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## **Original Article**

# Diet and Squamous Cell Carcinoma of the Oral Cavity and Pharynx: A Case-Control Study

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#### Abstract

Objective: To investigate if an association exists between diet and oral squamous cell carcinoma (OSCC) in a Brazilian population. Material and Methods: This populationbased study investigated food groups intaken by means of a quantitative food frequency questionnaire (QFFQ) validated for use in Brazil. It was included 665 individuals, being 133 cases of OSCC, selected from reference hospitals for cancer in Paraíba and 532 being part of a control group, paired by age, gender, place and smoking habit took part in the study. Food consumption related to cases and control groups were evaluated by QFFQ. The Chi-square test was carried out in order to verify if there was association between the categorical variables. The level of significance was 5%. Conditional logistic regression was performed by the Enter method in order to verify the odds ratio of independent variables that predict OSCC. Results: It was found statistical association between OSCC and: processed and variety meats (p=0.048), dairy products (p<0.001), oils and fats (p<0.001) and alcoholic beverages (p<0.001). The high consumption of cereals and tubers (OR=0.53; CI95%: 0.29-0.96; p=0.0039) acted as protection factor for OSCC. Conclusion: Data of the present research suggest that the ingestion of animal fat, food rich in salt and refined carbohydrates were associated with OSCC cases.

Keywords: Carcinoma; Case-Control Studies; Diet; Food and Nutrition.



#### Introduction

Oral cancer is a wide-ranging category of location for neoplasms and includes tumors of different etiologies and histopathological profiles, although the vast majority relate to squamous-cell carcinoma (SCC) [1]. Squamous-cell carcinoma of the oral cavity and pharynx (OSCC) is a malign neoplasm originating in the lining of the epithelium, and is considered to be the most common malign neoplasm of the oral cavity [2].

Very few cases of OSCC are exclusively due to hereditary, family or ethnic and intrinsic factors. Only 5 to 10% of cases of cancer are due to genetic mutations and the remaining 90 to 95% are associated with lifestyle factors or with environmental agents related to the process of urbanization and technological development, such as tobacco usage, diet, alcohol, exposure to the sun [3,4].

Disequilibrium and/or food shortage are responsible for 11 to 15% of oral and pharyngeal cancers [5]. Most people consume a wide variety of foods, with a combination of diverse nutrients, whose patterns of diet often change over time according to culture, socioeconomic conditions and geographical location in the various regions of Brazil [6].

The diet of the people of the Northeast region of Brazil has its roots sunk in the population of the countryside: rich in grain and cereals, legumes, tubers and roots (mainly cassava), a little meat or a small quantity of other foods of animal origin. The so-called "nutritional transition" caused a change in "traditional" eating patterns based on the consumption of grain and cereals, which has been gradually superseded by an eating pattern that has large quantities of foods of animal origin, fats, sugars, processed foods and relatively small amounts of complex carbohydrates and fiber, eating habits deemed to be potentially favorable to the development of oropharyngeal cancer [7].

An inverse relationship between the risk of developing oral and pharyngeal cancer and the consumption of fruit and vegetables has been observed in various case-control studies [8-10]. Moreover, the relationship was even more pronounced for the oral cavity than for the oropharynx/hypopharynx and larynx [11]. Compared to the other food groups, the results of the literature, based purely on case-control studies are scant and should be interpreted with caution.

Although advances have been made in terms of an understanding of the factors associated with cancer, its incidence is forecast to rise over the coming decades. There is a need for effective prevention strategies, remembering that eating habits are acknowledged to be modifiable factors that could have an influence on cancer risk [12]. Thus, by virtue of the high incidence and mortality through cancer, as well as the involvement of environmental factors in the etiopathogenesis of the lesion, the aim of the present study was to investigate if an association exists between diet and OSCC in a Brazilian population.

# Material and Methods

Location of Study



This is a population-based case-control study conducted in the only two centers of reference in the state of Paraíba, located in Campina Grande and João Pessoa at Paraíba state, located in the northeast region of Brazil, it has a population of 3,766,528, distributed over an area of 56,469,778 km2.

## Study Population

The study population consisted of individuals suffering from OSCC and non-sufferers, adults and elderly, aged between 29 and 92, resident in the state of Paraíba, selected between August 2011 and March 2012.

The case group was selected from qualifying patients (those who had not begun adjuvant treatment) from two hospitals, with the cancer diagnosis classified under codes C00 to C06 (oral cavity) and C09 to C14 (oropharynx) in accordance with the International Classification of Diseases (ICD-10). For each individual identified as a case (with histopathological confirmation of OSCC) the referral of four neighbors of similar age was requested (to within five years, either way), same sex, socioeconomic situation, similar profile, to make up the control group.

The control group was composed of clinically healthy individuals who were paired with individuals who make up the case group in terms of smoking habits, and they should not have a history or suspicion of squamous-cell carcinoma or any other type of malign neoplasm in the oral cavity or pharynx.

The decision was made to evaluate four control groups, with the aim of controlling confounding and increasing the power of the study, increasing the number in relation to the cases by a ratio of 1 to 4. The size of the sample was calculated in the two-tailed test to detect an Odds Ratio (OR) of 2.0 between the cases and controls, in order to obtain the 25% proportion of exposed cases, 14% proportion of exposed controls, a power of 80% difference between the groups, at a level of significance of 5%. These parameters were based on a previous case-control study on adults and elderly subjects in Brazil [13].

The online application (http://www.lee.dante.br/index.html) was used for the calculation of sample size, resulting in a minimum sample of 133 cases and 532 controls, assuming four controls per case. In order to compensate for possible dropouts, 50% of individuals were added to the case group and 22% to the control group, amounting to 848 individuals to be invited and screened for eligibility criteria. Excluded from the research study were individuals in the case group who had one or more of the following characteristics: patients with recurring OSCC; who were in adjuvant therapy prior to surgery; with a prior history of oral or pharyngeal cancer or other types of cancer; cases of cancer classified as C00.0-C00.2 (external lip), C07-C08 (salivary glands), C11 (nasopharynx) and C45-C49 (malign neoplasms of mesenchymal origin). The exclusion of these cases was based on the literature, which maintains that cancers in these sites do not share the same risk factors as the other regions of the oral cavity and pharynx [13].



#### Data Collection

The methodological tool selected to record the information was a face-to-face interview with the individuals in the case and control groups, using a pre-designed form as a guide, composed of two sections including socio-demographic-cultural data, habits and an inquiry into diet.

The research team was composed of a dentist (principal researcher) and five dental academics (field researchers) who, after calibration, visited a total of sixty-seven municipalities to collect data from the control groups.

The calibration exercise was carried out on 20 oral cancer patients (lesion located on the external lip) at the cancer reference hospital located in the Paraíba state capital. A second dentist (supervisor), who did not participate in the data collection, served as the gold standard with the aim of controlling quality and the replication of observations.

#### Evaluation of Diet

The food consumption was evaluated by Quantitative Food Frequency Questionnaire (QFFQ), developed and validated by a previous study [14]. The QFFQ has 68 items, which were divided into food groups, according to nutritional profile, namely pasta and pastries, meat and fish, pulses and eggs, rice and tubers, milk and dairy products, sauces, vegetables, fruits, breads and biscuits, alcoholic drinks, sweets and desserts. For this questionnaire, patients reported the frequency of consumption by the number of times a day, week, month or year, in addition to portion, small, medium, large or oversized size. An interviewer well trained for this activity was responsible for applying the QFFQ.

For the analysis, the food contained in QFFQ were grouped in 20 categories, according to the similarity of nutrient content. The categories were: 1) pasta and pastries: macaroni or lasagna, pizza, pastries, 2) Cereals, flours and tubers: rice, flours, oats, cassava and couscous/polenta, 3) White meat: chicken and boiled or fried fish; 4) Red meat: Cooked beef, roasted or grille and beef liver; 5) Processed and variety meats: Ham, sausage, salami and other cold; 6) Beans: any type of beans; 7) Eggs: fried or boiled egg; 8) Breads, cakes and cookies: breads, cakes and biscuits with and without stuffing; 9) Dairy products: milk, yogurt, cheese, fruit shakes; 8) Vegetables: lettuce, tomato, kale, beetroot, carrot, cucumber; 9) Oils and fats: oil or olive oil, margarine, butter, mayonnaise; 10) Fruit and juices: orange, banana, papaya, apple, water melon, mango, pineapple, guava, natural fruit juices (cashew, myrtleberry, orange); 11) Bread and biscuits: bread, savory biscuits, sweet biscuits with or without filling; 12) Alcoholic beverages: beer, cachaça, wine; 13) Non-alcoholic beverages: coffee without sugar, sweeteners and sodas; 14) Sweets and cakes: chocolate, fruit candies, cakes or pies and ice cream.

The average size of intake portion of foods from each group were summarized in a single value for each voluntary as frequency for consumption [15]. The formula for obtaining this measure is: ( $\Sigma$  of portion of foods contained in the food group)/Number of foods from the group \* maximum frequency consumed in the QFFQ used.



#### Covariates

The independent variables (exposure variables) were listed observing three categories of reference: socio-demographic variables (marital status, color, schooling, religion, income, occupation and type of residence), confounding variables (length of time as a smoker, type of tobacco usage, frequency of use, if a passive smoker, drinking habits, length of time using liquor, type of beverage, frequency of drinking and overall alcohol consumption) and variables related to diet and to the quantitative food frequency questionnaire (QFFQ): BMI, dietary practice and food groups.

The variables most commonly associated with increased OSCC risk are tobacco usage and alcohol usage [16]. The habit of smoking was split into two categories: smokers and non-smokers. For analysis purposes the cigarette was determined two categories smokers (smokers and former smokers) and nonsmokers. The drink variable was defined in two categories: alcohol or non-alcohol.

The variable associated with dietary practice was dichotomized into: no (baseline) or yes, based on the change in the usual diet, as a result of some preexisting pathology or alteration, for example excess weight, malnourishment, hypertension or diabetes. A diet of this kind should be under the monitoring of a nutritionist and should not interfere substantially with the data to be investigated in the QFFQ, i.e. those included in the selection that were on some form of diet, had an illness with monitoring of diet, but followed a normal dietary pattern.

For the variables related to the food frequency questionnaire the mean values of consumption of each food group obtained according to the methodology mentioned above were divided into percentiles, and these percentiles were classified as low ( $\leq 50$ th percentile), medium (> 50th percentile and  $\leq 75$ ) and high consumption (> 75th percentile) in each group studied food [15].

## Statistical Analysis

The statistical analyses were performed with the statistical software SPSS® for Windows® (Statistical Package for the Social Sciences Inc., IBM) version 22.0. Initially, the variables were analyzed by descriptive statistics that provided relative and absolute frequencies, means and standard deviations. The Chi-square test was carried out in order to verify if there was association between the categorical variables. The level of significance was 5%.

Conditional logistic regression was performed by the Enter method in order to verify the odds ratio of independent variables that predict OSCC. In the non-adjusted regression, the independent variables were added and a p-value less than 0.20 was obtained in the Chi-Square test. For the adjusted model, variables that had a p-value of less than 0.05 were selected in the simple regression and the confounding variables (smoking) were considered.

### Results

This study included 133 cases and 532 controls, with mean age of 62.31 ( $\pm 11.86$ ) years-old. The socio-demographic characteristics of the cases and controls participants is shown in Table 1.



There was statistical significant association between case-control and alcoholic consumption (p<0.001) (Table 1).

Table 1. Distribution of cases and controls according to socio-demographic and behavior variables.

	C	Cases			P	
Variables	n	%	n	%	_	
Gender						
Male	85	63.90	340	63.90	0.999	
Female	48	36.10	192	36.10		
Marital Status						
Married/Cohabiting	81	61.00	393	73.90	0.003	
Widow/widower/Divorced	36	27.00	103	19.40		
Single	16	12.00	36	6.70		
Schooling						
Illiterate	58	43.60	98	18.40	< 0.001	
Until 8 years of schooling	73	54.70	430	80.80		
University (incomplete/completed)	2	1.50	4	0.80		
Family Income (U\$ 160)						
< 3 basic salaries	123	92.50	501	26.10	0.468	
> 3 basic salaries	10	7.50	31	73.90		
Smoker						
Yes	71	53.40	261	49.10	0.372	
No	62	46.60	271	50.90		
Use Alcoholic beverages						
Yes	27	20.30	260	48.90	< 0.001	
No	106	79.70	272	51.10		

There was statistical significant association between case-control OSCC and: processed/variety meats (p=0.048), cereals/tubers (p=0.043), dairy products (p<0.001), oils/fats (p<0.001) and alcoholic beverages (p<0.001) (Table 2).

Table 2. Association between consumption of foods and case or control.

Variables	Cas	ses	Cont		
	n	%	n	%	p-value
Pasta and pastries					
Low intake <sup>1</sup>	37	27.80	157	29.50	0.208
Average intake <sup>2</sup>	43	32.40	212	39.80	
High intake <sup>3</sup>	53	39.80	163	30.70	
White meat					
Low intake	38	28.60	141	26.50	0.632
Average intake	46	34.60	208	39.10	
High intake	49	36.80	183	34.40	
Red meat					
Low intake	33	24.80	140	26.30	0.383
Average intake	62	46.60	214	40.20	
High intake	38	28.60	178	33.50	
Processed and variety meats					
Low intake	42	31.60	119	22.40	0.048
Average intake	45	33.80	231	43.40	
High intake	46	34.60	182	34.20	
Pulses and eggs					
Low intake	41	30,80	153	28,80	0.864
Average intake	50	37,60	200	37,60	
High intake	42	31,60	179	33,60	



Cereals and tubers					
Low intake	24	18.00	150	28.20	0.043
Average intake	56	42.10	207	38.90	
High intake	53	39.80	175	32.90	
Dairy products					
Low intake	18	13.50	157	29.50	< 0.001
Average intake	41	30.80	223	41.90	
High intake	74	55.60	152	28.60	
Vegetables					
Low intake	41	30.80	129	24.20	0.280
Average intake	51	38.40	215	40.40	
High intake	41	30.80	188	35.30	
Oils and fats					
Low intake	50	37.60	126	23.70	< 0.001
Average intake	54	40.60	185	34.80	
High intake	29	21.80	221	41.50	
Fruit and juices					
Low intake	38	28.60	134	25.20	0.075
Average intake	43	32.30	229	43.00	
High intake	52	39.10	169	31.80	
Bread and biscuits					
Low intake	40	30.10	152	28.60	0.621
Average intake	44	33.10	200	37.60	
High intake	49	36.80	180	33.80	
Alcoholic beverages					
Low intake	35	30.30	158	29.70	< 0.001
Average intake	21	15.80	165	31.00	
High intake	77	57.90	209	39.30	
Non-alcoholic beverages					
Low intake	25	18.80	133	25.00	0.152
Average intake	44	33.60	193	36.30	
High intake	62	46.60	206	38.70	
Sweets and cakes					
Low intake	28	21.10	135	25.30	0.382
Average intake	53	39.80	220	41.40	
High intake	52	39.10	177	33.30	

A participant who has high intakes of oils and fat was 3.02 (p<0.001) times more likely to present OSCC; this odds ratio (OR) was 3.35 (p<0.001) when adjusted for other associated factors. Cereals and tubers significantly protect against OSCC, both in simple regression (OR=0.52; p=0.018) and in multiple analysis (OR=0.53; p=0.003) (Table 3).

Table 3. Logistic regression (ENTER method) considering the presence of oropharyngeal cancer (case) as the outcome.

	Non-adjusted IC (95%)				Adjusted IC (95%)			
Variables								
	OR	Lower	Upper	p-value	OR	Lower	Upper	p-value
Marital status								
No partner	1				1			
With partner	1.815	1.219	2.703	0.003	1.803	1.165	2.791	0.008
Pasta and pastries					-			
Low intake <sup>1</sup>	1				-			
Average intake <sup>2</sup>	1.162	0.715	1.888	0.545	-			
High intake <sup>3</sup>	0.725	0.451	1.164	0.183	-			
Processed and variety meats								
Low intake	1				1			
Average intake	1.182	1.127	2.914	0.014	1.703	1.016	2.853	0.043



High intake	1.396	0.866	2.252	0.171	1.359	0.789	2.341	0.269
Cereals and tubers								
Low intake	1				1			
Average intake	0.591	0.351	0.997	0.049	0.483	0.273	0.854	0.012
High intake	0.528	0.311	0.897	0.018	0.530	0.290	0.967	0.039
Dairy products								
Low intake	1				1			
Average intake	0.624	0.345	1.126	0.117	0.683	0.371	1.257	0.683
High intake	0.235	0.134	0.413	< 0.001	0.258	0.143	0.465	0.258
Oils and fats								
Low intake	1				1			
Average intake	1.359	0.870	2.124	1.359	1.534	0.939	2.504	0.087
High intake	3.024	1.821	5.021	< 0.001	3.359	1.914	5.894	< 0.001
Fruit and juices								
Low intake	1				-			
Average intake	1.510	0.929	2.455	0.096	-			
High intake	0.922	0.573	1.483	0.737	-			
Non-alcoholic beverages								
Low intake	1				-			
Average intake	0.825	0.481	1.412	0.482	-			
High intake	0.622	0.372	1.038	0.069	-			
Alcoholic beverages								
Yes	1				1			
No	3.753	2.380	5.917	< 0.001	0.697	0.431	1.127	0.141
Smoker								
No	1				-			
Yes	0.841	0.575	1.231	0.373	-			

#### Discussion

The conclusions of previous studies concerning the consumption of dairy products and the risk of OSCC are inconsistent [17]. Contrary to the results of the present study, some studies report a positive association between the consumption of milk and dairy products and the increased risk of developing oral or oropharyngeal cancer [18,19]. This discovery of risk is supported by other authors who take into consideration the importance of increased animal fat in the diet and the presence of pesticides [6]. Other authors suggest an inverse relationship between the consumption of dairy products and oral and oropharyngeal cancer, due to the presence of calcium, phosphorous, potassium, vitamins A, B and D, as well as proteins [20,21]. These authors confirm the findings of the present study in which it was found that the increase in the intake of dairy products acts as a protective factor for OSCC. These findings suggest that retinol, present in substantial quantities of milk and its byproducts, could be considered as a protective factor [22]. Several studies have reported no association between the consumption of milk and cheese and the risk of oral and pharyngeal cancer [23].

The present study demonstrates that the interpretation of a direct association between the intake of soups and doughs and the risk of developing an OSCC may be considered to be complex. Despite there being a significant association with OSCC, the intake of soups and doughs does not constitute a direct risk for the development of the aforementioned lesion. However, some authors have suggested a direct association with regard to soups, which are normally rich in salt and which can cause frequent thermal lesions if drunk at very hot temperatures, but have not observed a similar



association with doughs [24]. As far as dough is concerned (bread and macaroni), which are rich in refined carbohydrates and have negative consequences in terms of cholesterol and weight, studies have observed a direct association with the risk of colorectal cancer [25] and oral cancer [26], as established in the present study.

As for the consumption of pizza, studies have shown it to be a protective factor for neoplasms of the digestive tract. This is because pizza does not only have varying quantities of carbohydrates (50%), but also tomato sauce (20%), mozzarella cheese (20%) and olive oil (4%), as well as other toppings in a good number of cases. The beneficial influence over the neoplasms investigated could be related to the tomato or the olive oil, which were shown to be inversely related to the risk of various cancers, including those in the digestive tract and the larynx. Cooked tomatoes (and tomato sauce in particular) are rich in lycopene, a carotenoid that has been shown to have an inverse relationship with cancer of the prostate, digestive tract and various other sites [26,27]. Nevertheless, these findings have not yet been tested in relation to OSCC, so it is recommended that further studies be conducted to shed more light on its potential for protecting against lesions.

The results of this case-control study demonstrate that red meat, variety meats and processed meats are related to oral and oropharyngeal cancer. These food types may form carcinogenic agents such as nitrous components, heterocyclic amines or aromatic polycyclic hydrocarbons. These compounds have the ability to react with and/or alter DNA and may be significantly involved in the carcinogenesis of OSCC [27]. However, this study did not evaluate the relationship between meat consumption and overweight. It is likely that other compounds present in meat, or are produced according to its form of preparation is that it can influence the relationship between consumption this food with cancer.

Results from a previous study [28] suggest that meats cooked at high temperatures could cause destructive reactions between amino acids and creatine and produce carcinogenic AQPs. Polycyclic aromatic hydrocarbons (PAH) are other cancerous substances formed during the cooking of meat over intense and usually direct flame (grilling) [29]. Carcinogenic may be produced, partially on account of the high fat content of meat or as a result of the reaction of nitrite and nitrate in the body. Nitrite and nitrate may or may not be produced by meat during the cooking process, or naturally, and they are also found in food sources [28]. As for white meats, we found no association with OSCC. Fish contains high quantities of polyunsaturated fatty acids (PUFA), which are recommended in some diets as they prevent carcinogenesis [29]. On the other hand, fish does have a propensity to accumulate pollutants, which could contain carcinogenic heavy metals or organic compounds which they store mainly inside their deposits of fat [30]. Evidence concerning the consumption of poultry and the risk of developing gastric cancer is so small that conclusive results cannot be verified [30].

Eggs (a food of animal origin), as well as pulses (plant foods), contain proteins of high biological value and unsaturated fat required for a healthy diet, however in the study in question, no association was found between the consumption of these foods and the risk of developing OSCC.



No association was found between the consumption of vegetables and OSCC. This may be explained due to the residual confounding of smoking and alcohol, as smokers with higher levels of tobacco consumption and individuals with a high consumption of alcohol tend to consume less fruit and vegetables than those who do not partake of these habits [31]. Moreover, in this study, as in other, similar studies, oral and pharyngeal cancer is very rare in people who have never consumed alcohol and mainly those who have never used tobacco [31,32].

The findings of the present study in terms of the consumption of oils and sauces rich in fat (soy and butter) did show an association with OSCC, and are regarded as a risk factor with increased intake. It is known that the high intake of saturated fats, increases the formation of secondary biliary acids (carcinogens for colon and rectum), reduces immune response and increases the risk of becoming overweight or obese, particularly in the more sedentary populations, which are risk factors for various types of cancer, including that of the oral cavity or pharynx [16,24].

Amongst the more consistent findings of epidemiological studies, which have investigated oral and pharyngeal cancer and diet, are the protective effects of fruit and vegetables, in which many studies have reported inverse relationships [5,24,31]. The results found in the present study are in accordance with those of previous investigations [13,33], which showed no association between the consumption of fruit, juices and OSCC. This may have occurred due to the low consumption of fruit and juices by the population studied.

Recent studies stressed that the availability of healthy foods seems to be a problem in areas with a greater proportion of individuals with low levels of schooling and income, seeing that the socio-economic disadvantage of this vulnerable population is the higher price of food, which could be connected with low-quality diet, to the higher BMI and to the greater risk of chronic disease, including some types of cancer [34,35].

The literature has suggested a positive association between alcohol consumption and cancer. The mechanism via which alcohol is connected to the occurrence of cancer is still unclear. However, hypotheses include its ability to alter the DNA, methylation, retarding DNA repair, altering the composition of the biliary salts or inducing cytochrome P450 to activate carcinogens [36].

Around 43.6% of patients with OSCC reported consuming non-alcoholic beverages, particularly coffee and sodas. With regard to coffee, this probably occurred due to the association with tobacco usage, as around 50% of the subjects (cases and controls) reported taking this hot beverage after smoking. Nevertheless, data in the literature concerning the intake of coffee and the development of OSCC are conflicting, since some authors describe this habit as an adjuvant risk factor [17,37], while others show an inverse relationship [38,39]. In the present study, no association was found with OSCC.

Epidemiological studies of the case-control type are generally criticized for being susceptible to random (selection) error. In order to minimize the selection bias, the controls were selected from the general public, paired by sex, age group and neighborhood with the cases (final pairing), rather than hospitalized controls, paired purely on the basis of sex and age [40].



It was a methodological option to use the food recording tool (QFFQ) and not to study nutrients but rather the foods and the food groups, given the complexity of diet, and due to the findings being easily transformed into recommendations the population can understand. In relation to the confounding factors, OSCC exhibited an inverse association in terms of the presence of a partner in the relationship, but amongst the subjects in the study, having a partner bore no correlation with the intake of any of the food groups under consideration.

#### Conclusion

The intake of foods rich in animal fat (dairy products, processed and variety meats), as well as sauces rich in fat, were positively associated with an increased risk of OSCC, regardless of skin color, schooling or the consumption of alcohol and tobacco. The consumption of fruit was not ubiquitously considered to be a protective factor for OSCC, seeing that other food groups had an influence on the risk of developing this pathology.

Therefore, placing it alongside other risk factors, diet plays a significant role in the development of oral and oropharyngeal cancer. Diet may be associated with cancers via a direct effect of the carcinogens present in foods or indirectly via the synthesis of carcinogens due to the metabolism.

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