RESEARCH COMMUNICATION

Nutrient-derived Dietary Patterns and Risk of Colorectal Cancer: a Factor Analysis in Uruguay

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Abstract

In order to explore the role of nutrients and bioactive related substances in colorectal cancer, we conducted a case-control in Uruguay, which is the country with the highest production of beef in the world. Six hundred and eleven (611) cases afflicted with colorectal cancer and 1,362 controls drawn from the same hospitals in the same time period were analyzed through unconditional multiple logistic regression. This base population was submitted to a principal components factor analysis and three factors were retained. They were labeled as the meat-based, plant-based, and carbohydrates patterns. They were rotated using orthogonal varimax method. The highest risk was positively associated with the meat-based pattern (OR for the highest quartile versus the lowest one 1.63, 95 % CI 1.22-2.18, P value for trend = 0.001), whereas the plant-based pattern was strongly protective (OR 0.60, 95 % CI 0.45-0.81, P value for trend <0.0001. The carbohydrates pattern was only positively associated with colon cancer risk (OR 1.46, 95 % CI 1.02-2.09). The meat-based pattern was rich in saturated fat, animal protein, cholesterol, and phosphorus, nutrients originated in red meat. Since herocyclic amines are formed in the well-done red meat through the action of amino acids and creatine, it is suggestive that this pattern could be an important etiologic agent for colorectal cancer.

Keywords: Nutrient patterns - meat-based - plant-based - carbohydrate - colorectal cancer - well-done meat

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Introduction

Colorectal cancer is the third malignancy among the Uruguayan population, following lung and breast cancer, representing 11 % of all cancers in this country (Barrios et al., 2010). According to a recent monograph by the World Cancer Research Fund/American Institute for Cancer Research, red meat, processed meat, alcoholic drinks, body fat, and adult attained height increase the risk of colorectal cancer (World Cancer Research Fund, 2007). In particular, beef production and consumption is an outstanding fact in Uruguay, which is the leading country in beef production in the world (Matos and Brandani, 2002). This could explain the high incidence of colorectal cancer in Uruguay.

Most studies have consistently found that the intake of red and processed meat increases the risk of this malignancy (Norat et al., 2005; Willett et al., 1990; Norat et al., 2002; Giovannucci et al., 1994; Tiemersma et al., 2002; Bravi et al., 2010; English et al., 2004; Sinha et al., 2001; Sinha et al., 1999; Le Marchand et al., 2002; Nowell et al., 2002). More recently, studies using exploratory factor analysis, have found that the Western pattern, characterized by red meat, processed meat, and the intake of eggs, has been positively associated with an increased risk of colon cancer (Randall et al., 1992; Slattery et al., 1998; Terry et al., 2001; Fung et al., 2003; Kim et al., 2005; Kesse et al., 2006; Dixon et al., 2004; Flood et al., 2008; Butler et al., 2008). To our knowledge, the role of nutrients in colorectal cancer has been explored through factor analysis in only one study conducted in Italy (Bravi et al., 2010). For this reason we decided to conduct a nutrient-derived factor analysis for colorectal cancer.

Materials and Methods

Selection of cases

In the time period 1996-2004 all the newly diagnosed and microscopically confirmed adenocarcinomas of the large bowel were considered eligible for this study. The initial number of cases was 625 and 14 refused the interview, leaving a final number of 611 cases (response rate 97.7 %), discriminated as follows: 320 with colon cancer (52.4 %) and 291 with rectal cancer (47.6 %).

Selection of controls

In the same time period and in the same hospitals, all

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the patients with non-neoplastic diseases, not related to tobacco smoking and alcohol drinking were considered eligible for the study. The initial number was 1403 patients and 41 of them refused the interview leaving a final number of 1362 controls (response rate 97.1 %). The controls presented the following conditions: eye disorders (347 patients, 25.5 %), abdominal hernia (265, 19.5 %), urinary stones (132, 9.7 %), diseases of the skin (120, 8.8 %), injuries (111, 8.1 %), varicose veins (100, 7.3 %), acute appendicitis (84, 6.2 %), hydatid cyst (71, 5.2 %), blood disorders (63, 4.6 %), fractures (29, 2.1 %), gallbladder stones (23, 1.7 %) and articular disorders (17, 1.2 %).

Interviews and questionnaire

All the participants (cases and controls) were interviewed in the hospitals by two trained social workers. No proxy interviews were accepted. The participants were administered a structured questionnaire which presented the following sections: sociodemographics (age, sex, residence, education, income), a complete occupational history based in the last four jobs and its duration, self reported weight and height five years before the date of the interview, family history of colorectal cancer in the first-degree relatives (mother, father, sisters, brothers), a complete smoking history (age at start, age at quit, number of cigarettes smoked per day, type of tobacco, type of cigarette), a complete drinking history (age at start, age at quit, number of glasses drunk per day, type of alcoholic beverage), a complete history of non-alcoholic beverages (mate, coffee, tea, soft drinks), menstrual and reproductive events, and a food frquency questionnaire (FFQ) on 64 items. This FFQ allowed the estimation of total energy intake and was considered as representative of the Uruguayan diet.

Nutrients and related-bioactive substances

The study included the following nutrients: animal protein, vegetable protein, saturated fatty acids, monounsaturated fatty acids, linoleic acid, alpha-linolenic acid, cholesterol, starch, dietary fiber, glucose, fructose, beta-carotene, lutein, beta-cryptoxanthin, vitamin C, vitamin E, folate, pyridoxine, cianocobalamine, thiamine, riboflavin, phytosterols, nitrates, nitrites, calcium, iron, sodium, and phosphorus. These nutrients were homogeneous by sex, and the P value for homogeneity showed a range between 0.06 for calcium to 0.99 for vitamin C. Also we have compared standardized nutrients and logarithmic transformation of nutrients and the results were very similar. Therefore, we used logarithmic transformation of the nutrients for subsequent analyses.

Statistical analysis

The nutrients were submitted to a factorability exploration with positive results. Therefore, these nutrients were included in a factor analysis among controls (Gorsuch, 2008; Mulaik, 2010). Using the Scree plot we retained 3 factors obtained through principal components factor analysis for which the communalities for most of the nutrients were close to one. All factors were rotated using the orthogonal varimax method and were then scored using Thomson's regression method (Thomson, 1951). The results of the scores were applied to cases and controls.

Table 1. Factorability of Nutrients

Bartlett test of sphericity <0.0001	
Overall sampling adequacy (Kaiser-Meyer-Olkin statistic): 0.86	
Middling	0.70-0.79
	Starch, Glucose, Fructose
Meritorious	0.80-0.89
	Vegetable protein, Saturated fat, Monounsaturated fat, Dietary fiber, Linoleic acid, Cholesterol, Lutein, Beta-cryptoxanthin, Folate, Pyridoxine, Cyanocobalamine, Thiamine, Riboflavin Phytosterols, Nitrites, Iron, Calcium
Marvelous	0.90+
	Animal protein, Alpha-linolenic Alpha-carotene, Vitamin C, Vitamin E Phosphorus, Nitrates

The scored patterns were categorized in quartiles following the distribution of the controls and were included into the final model, after adjusting for age, sex, residence, education, family history of colorectal cancer, body mass index, smoking intensity, years of smoking, alcohol drinking, and total energy intake (Rothman et al., 2008). Since all patterns were conditional on each other, they were included together in the final model. All the calculations were performed using the software STATA®, release 10 (StataCorp, 2007).

Results

The distribution of cases and controls by sociodemographic variables, family history of colorectal cancer among first-degree relatives, smoking, and alcohol drinking. The factorability of the nutrients (Table 1) showed an overall sampling adequacy of 0.86 and five nutrients (animal protein, linoleic acid, alpha-carotene, vitamin C, vitamin E, nitrate and phosphorus) displayed "marvelous" adequacy. Therefore all nutrients were adequate for performing factor analysis.

The factor loading matrix for controls is shown in Table 2. Factor 1 presented high loadings for animal protein, saturated fat, monounsaturated fat, linolenic acid, cholesterol, cianocobalamine, and phosphorus and was labeled as the meat-based pattern. This factor explained 27.7 % of the variance. Factor 2 showed high loadings for vegetable protein, glucose, fructose, vitamin C, vitamin E, phytosterols, and nitrates. This factor was labeled as the plant-based pattern and explained 22.5 % of the variance. Factor 3 displayed high loadings for starch, dietary fiber, folate, thiamine, and iron and was called the carbohydrates pattern, explaining 19.3 % of the variance. The complete model explained 70 % of the total variance. Furthermore, Cronbach alpha displayed an excellent reliability coefficient of 0.95.

The Spearman rank correlations between dietary patterns and foods are shown in Table 3. The meat-based pattern was positively correlated with red meat (rho=0.82), processed meat (rho=0.42), dairy foods (rho=0.37), fried

Table 2. Factor Loading Matrix Among Controls

Nutrient	Meat-based Factor 1	Plant-based Factor 2	Carbohydrate Factor 3
Animal protein	**0.94**	0.03	0.10
Vegetable protein	0.08	0.76	0.32
Saturated fat	**0.96**	0.02	0.15
MUFA 2	**0.94**	-0.02	0.18
Linoleic acid	0.53	0.08	0.41
Linolenic acid	**0.90**	0.14	0.19
Cholesterol	**0.85**	0.00	0.17
Starch	0.17	0.27	**0.75**
Dietary fiber	0.06	0.20	**0.88**
Glucose	-0.01	**0.84**	0.05
Fructose	-0.04	**0.76**	-0.01
Beta-carotene	0.04	0.56	0.30
Lutein	0.04	0.63	0.19
Beta-cryptoxanthin	-0.00	0.60	-0.00
Vitamin C	0.13	**0.82**	0.22
Vitamin E	0.35	0.67	0.38
Folate	0.28	0.42	**0.78**
Pyridoxine	0.57	0.51	0.35
Cobalamine	**0.92**	-0.03	0.05
Thiamine	0.21	0.03	**0.93**
Riboflavin	0.63	0.09	0.68
Phytosterols	0.06	**0.84**	0.15
Nitrates	0.06	**0.70**	0.24
Nitrites	0.37	0.42	0.08
Calcium	0.49	0.28	0.25
Iron	0.51	0.05	0.77
Phosphorus	**0.75**	0.19	0.50
Variance (%)	27.7	22.5	19.3
Cumulative variance (%)	27.7	50.2	69.6

[1]Loadings higher than 0.69 are bold; [2]Monounsaturated fatty acids

eggs (rho=0.32) and total eggs (rho=0.35). On the other hand, the plant-based pattern was directly associated with raw vegetables (rho=0.48), cooked vegetables (rho=0.42), total vegetables (rho=0.61), citrus fruits (rho=0.59), other fruits (rho=0.60), total fruits (rho=0.74), and total vegetables and fruits (rho=0.88). Finally, the

Table 3. Spearman Rank Correlations Between Nutrient Patterns and Food Groups

Food groups	Meat-based	Plant-based	Carbohydrates
Red meat	**0.82**	-0.06	0.07
Beef	**0.66**	-0.10	0.04
Lamb	**0.33**	0.03	-0.02
White meat	-0.04	0.20	-0.07
Poultry	0.02	0.13	0.22
Fish	-0.09	0.20	0.12
Processed meat	**0.42**	-0.14	-0.09
Cheese	0.24	0.09	0.01
Butter	0.19	0.05	0.07
Whole milk	0.24	0.03	0.11
Dairy foods	**0.37**	0.08	0.11
Boiled eggs	0.25	-0.08	-0.01
Fried eggs	**0.32**	-0.16	0.08
Total eggs	**0.35**	-0.16	0.03
White rice	0.08	0.04	0.23
White bread	0.04	-0.26	**0.80**
Polenta	0.01	0.25	0.09
Pasta	-0.07	0.14	0.24
Total grains	0.08	-0.17	**0.89**
Raw vegetables	-0.00	**0.48**	-0.05
Cooked vegetables	0.17	**0.42**	0.36
Total vegetables	0.13	**0.61**	0.26
Citrus fruits	-0.00	**0.59**	-0.01
Other fruits	0.04	**0.60**	0.00
Total fruits	0.03	**0.74**	0.00
All plant foods	0.09	**0.88**	0.18

[1]Correlations higher than 0.29 are typed in bold

carbohydrates pattern was correlated with white bread (rho=0.80), total grains (rho=0.89) and cooked vegetables (rho=0.36).

The odds ratios of colorectal cancer for scored patterns are shown in Table 4. The meat-based pattern was positively associated with colorectal cancer (OR 1.63, 95 % CI 1.22-2.18, P value for trend=0.001), while the plant-based pattern was inversely associated with colorectal cancer (OR 0.60, 95 % CI 0.45-0.81, P value for trend <0.0001). Finally the carbohydrate pattern was not

Table 4. Odds Ratios of Colorectal Cancer for Scored Patterns[1]

Pattern	Cases/Controls	Colon		Rectum		Both sites	
		OR	95 % CI	OR	95 % CI	OR	95 % CI
Meat-based	124/340	1.0	reference	1.0	reference	1.0	reference
	146/341	1.20	0.83-1.74	1.30	0.87-1.94	1.25	0.93-1.67
	163/341	1.44	1.00-2.06	1.45	0.97-2.17	1.44	1.08-1.92
	182/340	1.38	0.95-2.00	1.93	1.32-2.83	1.63	1.22-2.18
	P value trend	0.04		0.001		0.001	
	Continuous	1.22	1.07-1.40	1.33	1.15-1.54	1.27	1.14-1.41
Plant-based	179/340	1.0	reference	1.0	reference	1.0	reference
	190/341	1.05	0.76-1.46	0.85	0.60-1.21	0.95	0.73-1.24
	118/341	0.63	0.43-0.91	0.53	0.36-0.77	0.58	0.44-0.78
	124/340	0.58	0.39-0.86	0.63	0.43-0.92	0.60	0.45-0.81
	P value trend	0.0001		0.002		<0.0001	
	Continuous	0.79	0.69-0.89	0.81	0.71-0.93	0.80	0.72-0.89
Carbohydrates	140/340	1.0	reference	1.0	reference	1.0	reference
	147/341	1.07	0.73-1.55	1.09	0.74-1.59	1.08	0.81-1.45
	153/341	1.10	0.76-1.58	1.12	0.76-1.64	1.12	0.83-1.49
	171/340	1.46	1.02-2.09	1.10	0.75-1.61	1.28	0.96-1.70
	P value trend	0.04		0.58		0.09	
	Continuous	1.08	0.95-1.25	1.07	0.95-1.22	1.08	0.98-1.20

[1]Adjusted for age, sex, residence, urban/rural status, education, family history of colon cancer among first-degree relatives, body mass index, smoking intensity, smoking duration in years, alcohol drinking, and total energy intake

Table 5. Odds Ratios for Right and Left Colon Cancers[1]

	Proximal colon		Distal colon		
N° of cases	90		148		
Pattern	OR	95 % CI	OR	95 % CI	
Meat-based	1.04	0.85-1.29	1.35	1.10-1.64	0.06
Plant-based	0.72	0.60-0.88	0.89	0.74-1.08	0.11
Carbohydrates	1.02	0.82-1.27	1.09	0.88-1.34	0.68

[1]Adjusted for age, sex, residence, urban/rural status, education, family history of colon cancer among first-degree relatives, body mass index, smoking intensity, smoking duration, alcohol drinking, and total energy intake

associated with colorectal cancer (OR 1.28, 95 % CI 0.96-1.70). Colon cancer displayed moderately elevated risk for meat-based pattern (OR 1.38, 95 % CI 0.95-2.00, P value for trend=0.04). On the other hand, the plant-based pattern was inversely associated with colon cancer risk (OR 0.58, 95 % CI 0.39-0.86, P value for trend=0.0001). Finally, colon cancer was associated with the carbohydrates pattern (OR 1.46, 95 % CI 1.02-2.09, P value for trend=0.04). As happened with colon and colorectal cancers, rectal cancer was strongly protective for the plant-based pattern (OR 0.57, 95 % CI 0.39-0.84, P value for trend=0.002). Also, rectal cancer was strongly and positively associated with meat-based pattern (OR 1.93, 95 % CI 1.32-2.83, P value for trend = 0.001). On the contrary, the carbohydrates pattern was not associated with rectal cancer (OR 1.10, 95 % CI 0.75-1.61, P value for trend = 0.58).

Odds ratios for proximal and left colon for nutrient patterns are shown in Table 5. Whereas the meat-based pattern was not associated with risk of proximal colon (OR continuous 1.04, 95 % CI 0.85-1.29), the left bowel showed a continuous OR of 1.35 (95 % CI 1.10-1.64) resulting in a P value for heterogeneity of 0.06. Neither the plant-based nor the carbohydrates patterns were heterogeneous.

Discussion

According to our results, the meat-based and plant-based patterns were significantly associated with colorectal cancer. Whereas the pattern labeled meat-based was positively associated with an increased risk, the plant-based pattern was significantly protective. In the study of Bravi et al (2010) an increased risk for the carbohydrates pattern was found. In our study, this pattern was positively associated with colon cancer, but not with rectal cancer and colorectal cancer. The pattern matrix of the above quoted Italian study (Bravi et al., 2010) and the present study were submitted to a detailed comparison. The Italian study showed high loadings of vegetable protein, starch, and sodium, whereas our carbohydrates pattern loaded highly on dietary fiber, folate, thiamine, vegetable protein, starch, and sodium. The high loading of folate and dietary fiber, observed in our carbohydrates pattern could explain these lowest risks for rectal and colorectal cancers, acting as a counterbalance for the putative risk association of starch. It is clear that we were not able to replicate entirely the starch-like pattern of the previous study. Also, we did not replicate the animal product pattern found by the Italian authors, since our findings for the meat-based pattern loaded high on animal protein, saturated fat, polyunsaturated fats, vitamin B12, and phosphorus and was positively associated with colon cancer and rectal cancer. On the light of these considerations, we think that there are certain differences between dietary styles of Italian and Uruguayan populations: while the former is Mediterranean-type, the latter is Western-type. Red meat intake is substantially different: among Italians it is low and among Uruguayans is high. It would be more likely for the meat-based pattern to become a risk factor for Uruguayans than the animal pattern for the Italians. Besides, in Italy the starch-like pattern has a main source in pasta, but in Uruguay is based on bread. These aspects explain partially why resulting patterns from both studies could be not strictly comparable.

Some authors have questioned the use of nutrients and related bioactive substances, since they are not related to public health recommendations (Martínez et al., 1998). Nevertheless, the study of nutrients could be important in order of clarify the etiology of a given disease, in this case colorectal cancer. Furthermore, as aptly stated by Bravi et al (2010), nutrients are continuous at difference with foods (originated in a food-frequency quationnaire), which are generally discrete. This is an important advantage for performing factor analysis (Gorsuch, 2008; Mulaik, 2010).

Several studies have suggested that heterocyclic amines, present in well-done red meat, could be major etiologic agents for colorectal cancer (Sinha et al., 1999; Sinha et al., 2001; Le Marchand et al., 2002; Nowell et al., 2002). In particular, the studies by Sinha et al (1999; 2001; 2002; Nowell et al., 2002) strongly suggest the role of heterocyclic amines as major etiologic agents for colon cancer. Uruguayan population mainly consumed well-done red meat, rich in heterocyclic amines resulting from the effect of aminoacids and creatine. Our study supports these viewpoints, since the so-called meat-based pattern showed an increased risk of colorectal cancer.

Weisburger has suggested that whereas heterocyclic amines could be initiators, fats probably act as promoters (Weisburger, 2002). Our meat-based pattern displayed high loadings for animal protein, saturated fat, monounsaturated fat, and polyunsaturated fat, supporting the suggestion made by this author.

The mechanisms of carcinogenicity of heterocyclic amines are mostly unknown. It has been suggested that a greater percentage of MeIQx may be converted to metabolites such as the N-hydroxy derivative when CYP1A2 activity is higher. Before they can bind to DNA, heterocyclic amines require metabolic activation through N-oxidation by cytochrome P450 enzymes of the 1A family, followed by O-esterification by N-acetyltransferase-2 (NAT2) (Le Marchand et al., 2002). These authors found that having preference for well-done meat markedly increased risk of colon cancer only in individuals with both the rapid NAT2 and CYP1A2 phenotypes.

Nevertheless, as is aptly suggested by Sinha (2002), long term biomarkers such as DNA-adducts which reflect intake over months are needed for future epidemiologic studies.

The present study has limitations and strengths. The major strengths are related to the high response rate both for cases and controls as well as the microscopical validation of carcinomas of the colon. Furthermore, both cases and controls were drawn from the same hospital, which implies not only that they were treated in similar conditions and in the same hospital, but also that they belong to similar (low) socioeconomic strata of society. The present study is limited by the possibility of major biases like recall bias. This limitation is related to all retrospective studies, unlike prospective cohort studies.

In summary, the present case-control study showed increased risks associated with the meat-based pattern. This finding supports the importance of red meat and processed meat in the etiology of colorectal tumors. The plant-based pattern, which displayed high loadings of fructose, glucose, vegetable protein, vitamin C, phytosterols, and nitrates, is a source of nutrients mainly originated in plant foods, and, like the prudent pattern, is a diet rich in protective nutrients. Finally, the carbohydrates pattern increased moderately the risk of colon cancer, but was not associated with rectal and colorectal cancers.

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