values between 2nd and 3rd tertile; T3: DII values higher than 3rd tertile. Categories based on DII tertiles of controls. *Indicate statistical significance at $p < 0.05$.