THE ASSOCIATION BETWEEN DIETARY INTAKE AND THE RISK OF CANCERS OF THE UPPER AERO-DIGESTIVE TRACT: A CASE-CONTROL STUDY IN BRAZIL

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June 2002

A Thesis Submitted to the Faculty of Graduate Studies and Research in Partial Fulfillment of the Requirements for the Degree of Masters in Science

Your file Votre référence
ISBN: 0-612-85774-3
Our file Notre référence
ISBN: 0-612-85774-3

Abstract

Cancers of the upper aero-digestive tract (UADT) rank as the fifth most common neoplastic disease worldwide. Two identified risk contributors are consumption of tobacco and alcohol. Among all other potential etiological factors, diet has long been recognized to play an important role in the development of cancers of the UADT. Data from a multi-centre, hospital-based case-control study conducted in Brazil were used to assess the association of dietary intake with the risk of cancers of the UADT. Dietary assessment was made in terms of estimated intake of nutrients, specific foods and food groups. After adjusting for the effects of alcohol and tobacco consumption as well as empirical confounders, protective effects against cancer of the mouth (Odds Ratio (OR)=0.61, 95% confidence interval (95% CI): 0.4-1.0) and the pharynx (OR=0.51, 95%CI: 0.3-0.9) were found for consumption of citric fruits; High intake of grilled meat and *pinhao* showed increased risks for cancer of the mouth (OR=2.18, 95% CI: 1.1-4.4; OR=3.15, 95%CI: 1.1-9.1); Consumption of cheese, eggs, and peppers also presented positive associations with the risk of pharyngeal cancer (OR=1.88, 95% CI: 1.0-3.6; OR=2.79, 95%CI: 1.2-6.2 and OR=2.09, 95%CI: 1.3-3.4, respectively). Consumption of pickles appeared to increase risk for laryngeal cancer (OR=2.68, 95%CI: 1.0-7.3). Increased ingestion of zinc elevated the risk of cancer of the pharynx (OR=2.41, 95%CI: 1.2-4.8) and larynx (OR=1.95, 95%CI: 1.0-3.6). Vitamin C intake reduced the risk of pharyngeal cancer (OR=0.48, 95%CI: 0.3-0.9), whereas vitamin A, beta-carotene and folate intake showed protective effects for laryngeal cancer but with marginally statistical significance. Findings of this study support the claim that dietary factors may independently play a role in the risk of cancers of the UADT.

Résumé

Les cancers de l'oropharynx et des voies digestives supérieures se classent au cinquième rang des néoplasies, au niveau mondial. En plus des facteurs de risque reconnus, tels le tabagisme et la consommation d'alcool, les facteurs nutritionnels sont aussi des candidats au titre de facteurs de risque. Afin d'étudier la relation entre les facteurs nutritionnels et le risque de cancers de l'oropharynx et des voies digestives supérieures, des données ont été recueillies à partir d'une étude cas-témoins effectuée au Brésil, impliquant quelques hôpitaux. L'évaluation nutritionnelle fut réalisée en estimant l'apport en nutriments, en aliments spécifiques et en groupes alimentaires. La consommation d'agrumes s'est avérée représenier un effet protecteur contre le cancer de la bouche (Ratio de Cotes (RC)=0.61, intervalle de confiance à 95% (IC 95%): 0.4-1.0) et contre le cancer du pharynx (RC=0.51, IC 95%: 0.3-0.9). Par contre, une forte consommation de viande grillée et de *pinhao* est associée à une augmentation du risque de cancer de la bouche (RC=2.18, IC 95%: 1.1-4.4; RC=3.15, IC 95%: 1.1-9.1, respectivement). Parallèlement, la consommation de fromage, d'œufs et de piments, présente des associations positives avec le risque de cancer du pharynx (RC=1.88, IC 95%: 1.0-3.6; RC=2.79, IC 95%: 1.2-6.2 et RC=2.09, IC 95%: 1.3-3.4, respectivement). Finalement, la consommation de marinades semble augmenter le risque de cancer du larynx (RC=2.68, IC 95%: 1.0-7.3). Concernant les nutriments, l'ingestion élevée de zinc augmenterait le risque de cancer du pharynx (RC=2.41, IC 95%: 1.2-4.8) ainsi que celui du larynx (RC=1.95, IC 95%: 1.0-3.6). La prise de vitamine C, cependant, réduit le risque de cancer du pharynx (RC=0.48, IC 95%: 0.3-0.9), alors que l'ingestion de vitamine A, de bêta-carotène et de folate, démontre un effet protecteur , mais non statistiquement significatifo Les découvertes relatives à cette étude soutiennent l'affirmation que les facteurs nutritionnels jouent un rôle indépendant dans le risque de cancers de l'oropharynx et des voies digestives supérieures.

I dedicate this thesis, with my deepest love, to my father and mother

Acknowledgments

I am grateful to many individuals who have taught and guided me in pursuit of knowledge.

First and foremost I would like to thank my supervisor Dr. Eduardo Franco who gave me so much help during my thesis progress. Words simply cannot express my appreciation for the time, patience, encouragement and support he put towards me. I deeply appreciate his continuing effort to supervise my study – the benefits I derive from it are much more than just finishing this thesis.

I would like to extend my gratitude to Dr. Jean-François Boivin, Dr. Lawrence Joseph and Dr. Michal Abrahamowicz who led me to the field of epidemiology and biostatistics. Their dedicated teaching greatly enhanced my knowledge of epidemiology and biostatistics and enabled me to progress through my graduate studies with confidence.

I would also like to give thanks to Dr. Robert Platt. Thank you for your guidance and expertise in statistical analysis. I am grateful to Dr. Mark Goldberg for his valuable comments and for serving as my thesis committee member. His interest, time and advice were very beneficial and greatly appreciated.

Additionally, I thank all my colleagues and friends in the division of cancer epidemiology, Eliane Duarte-Franco, Anita Koushik, Harriet Richardson, Seungmi Yang

for their spirit support and encouragement. I am indebted to Javier Pintos and Nicolas Schlecht whose deeply understanding of epidemiology made their valuable suggestions indispensable for my thesis. I am also indebted to Marie-Claude Rousseau and Susan Brogly who offered advice and editorial assistance during the writing of the thesis. They were approachable and generous with their time. I am grateful to my two Brazilian friends who are invaluable in helping me in getting the Brazilian nutrition table, Inez Nishimoto and Amdré Carvalho, visiting PhD students from University of São Paulo. Words are not enough to show you how much I appreciated you all.

Completion of this thesis would not have been possible without my friend Bin Zhang for his constant patience, support and understanding. I cannot deny how much he has contributed to my life during these past few years.

Finally, my deepest gratitude goes to my parents for their everlasting love, unabated support and tireless encouragement that brought me to pursue this endeavour. My dear father and mother, you are always the sources of my inspiration and energy.

Table of contents

LIST OF TABLES:

LIST OF TABLES (CONTINUED):

LIST OF FIGURES:

LIST OF APPENDICES:

Introduction

The possible role of diet on the risk of cancer has intrigued researchers for centuries. In 1981, Doll and Peto estimated that about 35% of all cancers in the United States might be due to dietary factors. In 1997, American Institute for Cancer Research - a prestigious international group - made a similar estimate. Today, the importance of diet and nutrition in the etiology of certain human cancers has been widely accepted by the society.

Along with other cancers, malignant tumors of the upper aero-digestive tract (UADT), including cancers of the oral cavity, pharynx and larynx, have been important contributors to the burden of health, ranked as the fifth most common group of neoplastic diseases globally {IARC, 2000}. The etiology of cancers of the UADT is likely multi-factorial, with lifestyle, environmental and genetic influences. The two main risk contributors are tobacco and alcohol consumption {Blot et al. 1988, Mackenzie et al. 2000}. Among all other potential risk factors, the major candidate is diet (McLaughlin et al. 1988).

A substantial amount of research has been conducted to assess the role of dietary intake on developing cancers of the UADT. The most consistent finding is the protective effect of consumption of fruits and vegetables {Winn et al. 1984, McLaughlin et al. 1988, Zheng et al. 1993}. However, evidence related to other dietary or nutritional factors is inconsistent. The extremely complex nature of diet may partially explain these inconsistencies. As expected, dietary factors are often strongly interrelated. Thus, for a

limited sample size, isolating the independent effects of each food and nutrient becomes impossible due to insufficient statistical power. Also, many of the associations between dietary factors and disease risks are so subtle that very large studies are needed to detect statistically meaningful effects. In addition, dietary intake is highly associated with other lifestyle factors contributing to the etiology of cancer risk. This might lead to residual confounding or unmeasured confounding factors which may bias the estimates of risk when evaluating the association between dietary intake and cancers of the UADT. Moreover, the effect of dietary factors on the risk of developing cancer might vary across the specific anatomic sites within the UADT. This further complicates our understanding of the effect of diet on risk of cancers of the UADT.

The present thesis was developed to identify the role of diet on the development of cancers of the UADT, using data from a large multi-centre, hospital-based study conducted in Southern Brazil - an area in which the incidence of cancers of the UADT is very high. In this study, dietary intake was measured at three different levels including nutrients, individual food items and food groups to allow a better measurement of the associations between dietary determinants and risk of cancers of the UADT. Unlike previous studies, adjustment for confounders used all prior risk factors as well as all measured covariates that changed the estimates of effect for the dietary items by five percent or more to minimize the impact of empirical confounding on evaluating the effect of diet. In addition, the effects of dietary intake were examined not only on all cancers of the UADT but also on each anatomic site including mouth, pharynx and larynx.

Literature Review

1. General aspects of cancers of the upper aero-digestive tract

Cancers of the UADT are a group of malignant tumors that affect mucosal epithelium in the head and neck region {Batsakis 1979}. The dominant histological type of this group of tumors is squamous cell, representing over 90% of cancers of the UADT {Jacobs 1990}. In clinical practice, the sites are divided into the oral cavity, nasopharynx, oropharynx, hypopharynx, and larynx (Figure 1). However, as the histological characteristics of cancers originating from different sub-locations within the UADT are very homogeneous, it is often difficult to identify clearly the primary anatomic origin of

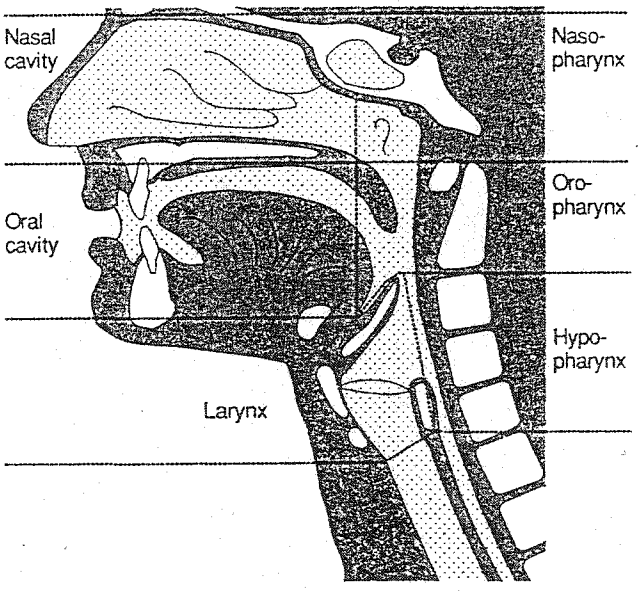

Figure 1. Sagittal section of the head and neck region (source: Ulfk, 1991).

the tumour, particularly when diagnosis is made at an advanced stage, tumours commonly spreading over anatomical boundaries.

In the epidemiological literature, cancers of the oropharynx and hypopharynx are often combined together as pharyngeal cancer, while cancers of the tongue, gum, mouth floor and other unspecified parts of the mouth are collectively called the oral cavity, or sometime considered jointly with pharyngeal cancer and referred to as oral cancer (usually excluding tumours of the salivary glands and nasopharynx). Such grouping of cancer subsites that share some common characteristics increases the number of cases for study in the broader diagnostic categories, and might reduce some of the classification problems due to the difficulty of determining the primary site. However, these broad combinations of sites may also have some disadvantages, such as obscuring possible differences in etiological factors for individual sites within the UADT. Indeed, there has been growing awareness of taking individual sites into consideration in epidemiological studies of cancers of the UADT.

Table 1 shows the classification of tumours in the head and neck region according to the International Classification of Diseases, version 9th (ICD-9).

Table 1: The classification of cancers in head and neck region according to the International Classification of Diseases, 9th version (ICD-9) {source: Boyle, 1990}.

SITE	ICD-9	SITE	ICD-9
Lip	140	Oropharynx	146
Tongue	141	Nasopharynx	147
Salivary gland	142	Hypopharynx	148
Gum	143	Pharynx unspecified	149
Floor of mouth	144	Nose, nasal sinuses and nasal cavity	160
Mouth (other)	145	Larynx	161

2. Descriptive epidemiology of cancers of the upper aero-digestive tract cancer

2.1. Global aspect of the incidence and mortality

According to recent data collected by the International Agency for Research on Cancer, cancers of the UADT ranked as the fifth most common cancer, following cancers of the lung, the breast, the colon and rectum, and the stomach, and the seventh most common cause of cancer-related death globally {IARC, 2000}. It was estimated that, when combined, cancers of the oral cavity, the pharynx and the larynx account for approximately 550,000 new cancer cases annually (5.48% of all cancer incidence) (Table 2) and caused nearly 300,000 deaths (4.75% of all cancer mortality) (Table 3) in 2000. The burden of cancers of the UADT was much more pronounced in developing countries where approximately two-thirds of these new cancer cases occurred. Cancers of the UADT were more common in men than in women. Male excess risk was more marked for laryngeal than that for oral and pharyngeal cancer. And, such gender difference in risk was greater in developed countries than that in developing countries. Male-to-female ratios for incidence of cancer of the oral cavity, the pharynx, and the larynx in developed countries were 2.5, 6.2, and 9.1, respectively. Corresponding ratios in developed countries were 1.5, 3.9 and 6.5, respectively {IARC, GLOBOCAN, 2000}.

Table 2: **Estimated incidence of cancers of the oral cavity, pharynx and larynx in 2000 worldwide (data source: GLOBOCAN 2000, IARC)**

Cancer site (ICD-9)	Developed countries		Developing countries		Total
	Male	Female	Male	Female	
Oral Cavity (140-145)	59959	24466	109553	72687	266665
Pharynx (146-149)	36972	6005	63934	16062	122973
Larynx (161)	62196	6845	79972	12390	161403
Total	159127	37316	253459	101139	551041

Table 3: **Estimated deaths caused by cancers of the oral cavity, pharynx and larynx in 2000 worldwide (data source: GLOBOCAN 2000 database, IARC)**

Cancer site (ICD-9)	Developed countries		Developing countries		Total
	Male	Female	Male	Female	
Oral Cavity (140-145)	22392	7572	58454	39490	127908
Pharynx (146-149)	19681	3500	44148	11202	78531
Larynx (161)	31108	2933	47460	7592	89093
Total	73181	14005	150062	58284	295532

2.2. Geographic variation in incidence

The geographic variation in the incidence of cancers of the UADT is striking. Assessing data from 49 different cancer registries in five continents between 1988 and 1992, Franceschi et al {2000} reported that sex-specific incidence rates of oral cancer combined (cancers of the oral cavity and pharynx) varied approximately 20-fold internationally. The highest combined rate recorded was found in Northern France (49.4/100,00 men). Other areas characterized by a high incidence of oral cancer among males were Southern India (20/100,000 men), Slovakia (19.7/100,000 men) and Slovenia (18.9/100,000 men), Latin America and blacks in the USA (17.8/100,000 men). In northern European countries, incidence rates of cancers of the oral cavity and pharynx in men were relatively lower, ranging between 3.1 in Finland and 7.1 in Scotland. Rates below 4 in men were also observed in China, Shanghai, and Israel, all Jews. Corresponding rates for women were much lower than those for men, but also showed substantial variation, ranging between the highest in India (over 10/100,000 women), Philippines (7.1/100,000 women), and the lowest in Spain (0.7/100,0000) and Africa, Algeria (0.5/100,000).

Similarly, cancer of the larynx also showed a wide variation in risk among areas. As mentioned in Parkin et al's report, for men, the difference in risk was some 7-fold

between the highest risk in Eastern Europe (12.0/100,000) and the lowest risk in Eastern Asia, China (1.7/100,000). Other areas of relatively high risk in men were Southern and Western Europe, Temperate South America and Western Asia. Risk for women was much lower than that for men. But corresponding ranges were wider in women, with an approximately 14-fold variation, ranging from the highest risk in North America (1.4/100,000) and Caribbean (1.3/100,000) to the lowest risk in Eastern Asia, Japan (0.1/100,000) and Middle Africa (0.2/100,000) {Parkin 1999}.

2.3. Cancers of the upper aero-digestive tract in Brazil

Brazil is among the areas with high incidence for cancers of the UADT. According to the data from the country's cancer registries in 2000, cancers of the oral cavity, pharynx and larynx combined are the most common group of neoplastic diseases in the country. With an estimated 17667 new cases occurred among men, accounting for 13.89% of all incident cancer cases for Brazilian men, and 3753 new cases in women were diagnostic, accounting for 2.52% of incident cancer cases for Brazilians women, it also caused 7628 male and 1614 female deaths in 2000. The sex specific age-standardized incidence rates for cancers of the oral cavity, pharynx and larynx were 10.52, 7.86, and 9.33 per 100,000 men and 2.89, 1.11, and 1.14 per 100,000 women {IARC, GLOBOCAN, 2000}.

2.4. Time trends in incidence of cancers of the upper aero-digestive tract

While several studies in the early 1970s indicated a decrease in the occurrence of oral cancer {Szpak et al. 1977}, in recent decades it has been suggested that the incidence of oral cancer may be increasing {Boyle et al. 1990, Macfarlane et al. 1994, Plesko et al. 1994}. Notably, increased trends are more often observed among younger people {Macfarlane et al. 1992, Johnson et al. 1993, Hindle et al. 1996}. In a review of incidence

trends for cancers of the oral cavity and pharynx worldwide, Franceschi et al. reported increasing trends for oral cancer in men were found in Scotland, England, New Zealand, Japan, Finland, and Eastern Germany, while increasing trends in women were observed in Switzerland and Scotland. Data from less developed countries including India, Puerto Rico, and Colombia suggested that there is a steady decline in oral cancer incidence in both sexes. As discussed by Franceschi et al., increases in pharyngeal cancer in Japan and in most Central, Southern, and Eastern European countries were likely to reflect increases in cigarette smoking which had taken place since 1950 in men in such areas. Conversely, downward trends in oral cancer in India were accompanied by a decline in tobacco chewing which had diminished in India three-fold from 1951-52 to 1980-81 {Franceschi et al. 2000}. However, beyond cigarette smoking and tobacco chewing, whether other factors were responsible for these increased or downward trends remains unknown.

More recently, data from nine population-based cancer registries in the United States showed that the annual age-adjusted incidence rates for in-situ (pre-invasive) head and neck carcinomas increased from 6.33/1,000,000 person-years (PY) in 1976 to 8.04/1,000,000 PY in 1995 {Reid et al. 2000}. As discussed by the authors, it is possible that increased surveillance was responsible for the climbing incidence of in-situ carcinoma. This can be further supported by the fact that larynx and oral cavity, two anatomic sites with early symptoms and easier access for diagnosis, had the greatest increases in incidence. On the other hand, data showed that the age-adjusted incidence rates for invasive head and neck carcinomas have decreased from 158.18/1,000,000 PY to 135.47/1,000,000 PY. More frequent early detection and removal of in-situ carcinomas may have contributed to a decline in the incidence of invasive carcinomas.

3. Determinants of risk of cancers of the upper aero-digestive tract

3.1. Demographic factors

Age

Cancers of the UADT are relatively more common in elderly people, primarily occurring in males in the 6th and 7th decade of life. It is rarely detected prior to age 40, and the incidence rates increase rapidly for each subsequent decade of life {Jacobs 1990}. However, as mentioned previously, an increased incidence of oral cancer among younger people has been observed worldwide: Johnson and his colleagues reported rising trends in oral cancer among young adults in UK {Johnson et al. 1993}. Significant increases in incidence and mortality due to oral cancer among younger men has also been observed in England and Wales {Hindle et al. 1996}. Llewellyn and his colleagues, reviewing 46 publications devoted to oral cancer in the young adult, reported that there is approximately 4-6% of oral cancers now occurring at ages younger than 40 years {Llewellyn et al. 2001}. The reason for these increases in the incidence of oral cancer among younger persons is unclear {Macfarlane et al. 1992}.

Gender

It is well recognized that cancers of the UADT predominantly affect males {Jacobs 1990, Parkin et al. 1999}. Using data on incidence from 49 different cancer registries in five continents, Parkin {1999} reported that the incidence of cancer of the mouth for males was about two times higher than that for females. The risk of pharynx cancer among males was over four times higher than that among females. For larynx cancer, such gender difference appeared even more striking, with a male: female ratio of 7:1 {Parkin et al. 1999}. The causes of the observed risk differences for cancers of the UADT between

male and female are not yet well understood. It has been suggested that the higher rates in men probably reflect the different lifestyle habits between men and women, such as smoking and alcohol consumption. Indeed, as smoking and drinking have become more socially acceptable amongst women, trends have changed and the usual male dominance is not the case in younger patients {Llewellyn et al. 2001}. However, this explanation for gender differences in risk may apply to all cancers of the UADT in general. For laryngeal cancer, there are other factors at play as well, but largely unknown.

Ethnicity

Ethnic differences in risk for oral cancer are highlighted by the existence of inter-country and intra-country variations in both incidence and mortality from oral cancer {Fleming et al.1982, Slotman et al. 1983, Johnson et al. 1996, Zain et al. 2001}. A review by Zain et al. {2001} showed differences in the incidence of oral cancer among different ethnic groups in several Asian countries: the Tamils had the highest frequency of oral cancer as opposed to the other ethnic groups in Sri Lanka {Hirayama 1966}. In Malaysia, the Indian ethnic group appears to have the highest risk of oral cancer, compared to the Malays, Chinese and other ethnic groups {Ng et al. 1985}. A cross-sectional study conducted in Northern Thailand also found a difference in oral cancer frequency among six different ethnic groups {Reichart et al. 1987}. The reason for these ethnic variations in the incidence of oral cancer may relate to some cultural risk factors, such as tobacco (smoking and smokeless), alcohol consumption, and dietary habits {Johnson et al. 1996, Scully & Bedi 2000, Zain et al. 2001}. Familial and genetic predisposition of certain ethnic groups towards a higher risk of oral cancer may also account for these ethnic variations {Scully & Bedi 2000, Zain et al. 2001}.

Socioeconomic status

It has long been recognized that socioeconomic status is inversely related to the risk of cancers of the UADT. Greenberg et al. {1991}conducted a large population-based case-control study to examine the association between socioeconomic status and risk of oral and pharyngeal cancer. Three primary indicators of socioeconomic status including education, occupational status, and percentage of potential working life spent in employment were examined in Greenberg's study. After adjustment for the effects of established risk factors including tobacco smoking, alcohol consumption and poor dentition, a relatively low percentage of years of working emerged as a single important risk factor for the increased risk (OR= 2.3, CI: 1.7-3.1), whereas education attainment and occupational status were not independently related to risk. These results suggested that social instability might be linked to an increased risk of oral cancer. Two other studies from Scotland and England, which used deprivation as indicator of low socioeconomic level, implied that material deprivation could also increase the risk of oral cancer. In Scotland, from 1968 to 1992, the largest increase in incidence of cancers of the mouth, tongue, and pharynx had occurred in socially deprived areas {Macfarlane, et al. 1992}. In Northeast England, between the mid-1970s and the early 1990s, oral cancer incidence and mortality were linked to material deprivation {O'Hanlon et al. 1997}. As mentioned by O'Hanlon, several possibilities may be responsible for this unfavourable trend in morbidity and mortality of oral cancer among peoples with lower socioeconomic status. Different risk factor behaviours, such as smoking, alcohol consumption and poor diet, would be more prevalent among persons subjected to poor living and working conditions. Besides having greater risk for developing oral cancer, socially disadvantaged groups

may also be less capable of changing behaviour and less exposed to health information, with lower access to early diagnosis and fewer therapeutic resources.

3.2. Tobacco smoking and alcohol consumption

Tobacco smoking and alcohol consumption have been consistently identified as two primary risk factors for cancers of the UADT {Blot et al. 1988, Zheng et al. 1990, Negri et al. 1993, Mackenzie et al. 2000}. These two agents together are estimated to account for approximately 75% of all cases of oral cancer worldwide {Boyle et al. 1995}.

Evidence for a causal relation between smoking and risk of cancers of the UADT is strong. Both the amount of tobacco consumed and the number of years of use exert a substantial impact on the risk {Melrose et al. 1985, Schlecht et al. 1999}. All forms of tobacco consumption including cigarettes, pipes, cigars, and snuff have been implicated in the development of oral cancer {Spitz et al. 1994}. One study conducted in India found that chewing tobacco increases the risk of oral cancer by an amount comparable to that observed for tobacco smoking, and moreover, the combined effect of smoking and chewing tobacco was nearly twice as great {Notani et al. 1987}. The uses of oral snuff and betel quid are also recognized as risk factors for oral cancer {Marshall et al. 1996}.

Numerous studies have also demonstrated a significantly increased risk for cancers of the UADT among patients who consume large amounts of alcohol {Graham et al. 1977, Franco et al. 1989, La Vecchia et al. 1991, Schlecht et al. 1999}. Using data from a case-control study, Negri et al. {1993} reported that, in Italy, approximately 60% of cancers of the oral cavity and pharynx in men and 15% in women are attributable to alcohol consumption. A study by Franceschi et al. {2000} observed a strong dose-dependent

association between alcohol consumption and risks for cancers of the oral cavity and pharynx. Very high intake (≥91 drinks weekly) was associated with an approximately 12-fold elevated risk of cancer of the oral cavity and pharynx compared with never drinkers, although moderate amounts of alcohol intake in the range of 1-20 drinks weekly were not associated with an increased risk {Franceschi et al. 2000}.

Distinguishing between the effects of these two risk agents has been difficult in practice, as drinkers of alcoholic beverages tend to be smokers, and vice versa. In a case-control study conduced in the United States, the elevated risks for oral cancer were observed among both non-drinkers with the amount of tobacco smoked increased and non-smokers with the level of alcohol intake increased. This finding supported the claim that tobacco and alcohol consumption may independently play a role in developing cancers of the UADT {Blot, 1988}. However, the combination of tobacco and alcohol consumption may multiply risk of cancer synergistically {Rothman 1972, Blot 1988, Sankaranarayanan 1990, Oreggia 1991, Marshall 1992}. Accordingly, a study by Schlecht et al. {1999} showed that the combined effect of tobacco smoking and alcohol consumption on risk is greater than the sum of the two independent effects.

3.3. Other risk factors

Occupational exposure

Epidemiological studies have shown inconsistent findings when studying occupational exposures as a risk factor for cancers of the UADT. In one earlier study, variations in the risk of oral cancer have been observed among different occupational categories {Dubrow & Wegman 1984}. Increased rates of oral cancer have also been reported among workers exposed to asbestos and mineral fibers {Merletti, et al. 1991}. Using data from a case-

control study, Huebner et al. {1992}reported an increased risk for pharyngeal cancer among male carpet installers (OR=7.7) and workers with inferred exposure to fossil fuel combustion (OR=2.0). But Huebner et al. failed to find any associations between oral cancer and occupation after adjusting for age, race, smoking and alcohol consumption.

Indoor air pollution

Indoor air pollution has long been suspected as a risk factor for head and neck neoplasms, but only limited evidence is available. Using data from a hospital-based case-control study conducted in Brazil, Pintos et al. {1998} concluded that the use of a wood stove increased risk for cancers of the UADT by 2.5-fold after adjusting for empirical confounding variables. According to the author's conclusion, this association seems unlikely to have resulted from insufficient control of confounding.

Oral hygiene

Velly et al. {1998} reported that history of oral sores secondary to ill-fitting dentures was associated with cancer of the mouth (OR=2.3, CI: 1.2-4.6). Less than daily tooth brushing was also associated with risk of cancer of the tongue (OR=2.1, CI: 1.0-4.3) and of other parts of the mouth (OR=2.4, CI: 1.0-5.4). These results speak in favour of the theory that oral hygiene is causally linked to oral cancer {Graham, et al. 1977, Blot, et al. 1983, Marshall, et al. 1992, Zheng, et al. 1990, Winn, et al. 1991}. As discussed by James et al {1981}, there are several ways that compromised oral hygiene could be related to increased risk of oral cancer: poor oral hygiene could reflect long-term exposure to carcinogenic agents such as tobacco and alcohol. Poor oral hygiene may also enhance the ability of infectious or microbial agents to initiate or promote carcinogenesis and facilitate oral trauma so that an injury to the oral mucosa could more likely result in carcinogenesis.

Human Papillomavirus

As viral DNA of human papillomaviruses (HPV), mostly of HPV type 16 (HPV-16), has been found in tumour tissue of epithelial cancers, infection with HPV has also been suspected as a cause of carcinoma of the head and neck {McKaig, 1998}. Using samples from Japanese and Chinese populations to examine the prevalence of HPV in oral squamous cell carcinomas (SCCs), Uobe et al. {2001} found HPV DNA was present in all cases of SCC in Japanese (10/10) and Chinese (10/10) subjects. However, this study featured a very small sample size and used only prevalent cases.

Mork et al. {2001} conducted another nested case-control study using serum samples collected from almost 900,000 residents of Norway, Finland and Sweden. Among 292 subjects with squamous-cell carcinoma of the head and neck and 1568 matched controls (matched on gender, age, the diagnosis of cancer and the length of serum storage), a positive association between HPV-16 sero-positive and risk of squamous-cell carcinoma of the head and neck was observed (OR=2.2, 95% CI: 1.4-3.4), even after adjusting for serum cotinine level - a biologic marker of smoking, whereas no significantly increased risks were observed for other HPV types. Although this finding supported the notion that infection with HPV-16 is associated with increased risk of cancers of the UADT, it was unable to show that HPV's presence in oral squamous-cell carcinoma was not due to a secondary viral infection in the already developed carcinoma. To elucidate the causality of HPV on developing carcinoma of the head and neck, additional studies are needed especially those with longitudinal designs.

Summary

As cancers of the UADT are important contributors to the overall burden of human diseases, intensive efforts have been made to identify the causative factors responsible for these cancers. Two identified risk contributors are tobacco and alcohol consumption. Other factors, including industrial carcinogens, indoor air pollution, poor oral hygiene, infection with HPV and genetic predisposition have also been suggested to be associated with the risk but with insufficient evidence. Another important candidate of risk factor is diet. The following literature review summarizes the information pertaining to dietary factors in the etiology of cancers of the UADT.

4. Dietary intake and cancers of the upper aero-digestive tract

Vegetables and fruits

Nine case-control studies that examined consumption of vegetables and fruits and risk of oral cancer have been documented in this thesis. Except for one earlier study {Graham et al. 1977} where no association was observed between a specific dietary item and increased risk of cancer of the UADT, all other eight studies reported a statistically significant protective effect for at least one vegetable and /or fruit category. Of these, fruit intake has been most consistently linked to lower oral cancer risk. Inverse associations with oral cancer were found for fresh fruit in two studies (OR=0.6, CI: 0.4-0.8 {Winn et al. 1984} and OR=0.1, CI: 0.1-0.2 {La Vecchia et al. 1991}). The protection of citrus fruits against oral cancer was observed in all other three studies (OR=0.5, P-value<0.001 {McLaughlin et al. 1988}; OR=0.4, CI: 0.2-0.6 {Franco et al. 1989}; OR=0.4, CI: 0.2-0.7 {Levi et al. 1998}).

Compared to fruit intake, studies of consumption of vegetables and oral cancer have shown a less consistent pattern in results. Notani et al. {1987} observed a significant two - to - three - fold increase in risk of oral cancer among those who did not consume vegetables daily vs. those who did (comparison group was population controls). However, no difference was observed when used hospital controls as the comparison group. A high intake of cruciferous vegetables was significantly inversely related to the risk of oral cancer in one study {Mclaughlin et al. 1988}, but was not related to risk in another study {Franceschi et al. 1991}. Similarly, a significantly protective effect of consumption of green vegetables was observed in one study {La Vecchia et al. 1991}, but not in two others {McLaughlin et al. 1988, Franco et al. 1989}.

The protective effect of vegetable and fruit consumption against laryngeal cancer has also been accumulating worldwide. High consumption of fruits was found to be associated with a statistically significant decrease in risk of laryngeal cancer in Uruguay {De Stefani et al. 1987}, India {Notani et al. 1987}, Italy {La Vecchia et al. 1990}, China {Zheng et al. 1992}, and Southwestern Europe {Esteve et al. 1996}. A negative association between consumption of vegetables and laryngeal cancer was observed in three studies {Notani et al. 1987, La Vecchia et al. 1990, Esteve et al. 1996}.

Vitamin C

In one earlier large population-based study conducted in four areas of the USA, McLaughlin et al. {1988} observed that the consumption of dietary vitamin C was related to a decreased risk of oral cancer. After distinguishing vitamin C consumption from fruit and vegetable sources, they found that most of the protective effect of vitamin C was indeed from fruit sources, while vitamin C from vegetables did not provide similar

protection. It is possible that cooking vegetables may have a nutrient-diminishing effect. However, in a subsequent study conducted in China, vitamin C consumption derived from both vegetables and fruits was inversely associated with the risk of oral cancer irrespective of source (Zheng et al. 1993}. A protective effect against cancers of the oral cavity and pharynx due to intake of dietary vitamin C was also seen in one more recent Italian study {Negri et al. 2000}. In addition to dietary vitamin C, use of vitamin C supplement also showed a reduced risk for oral cancer in two studies {Rossing et al. 1989, Gridley et al. 1992}.

Vitamin A

HoGridley et al. {1992} found that users of supplements of vitamin A were at lower risk after controlling for the effects of tobacco, alcohol and other risk factors for oral and pharyngeal cancers. Study of people with oral leucoplakia also showed that serum vitamin A is lower in oral leukoplakia patients compared with that in controls {Ramaswamy et al. 1996}. However, two other studies {Rossing et al. 1989, Zheng et al. 1993}noted no overall effect of dietary vitamin A consumption after adjustment for smoking and alcohol consumption. Even more troubling, McLaughlin et al. {1988} reported that vitamin A from animal sources was associated with a slightly increased risk of oral and pharyngeal cancer. Other investigations also found that high retinol intake was associated with increased risks of cancers of the UADT {Marshall, et al. 1992, Negri, et al. 2000}. Vitamin A can be found in vegetables and fruits in the form of beta-carotene. Beta-carotene has to be converted to retinol (a pure and active form of vitamin A-the body readily uses this form) in the body in order to be used by it. Vitamin A from animal sources is more efficiently absorbed and converted to retinol in comparison to vitamin A

from vegetables and fruits. However, few studies distinguished the source of intake of dietary vitamin A or separated the effect of vitamin A from the sources of animal and plants when examining the association between dietary vitamin A and cancers of the UADT. This might partially explain why the literature documents mixture results.

Dietary fiber

An inverse association between intake of dietary fibre and the risk of oral cancer has been observed in several studies. Zheng et al {1993} and Marshall et al {1992} found that dietary fibre derived either from fruits or vegetables showed a strong protective effect against oral cancer, whereas fibre derived from other sources did not exhibit any protective effect. McLaughlin et al. {1988} reported an inverse relationship between dietary fibre and oral cancer. But most of this inverse association reflected fibre from fruits, as fibre from vegetables did not provide similar protection. These findings suggested that the effect of dietary fibre might be only a marker for other constituents in fruits or vegetables that provide a protective effect on cancer risk.

Vitamin E

Intake of vitamin E has been analyzed in only a few studies with no consistent pattern emerging. In one earlier study by McLaughlin et al. {1988} dietary vitamin E showed no relationship with the risk of oral and pharyngeal cancer. Ramasawamy {1996} also found no significant difference in serum levels of vitamin E between cases with oral leucoplakia and normal controls. However, a large case-control study conducted by the US National Cancer Institute reported that people who regularly took vitamin E supplements had a substantially and significantly lower risk for oral cancer as compared with those who did

not take them {Gridley et al. 1992}. More recently, Negri et al. {2000} observed an inverse association between dietary vitamin E and the risk of oral cancer.

Other nutrients and minerals

Studies on dietary factors other than vegetable, fruits, vitamin A, vitamin C, vitamin E, and dietary fibers were limited and provided less inconsistent findings. A high intake of thiamin and niacin was protective against oral cancers in two studies {Marshall 1992, Negri 2000}, but was not related to risk in two others {McLaughlin 1988, Zheng 1993}. An increased risk with high intake of riboflavin was observed in some studies {McLaughlin 1988, Marshall 1992}, but no association was found in others {Zheng 1993, Negri 2000}. Mean serum levels of folate were significant lower in cases of oral leucoplakia compared with normal controls {Ramasawamy 1996}, but no association was observed in one other study {McLaughlin 1988}. Zhang {1993} and Negri {2000} found a protective effect against oral cancer for iron intake, but no association was observed in two other studies {McLaughlin 1988, Gridley 1992}. Marshall {1992} reported increased risk with high intake of calcium, but no such an association was found in two other studies {Roger 1993, Zheng 1993}. Studies of zinc intake generally suggested no association {Rogers 1991 & 1993, Negri 2000}.

Table 4 presents a summary of thirteen case-control studies that examined the relationship between dietary intake and the risk of oral and pharyngeal cancer.

Table 4. Summary of findings from reviewed case-control studies of dietary intake and oral and pharyngeal cancer.

Author (Location, year)	Cases	Control	Food Items	Adjustment	Major Findings
Graham et al. (New York, 1977)	584 males with oral cavity	1222 hospital controls	27 food items.	Age-matched, smoking and alcohol consumption.	No associations with the basic food frequencies.
Winn et al. (North Carolina, 1984)	227 females with oral cavity and pharyngeal cancers	405 matched hospital controls	21 food items and 4 food groups.	Race, education, smoking-snuff, alcohol consumption and other confounders.	Fruits and vegetables, breads and cereals decreased risk. Meat and fish increased risk.
Notani et al. (India, 1987)	503 oral cavity and pharyngeal cancers	392 hospital/ community controls	6 food groups.	Age, habits of chewing and/or smoking tobacco.	Vegetables and fish intake decreased risk. Red chili powder increased risk.
Mclaughlin et al. (4 USA sites, 1988)	871 oral cancers	979 population controls	61 food items	Smoking and alcohol consumption.	Fruit intake decreased risk. Meat and dairy products increased risk among men but not women.
Franco et al. (Brazil, 1989)	232 oral cavity	464 matched hospital controls	20 food items	Matching variables (age, sex, study site, and admission period). Smoking and alcohol consumption	Carotene-rich vegetables, citric fruits decreased risk. Grilled meat, cassava increased risk.
Rossing et al. (Washington, 1989)	166 pharyngeal cancers	547 matched population controls	48 food items and vitamin supple-ments	Age, sex, smoking and alcohol consumption	Vitamin C from foods, vitamin C and vitamin A supplements showed protective effect.
Franceschi et al. (Pordenone, Italy, 1991)	302 oral cavity and pharyngeal cancers	699 hospital controls	40 food items	Age, sex, occupation, smoking and drinking habits.	Carrots, fresh tomatoes, green peppers decreased risk. Pasta, rice, polenta, cheese, eggs, pulses increased risk.

Table 4 (continued) Summary of findings from reviewed case-control studies of dietary intake and oral and pharyngeal cancer.

Author (Location, year)	Cases	Control	Food Items	Adjustment	Major Findings
La Vecchia et al. (Milan, Italy 1991)	105 oral and phary-ngeal cancers	1,169 hospital controls	17 food items	Age, area of residence, education, social class, smoking, and dietary factors.	Fruit intake showed strongest protective effect. Milk, meat, and carrots intake also decreased risk.
Marshall et al. (Western New York, 1992)	290 oral cancers	290 matched (age and sex) neighbor hood controls	120 food items	Total calories, Quetelet index, smoking, alcohol, and teeth lost but not replaced.	Fat, calcium, sodium, riboflavin and retinol increased risk. Thiamin, niacin, and dietary fiber decreased risk.
Gridley et al. (4 US cities, 1992)	1,103 oral and phary-ngeal cancers	1,262 populatio n controls.	9 vitamin & mineral supple-ments	Sex, race, tobacco, alcohol consumption.	Vitamin E supplements reduced risk after adjusting for tobacco, alcohol and other supplements.
Zheng et al. (Beijing, 1993)	404 oral cancers	404 matched (sex, age, referral pattern) hospital controls	63 food items	Quetelet index, education, total energy intake, inadequate dentition, alcohol and smoking.	Vitamin C, carotene, dietary fiber derived from fruits & vegetables, protein and fat intake decreased risk. Carbohydrate intake increased risk.
Levi et al. (Swiss, 1998)	156 oral and phary-ngeal cancers	284 hospital controls	79 foods, food groups and recipes.	Age, sex, education, smoking, alcohol, and non-alcohol total energy intake.	Milk, fish, raw vegetables, cooked vegetables, citrus fruits and other fruits decreased risk. Eggs, red meat, pork and processed meat increased risk.
Negri et al. (Italy and Switzerland, 2000)	754 oral cavity and pharyngea l cancers	1,775 hospital controls	78 foods, groups of foods or dishes	Age, sex, study center, education, occupation, body mass index, alcohol, smoking, and non-alcohol energy.	The protective effects were observed for carotene, vitamin E, C, B_6, thiamine, folic acid, niacin, potassium, and iron intake.

5. Considerations on measurements of dietary intake

In nutritional epidemiology, assessment of exposure (dietary intake) is a particularly difficult task due to the complexity of diets. To quantify the dietary variables, various approaches have been applied according to the type of study design and research questions. The most common methods include dietary recall, food records and food frequency questionnaire. Each method has its own value and limitation.

24-hour dietary recalls

For 24-hour dietary recalls, study subjects are asked to report their food intake during the preceding 24 hours {Willett 1998}. It has been the most widely used dietary assessment method in nutritional epidemiology as this technique of assessment is relatively quick (it usually takes 20-30 minutes) and simple. The major criticism of 24-hour dietary recalls is that they will only provide information on the current diet. This makes them inappropriate for most case-control studies as the relevant exposure will have occurred much earlier and the diet may have changed as a result of the cancer or its treatment. Another important limitation of this method is that because dietary intake has high day-to-day variability, a single 24-hour recall is not adequate for measurement of an individual's usual intake. In addition, the actual collection and processing of recall information can be quite labor-intensive and may be subject to error.

Food records

Food records are detailed meal-by-meal recordings of types and quantities of foods consumed over a specified time period, usually 3 to 7 days {Willett 1998}. Subjects may be asked to weigh foods before eating. If subjects cooperate well, food records tend to be more exact than other dietary assessment methods. Accordingly, the weighed food records are often considered as the "gold standard" for measuring food intake and the

optimal method for validating food-frequency questionnaires. However, food records place considerable responsibility on the study subject. Thus, this method can be used only with highly motivated and literate individuals. Food records are expensive to administer requiring experienced dieticians or highly trained staff for reviewing and coding of the entries. Food records are also affected by daily variability of food intake and cannot represent fully the usual dietary intake. Additionally, the subject will become more acutely aware of what he/she is eating and self-induce an alteration in the diet. This may lead to important biases in the results. Food records are best suited to obtaining information on present diet rather than diet in the distant past. In case-control studies where past diets are of interest, such records are not appropriate.

Food frequency questionnaire

The basic food-frequency questionnaire (FFQ) consists of two components: a food list and frequency response section for subjects to report how often each food was eaten {Willett 1998}. Unlike 24-hour recall and food records, this method focuses on subject's usual intake. Since diets tend to be reasonably correlated from year to year, most questionnaires are designed to answer the questions in regard to diet for the preceding year. The answers are requested in terms of frequency per day, week or month using the multiple-choice format with the number of responses ranging from five to ten. This can also provide an entire range of seasons, so that the responses can be independent of time of year. Portions are estimated by using a description, a picture, or food models. The food list itself depends on the objective of the questionnaire. Lists will be different if one's objective is to measure only a few specific food items or if one wants to conduct a comprehensive assessment of dietary intake. In the latter case, the list will be very long.

Summary

As dietary intake has long been recognized as an important etiological factor of the risk of certain human cancers, numerous dietary and nutritional factors has also been studied with respect to cancers of the UADT. Such investigations have been conducted across multiple cultural settings, geographically as diverse as Brazil, India, Italy, China, USA, and Switzerland, which encompass many different types of diet.

The most consistent dietary findings are inverse associations between vegetable and fruit intake and risk of cancers of the UADT {Boyle, et al. 1995}. In addition to consumption of fruits and vegetables, the role of other specific foods and nutrients remains largely undefined {Marshall, et al. 1996}. Also, which constituents in fruits and vegetables are responsible for their protective effects is unclear. As known, fruits and vegetables contain many biologically active chemicals and many more non-nutritive constituents. Although vitamins A and C, carotenoids and fibre might account for the protective effect of the intake of fruits and vegetables {Rossing et al. 1989}, such inverse association may also be explained by other nutrients or dietary constituents in fruits and vegetables as well. Thus, further work is needed to clarify specific protective constituents or combination of constituents in fruits and vegetables.

Evidence regarding the relation between dietary intake and risk of cancers of the UADT was mostly provided by case-control studies. To explain the cause and effect relationships, data from longitudinal studies or randomised controlled trials are needed.

Caution should be taken when interpreting findings from studies on diet and cancers of the UADT. Firstly, as known, dietary intake is strongly correlated with other factors that

influence the risk of cancers of the UADT, such as age, ethnicity, dental hygiene, smoking and alcohol use. When evaluating the association between dietary intake and cancers of the UADT, residual confounding or unmeasured confounding factors may bias the estimates of risk. Also, the interpretation of results may change depending on whether potential confounding variables are taken into account. Secondly, many of the associations between diet and disease are relatively subtle, very large studies were needed to detect statistically meaningful effects for such a weak association. Thirdly, it is particularly difficult to estimate the separate effects of different foods and nutrients due to the high degree of correlation between the different foods and nutrients. Fourthly, diet was usually poorly measured due to rudimentary dietary instruments used. Taken together, it is very difficult to determine whether relatively weak associations between diet and diseases are real or whether they reflect some type of subtle bias or measurement error that the researchers were unable to eliminate.

In summary, the study of the nutritional determinants of disease in human populations is a particularly challenging field of research. Measurement of the exposures of interest-dietary intakes –is extremely complex. It is very important to appreciate the inherent limits of epidemiology in the detection of weak associations and the complexities involved in measuring dietary intake, avoiding bias, assessing causality, and dealing appropriately with confounding factors. Accordingly, findings from nutritional epidemiology must be interpreted with caution. If, however, the findings from nutritional epidemiology are interpreted appropriately and applied judiciously, they can provide insights into the causation and prevention of many of today's most crucial health problems including cancers of the UADT.

Objective of the study

The present thesis was developed to identify the role of dietary intake on the development of cancers of the upper aero-digestive tract. Specific objectives of the study are as follows:

- To investigate the association between dietary intake and the risk of developing cancers of the upper aero-digestive tract, in terms of estimated intake of nutrients, specific foods, and food groups.
- To evaluate the confounding effect of several covariates on the association between dietary intake and UADT cancer risk.
- To examine if the effect of dietary factors varies across the three main cancer sites along the upper aero-digestive tract including the mouth, pharynx, and larynx.

Methodology

1. Overview

A large case-control study was sponsored by the Ludwig Institute for Cancer Research, São Paulo, Brazil, to investigate the main determinants of cancers of the upper aero-digestive tract (UADT) {Franco et al. 1989}. It was conducted in three metropolitan areas in Brazil: São Paulo (Southeast), Curitiba (South), and Goiânia (Central-West). To date, this multi-centre hospital-based case-control study is the second largest investigation worldwide to quantify the importance of risk factors for cancers of the UADT.

The present thesis is based on this study and utilized the interview data on food consumption as well as other risk factors to identify the role of diet and nutrient intake on the development of cancers of UADT. Detailed information on data collection and assessment of dietary intake are described in the corresponding section.

2. Subject recruitment

2.1 Case ascertainment

Cases of cancers of the UADT were identified through review of hospital discharges at three head and neck surgery centres in Brazil: São Paulo (Heliópolis Hospital), Curitiba (Erasto Gaertner Hospital), and Goiânia (Araújo Jorge Hospital). Patients with newly diagnosed carcinomas of the head and neck between February 1986 and January 1989

were considered eligible for the study, including patients with mouth cancer [International Classification of Diseases, 9th revision (ICD-9) 141-145] {Boyle, et al. 1990}, pharyngeal cancer (ICD-9 146-149), and laryngeal cancer (ICD-9 161). All patients with malignant neoplasm of the lip (ICD-9 140), salivary glands (ICD-9 142) and nasopharynx (ICD-9 147) were excluded. All recruited case subjects had no prior treatments for any type of cancer. All diagnoses were confirmed histologically and the anatomical sites were ascertained surgically.

It was estimated that the head and neck surgery service in the cities of Curitiba and Goiânia, two centres (Erasto Gaertner Hospital and Araújo Jorge Hospital) admitted 100% of all incident cancer cases in their respective areas during the period of study. However, due to the large population in the city, which limited the number of patients that can be admitted in one hospital, Heliópolis Hospital was responsible for treating only approximately 20% of all incident cancer cases in São Paulo during the same study period.

2.2 Control selection

Controls were sought from the same hospital as the case or from neighbouring general hospitals. Two controls were matched to each case on the basis of gender, 5-year age group, and trimester of hospital admission. Control patients with mental disorders (ICD-9: 290-319) or other cancers (ICD-9: 140-239) were ineligible.

3. Data Collection

3.1 Interview

Two trained nurses conducted interviews for all study subjects. The interviewers were unaware of the etiologic hypotheses being tested. Interviews lasted approximately 40-60 minutes. Given the sensitive nature of some items, the interviews were conducted in privacy. Interviews were immediately interrupted if patients complained of physical discomfort or if the interviewer suspected of difficulty in communicating with patients due to their pain or speech problems. In total, nine cases were eliminated from the study prior to matching because of refusal (1), physical conditions (7), and the inability to identify suitable controls (1).

3.2 Questionnaire

A standardized questionnaire was administered. The questionnaire comprised detailed information on socio-demographic characteristics, usual dietary and non-alcohol drinking habits during adulthood, family disease history, environmental and occupational exposures, tobacco and alcohol consumption, and oral hygiene habits. For cases, exposure histories other than dietary intake were obtained for the period before diagnosis of cancer and for controls, this information was acquired for the period prior to the date of interview. All questions about dietary intake for both cases and controls were asked about the subject's usual diet during adulthood.

The original questionnaire was written in Portuguese and is presented in Appendix I.

4. Measurement

4.1 Measurement of dietary exposure

Dietary practices were assessed in terms of the measurement of the intake of individual foods, food groups and nutrients.

4.1.1 Individual foods

Information on the usual frequency of consumption of foods was collected. There were 20 food items included in the original questionnaire. These selected food items were thought to represent the major sources of foods consumed by the Brazilian population during the study period. During the interview, the interviewer stated "How many times per week or month did you eat the following foods?" The options for frequency of consumption included eight categories as follows: 1) never, 2) less than once per month, 3) once a month, 4) 2-3 times per month, 5) 1-3 times per week, 6) 4-6 times per week, 7) once a day, and 8) unknown. The "Unknown" group comprised subjects who were known to eat an item but with an unknown frequency of consumption.

To increase statistical power, frequency of consumption for each food item was collapsed into 1) "less than once per month", 2) "once per month to 3 times per week", and 3) "equal to or more than 4 times per week". This was done by dividing the distribution of total consumption for both cases and controls into approximate tertiles.

Corresponding to the above three ordinal levels of consumption, two dummy variables for each dietary factor were created. An additional dummy variable was created for all missing values to permit the inclusion of all study subjects in the analysis and to explore the effect of missing variable on the outcome. Thus, in total, there were three dummy

variables plus one reference category for each food item. These dummy regressors were employed for dietary factors of interest in all models, except the models aiming to identify empirical confounders.

To facilitate the identification of empirical confounding variables, the dietary factor was further dichotomised based on the similarity of risk estimates in the crude model which included the dietary factor under investigation alone. In this scenario, missing values were treated as missing.

Table 5 lists the food items, which were included in the food questionnaire.

Table 5: Food items included in the questionnaire.

Food items	Description of foods in the questionnaire	Food items	Description of foods in the questionnaire
Fruits		**Vegetables**	
Lemon	Lemonade or product containing juice of lemon	Vegetable	Including cauliflower, spinach and broccoli
Orange	Orange or orange juice	Carrot	Any mode of preparation
Papaya	Papaya	Lettuce	Lettuce
Pequi	*Pequi*	Cassava	Flour or non-flour
Pinhao	*Pinhao*	Pumpkin	Any mode of preparation
		Tomato	Tomato or products which contain tomato paste
Meat		**Others**	
Smoked meat	Smoked meat	Pepper	Pepper in the pure form or as dressing
Grilled meat	Any type of meat that is prepared grilled or BBQ (not including other types)	Corn	Any mode of preparation
Dairy products		Eggs	Eggs
Milk	Milk	Pickles	Pickles
Cheese	Cheese or cheese derivative	Honey	Honey

4.1.2. Food groups

Three specific food categories were generated based on similarities in dietary constituents. These food groups included carotene-rich foods, citric fruits and spicy foods. The frequency of consumption of each food group was determined by the highest frequency of consumption of any of the food items included in that food group instead of summing them up. This approach was employed because it tended to reduce the correlation among components of food intake in the same food group. The level of consumption was thereafter categorized by dividing the distribution of total consumption for both cases and controls into approximate tertiles to increase the statistical power. The strategies used to create dichotomous and dummy variables were the same as that used for the food items.

Table 6 presents the food items included in each food group and their categories of consumption.

Table 6: Food groups, specific food items included in that food group and its associated categorized consumption.

Food group	Included food items	Categorized consumption
Carotene-rich foods	Carrots	Once or less than once per month
	Pumpkins	Twice per month to 3 times per week
	Papaya	Equal to or more than 4 times per week
Citric fruits	Lemon	Once or less than once per month
	Orange	Twice per month to 3 times per week
		Equal to or more than 4 times per week
Spicy foods	Peppers	Less than once per month
	Pickles	Once per month to 3 times per week
		Equal to or more than 4 times per week

4.1.3. Nutrients

To examine the relationships between nutrient intakes and the risk of cancers of the UADT, the food consumption data was additionally transformed into estimates of nutrient intake. Information on frequency and quantities usually consumed for each food item was used to develop nutrient intake. Based on findings suggesting associations between nutrients and the risk of cancers of the UADT in the literature, eight nutrient indices were generated including vitamin A, vitamin C, vitamin E, beta-carotene, folate, calcium, iron and zinc. The total daily nutrient intake was calculated as the sum of the individual daily consumption for all 20 selected food items containing the nutrient of interest. The relevant formula is listed as below:

$$\text{Daily nutrient intake} = \sum \text{frequency of food consumption} * \text{quantities of food consumption} * \text{nutrient composition}$$

Frequency of food consumption

The midpoint of values for each category of consumption was assigned as the frequency of food consumption to convert food consumption into nutrient intake. For example, if in the questionnaire, one category of frequency of food consumption ranged from 4 to 6 units, a value of 5 was assigned for that category. For the category of "unknown", the values of the frequency of food consumption for controls and cases were calculated separately based on the average frequency of consumption of that food among controls and cases, respectively.

Quantities of food consumption

Because the original questionnaire lacked data indicating the quantity of the food items consumed per serving, these values were determined by assigning the particular amount or portion size typically eaten in a Brazilian diet.

Nutrient composition table

The US Department of Agriculture (USDA) nutrient database {USDA, release 13} was used to obtain the nutritional value for the specified quantity of each food. Because there are some local Brazilian foods not contained in the USDA database, one Brazilian food composition tables (BFCT){Guilherme Franco 1987} was also employed. In addition, nutritional values used from USDA were compared to those corresponding to the BFCT. Whenever the nutritional value between USDA and BFCT differed by more than 10%, the value from the latter was used. However, for two food items: *pinhao* (common in Southern Brazil) and *pequi* (common in Central Brazil), information was not available from both sources of nutritional value. These two items were therefore excluded from the estimation of total nutrient intake.

The daily nutrient intake value was classified into four groups on the basis of the quartile cut-points corresponding to the distribution of exposure in the controls. Afterwards, the procedure used to create the dichotomous and dummy variables for each nutrient factor of interest was the same as that used for individual foods.

The nutrient values for each selected food item according to the USDA food composition database and Brazilian food composition table are presented in Appendix II.

4.1.4 The proportion of missing values of food intake

The proportion of missing values on food consumption for each of 20 food items in the questionnaire ranged from 0.1% to 1.7%. No subject had more than one food item of unknown frequency of consumption. However, missing values for each food item were grouped separately and coded as a dummy variable to maximise statistical power.

4.2 Measurement of smoking and alcohol consumption

Detailed information was collected on smoking and alcohol consumption. As these two factors are not only the two main determinants of cancers of the UADT, but also are strongly associated with dietary intake, they were considered as a priori confounding variables for the various dietary factors under investigation.

Tobacco consumption

Respondents were asked to indicate whether they considered themselves to be regular smokers, ex-smokers or non-smokers. For both current and ex-smokers, information on the type of cigarette smoked (with or without filter), the total number of years of smoking each type of cigarette (cigar, paper cigarette, pipe, and hand-rolled cigarette), and smoking cessation history was ascertained.

The intensity and duration of tobacco consumption were translated into a cumulative exposure variable (pack-years): one pack-year was defined as the cumulative exposure equivalent to smoking one pack of cigarettes daily during one year. In addition to cigarette smoking, other types of tobacco use, such as hand-rolled cigarettes, cigars, and pipes were also included to compute the pack-years of tobacco consumption. Doses were calculated as follows: 20 commercial-brand cigarettes = 4 hand-rolled, black tobacco cigarettes* = 4 cigars = 5 pipefuls with regular pipe tobacco = 1 pack. {Pintos, et al. 1998, Schlecht, et al. 1999}

* Black tobacco in Brazil is a non-commercial form of tobacco usually rolled in cornhusk leaves with an approximate tar content 5 times higher than that of commercial tobacco.

Six categories of tobacco consumption were used in data analysis: one baseline category for non-exposure, four exposure categories defined by the quartile cut-off values within exposed controls, and one category of missing value. These categories include 1) "never smokers", 2) "1-22 pack-years", 3) "23-45 pack-years", 4) "46-91pack-years", 5) "≥92 pack-years" and 6) "Unknown".

Alcohol consumption

Information was also collected on the number of years spent drinking, the daily and weekly quantities of drinks consumed for each type of alcohol (beer, wine, hard liquor, and *cachaca**), and the number of years since the drinking habit ceased.

Lifetime consumption of alcohol was determined for all types of alcoholic beverages, including beer, wine, hard liquor, and *cachaca*. Lifetime consumption of the different types of alcohol was expressed in terms of kilograms of ethanol. Ethanol concentration was estimated as follows: Beer = 5%, wine = 10%, hard liquor and *cachaca* = 50% {Pintos, et al. 1998, Schlecht, et al. 1999}.

Following the same procedure used for grouping categories of tobacco consumption, lifetime exposure of alcohol drinking was then defined as 1) "0-10 kg", 2) 11-133 kg", 3) "134-793 kg", 4) "794-1248 kg", 5) "≥1249 kg" and 6) "Unknown".

For the interest of capturing the confounding effect, all models adjusted for smoking and alcohol consumption contained five dummy variables for each of these two factors accommodating the ordinal categories of exposure and one for missing values.

* *Cachaca* is a distillate from sugar cane containing approximately 50% alcohol.

4.3 Measurement of other covariates

In addition to tobacco and alcohol consumption, information on other potential confounding variables was also collected. These variables can be classified into seven categories as listed below:

1) Socio-demographic characteristics: ethnicity, area of residence, education level, and household income.
2) Environmental risk exposure during previous employment or living condition: textile, wood and paper, mining, leather, metal, sugar and alcohol refining, rubber industries, printing, petroleum refining, and soybean industry.
3) Dental hygiene: dental health history, denture usage history, toothache (denture user), toothache (bad teeth) and brushing habits.
4) Family disease history: number and type of cancers for each family member including father, mother, sibling, children, uncle or aunt, cousin and others.
5) Lifestyle factors: consumption of hot meals or beverages.
6) Consumption of non-alcoholic drinks: *chimarrão**, tea, coffee and chocolate.
7) History of chewing tobacco.

*_Chimarrão_ is an infusion of the herb *Ilex paraguariensis*, which is cultivated on a commercial scale throughout South America. It is normally drunk very hot through a metal straw with a filtering tip.

5. Statistical Analysis

5.1. Conditional logistic regression

Relative Risk (RRs), as estimated by the exposure odd ratios (ORs), and their respective 95% confidence intervals (CI), were calculated for high and moderate consumption relative to low consumption to estimate the risk of developing cancers of the UADT with each dietary factor {Breslow & Day 1980}. Point and interval estimates for the RRs were computed from conditional logistic regression analyses to account for the 2:1 matching design of study.

5.2. Method of confounding selection

The selection of confounding variables was based on a change-in-estimate criterion {Mickey & Greenland 1989, Maldonado & Greenland 1993}, when comparing the adjusted OR with the baseline OR for a selected dietary factor. All covariates whose confounding ratio showed a 5% or greater change in either the negative or positive direction [(1-adjusted OR/baseline OR) $\geq \pm$ 5%] were considered as empirical confounding variables and were thereafter included in the final model for the dietary factor under investigation adjusting for all identified empirical confounders.

Baseline Model included a particular dietary factor of interest and adjusted for tobacco and alcohol consumption (prior confounding variables). The OR obtained from the baseline model for each dietary factor of interest was considered as baseline OR.

Adjusted Model was obtained by individually adding each additional potential confounding variable to the baseline model that was already adjusted for tobacco and

alcohol consumption. The OR obtained from the adjusted model for each dietary factor of interest was considered as adjusted OR.

Confounding ratio

The ratio between the adjusted OR and the baseline OR for each dietary factor of interest was considered as the confounding ratio (adjusted OR/baseline OR).

In addition to tobacco and alcohol consumption, factors related to socio-demographics, living conditions, living and occupational settings, lifestyle, dental health, and chewing tobacco were examined as potential confounders for the dietary variables of interest. Furthermore, excluding the food or food group variable of interest itself, other individual foods and food groups were also evaluated as potential confounding variables of the food or food group item of interest. However, individual foods, which comprise the food group, were not considered potential confounding variables for that food group. And, to avoid collinearity problems, no food or food group item was examined as potential confounding variable for the variable of nutrient index.

In the model used to identify empirical confounding variables, as previously discussed, a dichotomous variable specified the particular dietary factor of interest, while dummy regressors were employed for dietary factors that were considered as potential confounders. For the interest of capturing the confounding effect, all potential confounding variables with multiple categories were preserved as dummy regressors retained their original coding when added to models.

Table 7 shows the detailed information on all selected factors examined as potential confounding variables.

Table 7. Definition of selected factors examined as potential confounding variables.

Definition of variables	Categories
Race	White Black Mulatto
Place of residency	Rural Urban
Schooling level	Illiterate Primary school High school College or University
Monthly household income in US dollars	"0-30" "31-60" "61-200" "?201"
Piped water	Yes/No
Wood stove	Yes/No
Refrigerator	Yes/No
Lived within 1km of textile industry for at least 1 year	Yes/No
Lived within 1km of wood processing industry for a least 1 year	Yes/No
Lived within 1km of paper or cellulose industry for a least 1 year	Yes/No
Lived within 1km of mining industry for a least 1 year	Yes/No
Lived within 1km of leather or shoe manufactory for a least 1 year	Yes/No
Lived within 1km of metal processing industry for a least 1 year	Yes/No
Lived within 1km of sugar or alcohol production industry for a least 1 year	Yes/No
Lived within 1km of plastic or rubber industry for a least 1 year	Yes/No
Worked in textile industry for 6 months or more	Yes/No
Worked in wood processing industry for 6 months or more	Yes/No
Worked in paper or cellulose industry for 6 months or more	Yes/No
Worked in mining industry for 6 months or more	Yes/No
Worked in leather or shoe manufactory for 6 months or more	Yes/No
Worked in metal processing industry for 6 months or more	Yes/No
Worked in sugar or alcohol production industry for 6 months or more	Yes/No
Worked in plastic or rubber industry for 6 months or more	Yes/No
Worked in printing industry for 6 months or more	Yes/No
Worked in petroleum refining industry for 6 months or more	Yes/No
Worked in soybean industry for 6 months or more	Yes/No
Tonsillectomy	Yes/No
Cancer in first degree family member (father, mother, sibling and children)	Yes/No

Table 7 (continued): Definition of selected factors examined as potential confounding variables.

Definition of variables	Categories
Denture use	Yes/No
Denture use causing sores	Yes/No
Bad teeth	Yes/No
Poor dentition	Yes/No
Frequency of brushing	Rarely/Daily
Coffee drinking	Never drink café Drink café but not hot Drink hot café
Chimarrão drinking	Never drink *chimarrão* Drink *chimarrão* but not hot Drink hot *chimarrão*
Tea drinking	Never drink tea Drink tea but not hot Drink hot tea
Chocolate drinking	Never drink chocolate Drink chocolate but not hot Drink hot chocolate
Ate hot foods	Yes/No
Type of smoker	Never smoked Smoked only paper cigarette Smoked any type of cigarette Smoked pipefuls or cigars or hand rolled cigarette
Total lifetime pack-years of smoking	"1"=0, "1-22"=1, "23-45"=2, "46-91"=3, ">=92"=4
Kilograms of lifetime alcohol consumption	"0-10"=1, "11-133"=2, "134-793"=3, "794-1248"=4, ">=1249"=5
Tobacco chewing	Yes/No

5.3. The conservative approach for confounding selection

In this study, an overly conservative approach was used in which we only adjusted for those confounding variables whose inclusion in the models caused the ORs of the dietary variable of interest to shift towards null value. For dietary factors that showed a positive association with the risk of cancer (OR>1), the ORs were estimated adjusting only for "positive confounders". "Positive confounders" refers to those empirical confounders that decreased, but not those that increased, the point estimate of the dietary factor under investigation by 5% or more in the adjusted model. Conversely, if the dietary factor indicated a reduction in the risk of cancer (OR<1), then only "negative confounding variables", which increased the point estimate for the adjusted odd ratio, were included in the conservative model.

It was clear that this model was not valid for risk estimation as it biases the estimates towards a null association. However, if a significant risk for cancers of the UADT persisted for the selected dietary factor despite this overly conservative approach, it was then concluded that the effect was unlikely to be explained by confounding and was possibly indicative of a causal association.

5.4. Site-specific analysis

Since the effect of dietary factors could differ with respect to tumor site along the UADT, analyses were repeated for all cancers of the UADT combined as well as for each anatomical site: the mouth, pharynx, and larynx. All analyses followed the same procedure to identify potential confounders empirically, using a 5% change-in-estimate criterion.

In the interest of uniform style, all risk associations are described as per the ORs and their respective 95% CIs. The RR designation, considered synonymous in this context, will not be used in subsequent sections.

All statistical analyses were carried out using the SAS version 6.12 software program.

Results

1. Descriptive statistics

1.1 Study population

1.1.1 The referral pattern for cases

In total, 784 patients with newly diagnosed carcinomas of the head and neck were included in the study as case subjects. Among these case subjects, 373 (47.6%) were patients with oral cancer [(ICD-9) 141-145], 217 (27.7%) with pharyngeal cancer (ICD-9 146-149), and 194 (24.7%) with laryngeal cancer (ICD-9 161). Subjects were recruited from three head and neck surgery centers in Brazil: 213 (27.2%) in São Paulo (Heliópolis Hospital), 380 (48.5%) in Curitiba (Erasto Gaertner Hospital), and 191 (24.4%) in Goiânia (Araújo Jorge Hospital). The distributions of eligible cases according to the city of enrollment and the anatomic site of cancer are presented in Table 8.

Table 8. Recruitment of cases by area and anatomic site of cancer.

Site of cancer / City of enrolment	Mouth	Pharynx	Larynx	Total number of cases (column %)
	Cases (column %)	Cases (column %)	Cases (column %)	
São Paulo	107 (28.7)	62 (28.6)	44 (22.7)	213 (27.2)
Curitiba	170 (45.6)	113 (52.1)	97 (50.0)	380 (48.5)
Goiânia	96 (25.7)	42 (19.3)	53 (27.3)	191 (24.3)
Total number of cases (row %)	373 (47.6)	217 (27.7)	194 (24.7)	784

1.1.2 The underlying causes of hospitalization among controls

1568 hospital patients were selected as controls. The underlying causes of hospitalization among matched controls could be grouped into 13 diagnostic categories, coded according to the ICD-9 (Table 9). As can be seen, the most common causes of hospitalization among controls were digestive system diseases (26.0%) and cardiovascular system diseases (24.9%).

Table 9. Underlying causes for hospitalization among controls ranked according the frequency.

Rank	Diagnostic Categories	Code ICD-9	Number of Patients	%
1	Digestive system diseases	520-579	407	26.0
2	Cardiovascular system diseases	390-459	390	24.9
3	Ill-defined diagnostic conditions	780-799	165	10.5
4	Trauma and poisoning	800-999	135	8.6
5	Genito-urinary tract diseases	580-629	118	7.5
6	Respiratory system diseases	460-519	95	6.1
7	Infectious and parasitic diseases	001-139	64	4.1
8	Nervous and sensory system diseases	320-389	53	3.4
9	Osteo-muscular diseases	710-739	49	3.1
10	Endocrine, metabolic and blood disorders	240-289	48	3.1
11	Skin diseases	680-709	31	2.0
12	Congenital disorders	740-759	8	0.5
13	Pregnancy-associated diseases	630-676	5	0.3
14	Neoplasm	140-239	0	0.0
15	Mental disorders *	290-319	0	0.0
	Total		1568	100.0

* Patients with neoplasms (ICD-9: 140-239) and mental disorders (ICD-9: 290-319) were considered ineligible as controls.

1.2. Sociodemographic characteristics

Table 10 describes general characteristics and established risk factors for cancers of the UADT in the study population. Given the matched design used in this study, the distributions of age and gender for cases and controls are identical. The average age was 56 and there were over six times more male subjects than female in each group. The percentage of white patients among cases (84%) was slightly higher than among controls (79%). There were more illiterate cases than controls (32% vs 27%). Also, cases had less education and lower median family income. For both cases and controls, more than 75% of them had lived in a rural area. Nearly half of the subjects resided in the Southern part of Brazil (Curitiba).

Cases and controls differed substantially according to the intensity of smoking and alcohol drinking: 28% of the controls had never smoked compared with only 4% of the cases. Likewise, for alcohol drinking, 25% of the controls compared with 9% of cases were non-drinkers. This was expected, because smoking and alcohol are two established risk factors for upper aero-digestive tract cancer.

Table 10: Distribution of selected characteristics for cases with cancers of the upper aero-digestive tract and controls in the Brazilian study.

Variable	Categories	Cases	%	Controls	%
Age (years)	<50	169	21.6	338	21.6
	50-59	278	35.5	556	35.5
	60-69	218	27.8	438	27.9
	>70	119	15.2	236	15.1
Gender	Female	101	12.9	202	12.9
	Male	683	87.1	1366	87.1
Ethnicity	White	660	84.2	1236	78.8
	Mulatto	86	11.0	236	5.1
	Black	31	4.0	78	5.0
	Other	4	0.5	10	0.6
	Unknown	3	0.4	8	0.5
Education level	Illiterate	252	32.1	433	27.6
	Grade school	467	59.6	961	61.3
	High school	51	6.5	124	7.9
	College	14	1.8	49	3.1
	Unknown	0	0.00	1	0.1
Monthly household income (US dollars)	<30	200	25.5	295	18.8
	31-60	167	21.3	320	20.4
	61-110	124	15.8	296	18.9
	111-200	130	16.6	299	19.1
	>=201	147	18.8	315	20.1
	Unknown	16	2.04	43	2.7
City of residence	São Paulo	213	27.2	426	27.2
	Curitiba	380	48.5	760	48.5
	Goiânia	191	24.4	382	24.4
Ever lived in rural area > 5 years	No	193	24.6	370	23.6
	Yes	591	75.4	1198	76.4
Marital status	Never married	63	8.1	123	7.9
	Currently married	573	73.4	1184	75.7
	Formerly married	145	18.6	257	16.4
Tobacco smoking (in pack-years)	<1	30	3.8	358	23.0
	1-22	142	18.2	362	23.2
	23-45	207	26.5	333	21.4
	46-91	200	25.6	267	17.1
	>91	202	25.9	239	15.3
Alcohol consumption (in kg)	<11	95	12.1	416	26.7
	11-133	80	10.2	295	18.9
	134-793	181	23.1	366	23.5
	794-1248	166	21.2	233	14.9
	>1248	261	33.3	249	16.0

1.3. Characteristics of dietary intake

Table 11 presents the frequencies of intake of 20 selected food items for cases and controls. Referring to the consumption of fruits, control subjects reported higher frequencies of consumption of lemon, orange and papaya than those reported by cases in each of anatomical cancer sites. Control subjects reported a lower frequency of intake of *pinhao*, however, there are only few subjects in the highest consumption level (ate at least 4 times per week) for both case and control groups. Although the frequency of intake of vegetables in general did not differ markedly between cases and controls, cases in each of the anatomical cancer sites were more likely to report a higher frequency of consumption of cassava. Cases with laryngeal cancer reported a lower frequency of consumption of carrot and cases with pharyngeal cancer ate pumpkin less often than controls. Cases also reported higher frequencies of consumption of smoked meat, grilled meat, egg, corn, peppers, and pickles than those reported by controls.

In addition to using foods to represent dietary intake, diet was also described in terms of nutrients. Table 12 provides the statistics of mean, median, and quartile range of each nutrient index for cases and controls, including vitamin A, vitamin C, vitamin E, beta-carotene, folate, calcium, iron and zinc. Controls had higher mean and median values of daily consumption of vitamin A, vitamin C, beta-carotene, and folate than cases in each of the anatomical cancer sites. Cases had higher mean and median value of daily consumption of iron and zinc than controls.

Table 11: Distribution of the frequency of intake of selected food items for cases and controls.

Food items	Frequency of consumption	Controls (%)		Cases (%)					
				Mouth		Pharynx		Larynx	
Fruits									
Lemon	<1/Month	745	47.7	195	52.7	116	53.7	99	51.3
	1/Month-3/Week	534	34.2	120	32.4	69	31.9	61	31.6
	>=4/Week	282	18.1	55	14.9	31	14.4	33	17.1
Orange	<1/Month	538	34.5	176	47.3	99	46.3	92	47.9
	1/Month-3/Week	643	41.2	123	33.1	77	36.0	61	31.8
	>=4/Week	379	24.3	73	19.6	38	17.8	39	20.3
Papaya	<1/Month	813	52.4	220	60.1	126	58.6	123	64.4
	1/Month-3/Week	603	38.8	125	34.2	79	36.7	54	28.3
	>=4/Week	137	8.8	21	5.7	10	4.7	14	7.3
Pequi	<1/Month	1447	93.1	335	92.3	202	94.0	175	90.7
	1/Month-3/Week	101	6.5	26	7.2	12	5.6	17	8.8
	>=4/Week	6	0.4	2	0.6	1	0.5	1	0.5
Pinhao	<1/Month	1394	90.2	330	90.4	188	87.0	169	88.5
	1/Month-3/Week	141	9.12	29	8.0	24	11.1	17	8.9
	>=4/Week	11	0.7	6	1.6	4	1.9	5	2.6
Vegetables									
Carrot	<1/Month	756	48.7	203	55.5	115	53.2	115	59.9
	1/Month-3/Week	676	43.5	135	36.9	86	39.8	66	34.4
	>=4/Week	121	7.8	28	7.7	15	6.9	11	5.7
Cauliflower	<1/Month	480	30.9	124	33.5	80	37.0	75	39.7
or Spinach	1/Month-3/Week	984	63.4	221	59.7	125	57.9	100	52.9
or Broccoli	>=4/Week	88	5.7	25	6.8	11	5.1	14	7.4
Lettuce	<1/Month	350	22.4	105	28.4	67	30.9	48	24.9
	1/Month-3/Week	878	56.2	195	52.7	114	52.5	102	52.9
	>=4/Week	334	21.4	70	18.9	36	16.6	43	22.3
Cassava	<1/Month	363	23.2	75	20.2	55	25.5	46	23.7
	1/Month-3/Week	856	54.8	197	53.0	111	51.4	98	50.5
	>=4/Week	343	22.0	100	26.9	50	23.2	50	25.8
Pumpkin	<1/Month	782	49.9	196	52.6	120	55.3	103	53.4
	1/Month-3/Week	661	42.2	148	39.7	87	40.1	76	39.4
	>=4/Week	123	7.9	29	7.8	10	4.6	14	7.3
Tomato	<1/Month	259	16.6	81	21.8	42	19.6	38	19.6
	1/Month-3/Week	890	56.9	201	54.2	115	53.7	105	54.1
	>=4/Week	414	26.5	89	24.0	57	26.6	51	26.3

Table 11 (continued): Distribution of the frequency of intake of selected food items for cases and controls.

Food items	Frequency of consumption	Controls (%)		Cases (%)					
				Mouth		Pharynx		Larynx	
Meat									
Smoked	<1/Month	1215	78.5	264	72.9	155	72.8	142	74.7
	1/Month-3/Week	282	18.2	82	22.7	51	23.9	39	20.5
	>=4/Week	50	3.2	16	4.4	7	3.3	9	4.7
Grilled	<1/Month	1109	71.3	261	70.9	145	67.8	129	66.8
	1/Month-3/Week	409	26.3	86	23.4	65	30.4	59	30.6
	>=4/Week	38	2.4	21	5.7	4	1.9	5	2.6
Milk	<1/Month	305	19.5	84	22.6	45	20.8	43	22.2
	1/Month-3/Week	340	21.7	86	23.2	47	21.8	38	19.6
	>=4/Week	920	58.8	201	54.2	124	57.4	113	58.3
Cheese	<1/Month	805	51.5	183	49.5	103	47.5	92	47.9
	1/Month-3/Week	531	34.0	136	36.8	73	33.6	76	39.6
	>=4/Week	226	14.5	51	13.8	41	18.9	24	12.5
Eggs	<1/Month	201	12.9	42	11.3	16	7.4	14	7.22
	1/Month-3/Week	936	59.9	218	58.6	130	59.9	124	63.9
	>=4/Week	425	27.2	112	30.1	71	32.7	56	28.9
Corn	<1/Month	459	29.4	119	32.0	57	26.6	54	27.8
	1/Month-3/Week	899	57.6	202	54.3	117	54.7	101	52.1
	>=4/Week	203	13.0	51	13.7	40	18.7	39	20.1
Peppers	<1/Month	723	46.7	129	35.1	73	33.6	78	40.6
	1/Month-3/Week	333	21.5	92	25.0	45	20.7	47	24.5
	>=4/Week	492	31.8	147	40.0	99	45.6	67	34.9
Pickles	<1/Month	1235	79.7	271	73.8	162	74.7	146	76.0
	1/Month-3/Week	199	12.9	55	15.0	37	17.1	25	13.0
	>=4/Week	115	7.4	41	11.2	18	8.3	21	10.9
Honey	<1/Month	1289	82.9	309	85.1	180	84.9	146	76.8
	1/Month-3/Week	167	10.7	41	11.3	14	6.6	28	14.7
	>=4/Week	99	6.4	13	3.6	18	8.5	16	8.4

Table 12: Mean, median and quartile values of daily nutrients intake derived from food consumption reported for cases and controls.

Nutrient	Statistic	Controls	Cases		
			Mouth	Pharynx	Larynx
Vitamin A (ug)	Mean	408.6	389.5	405.9	377.0
	Median	375.9	344.4	348.3	333.9
	25th quartile	228.0	223.7	220.4	204.0
	75th quartile	546.4	521.8	535.6	479.7
Vitamin C (mg)	Mean	161.3	137.1	135.1	131.9
	Median	126.5	59.9	68.6	56.4
	25th quartile	37.7	34.2	32.7	32.9
	75th quartile	203.8	170.9	164.9	169.0
Vitamin E (mg)	Mean	1.1	1.1	1.1	1.1
	Median	1.0	1.0	1.0	0.9
	25th quartile	0.6	0.6	0.6	0.6
	75th quartile	1.5	1.4	1.4	1.4
Beta-carotene (ug)	Mean	1643.6	1486.9	1427.4	1379.2
	Median	1369.2	1163.3	1035.4	821.5
	25th quartile	512.1	426.0	408.3	424.4
	75th quartile	2431.4	2099.7	1971.3	2076.0
Folate (ug)	Mean	79.1	72.7	73.0	73.5
	Median	69.0	59.5	61.4	62.9
	25th quartile	41.7	38.0	38.9	37.4
	75th quartile	109.2	100.3	97.7	97.8
Calcium (mg)	Mean	270.9	252.5	274.1	262.8
	Median	313.7	267.2	310.6	309.0
	25th quartile	103.1	72.7	102.5	100.7
	75th quartile	391.9	385.2	387.1	377.3
Iron (mg)	Mean	1.3	1.4	1.4	1.4
	Median	1.1	1.2	1.2	1.1
	25th quartile	0.7	0.8	0.7	0.7
	75th quartile	1.7	1.8	1.8	1.7
Zinc (mg)	Mean	1.8	2.0	2.0	2.0
	Median	1.6	1.6	1.8	1.7
	25th quartile	0.9	0.9	1.1	1.0
	75th quartile	2.3	2.5	2.4	2.5

2. Dietary intake and the risk of cancers of the upper aero-digestive tract

2.1. Associations with individual foods

2.1.1. All cancers of the upper aero-digestive tract combined

Table 13 lists the ORs from the crude, alcohol and tobacco adjusted, all empirical confounders adjusted, and conservatively adjusted models for all cancer sites combined. Referring to consumption of fruits, a significantly protective effect of lemon, orange, and papaya intake was observed after adjusting for smoking and alcohol consumption (OR= 0.73, 95% CI: 0.5-1.0; OR= 0.58, 95% CI: 0.4-0.8; OR= 0.51, 95% CI: 0.3-0.8, respectively). After adjustment of smoking and alcohol consumption, additionally controlling for all confounders identified empirically using a 5% change-in-estimate, the protective effects of orange and papaya intakes were maintained (OR= 0.65, 95% CI: 0.5-0.9 and OR= 0.48, 95% CI: 0.3-0.8), whereas the protective effect of lemon intake was no longer found. More impressively, in the conservative models that only adjusted for those confounding variables that always bring the ORs of the dietary variable of interest towards null value, intake of orange and papaya had a persistently protective effect with significant ORs. The intake of *pequi* and *pinhao* appeared to be associated with an increased risk for cancers of the UADT in the crude model. After adjusting for smoking and alcohol consumption as well as empirical confounders, such trend was only maintained for the consumption of *pinhao* (OR= 2.97, 95% CI: 1.1-8.3) (OR= 3.15, 95% CI: 1.1-9.1) but not for *pequi*.

Referring to consumption of vegetables, intakes of carrot, lettuce, pumpkins, and tomato showed an inverse association with the risk of cancers of the UADT in the crude model. However, the significant protective effect was only observed for the consumption of

tomato after adjusting for smoking and alcohol consumption (OR=0.73, 95% CI: 0.5-1.0). Additionally, controlling for all empirical confounders, no significantly protective effect on the risk of cancers of the UADT was maintained for the consumption of any type of vegetables.

Increased consumption of smoked and grilled meat was associated with an increased risk for cancers of the UADT in the crude model. However, after adjusting for smoking and alcohol consumption, a substantial increase in risk was only observed for grilled meat (OR=2.15, 95% CI: 1.1-4.1). Such trend was maintained significantly even after adjusting for all empirical confounders (OR=2.14, 95% CI: 1.0-4.1).

Similarly, elevated but less pronounced risk levels were seen with increased consumption of eggs, peppers, and cheese. Increases in risk with increased consumption of eggs and peppers persisted after adjusting for smoking and alcohol (OR=1.39, 95% CI: 1.0-2.0 and OR= 1.28, 95% CI: 1.0-1.6) as well as all empirical confounders (OR= 1.62, 95% CI: 1.1-2.4 and OR= 1.28, 95% CI: 1.0-1.6). Even after controlling for "positive confounders", such positive associations remained significant (OR= 1.39, 95% CI: 1.0-2.0 and OR= 1.28, 95% CI: 1.0-1.6). Interestingly, increased intake of cheese showed a significantly positive association with the risk of cancers of the UADT after adjusting for all empirical confounders (OR= 1.39, 95% CI: 1.0-2.0), while such an association was not observed when adjusting only for smoking and alcohol consumption.

All confounders identified empirically using a 5% change- in- estimate for each individual food are presented in Appendix III.

Table 13. Relative risks of the cancers of the upper aero-digestive tract (all sites combined) associated with the intake of specific food items.

Food items	Frequency of consumption	Crude[1] OR	Adjusted for smoking & alcohol OR	95% CI		Fully adjusted[2] OR	95% CI		Conservatively Adjusted[3] OR	95% CI	
Fruits											
Lemon	<1/Month	1.00	1.00	(ref)		1.00	(ref)		---	---	---
	1/Month-3/Week	0.82	0.86	0.7	1.1	1.05	0.8	1.4	---	---	---
	>=4/Week	0.72	0.73	0.5	1.0	0.95	0.7	1.3	---	---	---
Orange	<1/Month	1.00	1.00	(ref)		1.00	(ref)		1.00	(ref)	
	1/Month-3/Week	0.52	0.60	0.5	0.8	0.66	0.5	0.8	0.66	0.5	0.8
	>=4/Week	0.48	0.58	0.4	0.8	0.65	0.5	0.9	0.65	0.5	0.9
Papaya	<1/Month	1.00	1.00	(ref)		1.00	(ref)		1.00	(ref)	
	1/Month-3/Week	0.68	0.74	0.6	0.9	0.77	0.6	1.0	0.82	0.6	1.0
	>=4/Week	0.52	0.51	0.3	0.8	0.48	0.3	0.8	0.55	0.4	0.8
Pequi	<1/Month	1.00	1.00	(ref)		1.00	(ref)		---	---	---
	1/Month-3/Week	1.18	0.96	0.6	1.5	1.01	0.6	1.6	---	---	---
	>=4/Week	1.35	1.42	0.3	5.9	1.85	0.4	7.7	---	---	---
Pinhao	<1/Month	1.00	1.00	(ref)		1.00	(ref)		1.00	(ref)	
	1/Month-3/Week	1.03	1.02	0.7	1.5	1.09	0.7	1.6	0.97	0.7	1.4
	>=4/Week	3.13	2.97	1.1	8.3	3.15	1.1	9.1	2.20	0.8	6.1
Vegetables											
Carrot	<1/Month	1.00	1.00	(ref)		1.00	(ref)		---	---	---
	1/Month-3/Week	0.71	0.77	0.6	1.0	0.93	0.7	1.2	---	---	---
	>=4/Week	0.74	0.79	0.5	1.2	1.02	0.7	1.6	---	---	---
Cauliflower	<1/Month	1.00	1.00	(ref)		1.00	(ref)		---	---	---
or Spinach	1/Month-3/Week	0.78	0.80	0.6	1.0	0.98	0.8	1.2	---	---	---
or Broccoli	>=4/Week	0.98	1.03	0.7	1.6	1.26	0.8	2.0	---	---	---
Lettuce	<1/Month	1.00	1.00	(ref)		1.00	(ref)		---	---	---
	1/Month-3/Week	0.71	0.78	0.6	1.0	0.92	0.7	1.2	---	---	---
	>=4/Week	0.66	0.77	0.6	1.1	0.97	0.7	1.4	---	---	---
Cassava	<1/Month	1.00	1.00	(ref)		1.00	(ref)		---	---	---
	1/Month-3/Week	0.98	0.94	0.7	1.2	0.96	0.7	1.2	---	---	---
	>=4/Week	1.20	1.08	0.8	1.4	1.02	0.8	1.4	---	---	---
Pumpkin	<1/Month	1.00	1.00	(ref)		1.00	(ref)		---	---	---
	1/Month-3/Week	0.81	0.85	0.7	1.1	0.98	0.8	1.3	---	---	---
	>=4/Week	0.71	0.73	0.5	1.1	0.81	0.5	1.3	---	---	---
Tomato	<1/Month	1.00	1.00	(ref)		1.00	(ref)		---	---	---
	1/Month-3/Week	0.73	0.74	0.6	1.0	1.01	0.7	1.4	---	---	---
	>=4/Week	0.72	0.73	0.5	1.0	1.14	0.8	1.7	---	---	---

Table 13 (continued): Relative risks of cancers of the upper aero-digestive tract (all sites combined) associated with the intake of specific food items.

Food items	Frequency of consumption	Crude[1] OR	Adjusted for smoking & alcohol OR	95% CI		Fully adjusted[2] OR	95% CI		Conservatively Adjusted[3] OR	95% CI	
Meat											
Smoked	<1/Month	1.00	1.00	(ref)		1.00	(ref)		1.00	(ref)	
	1/Month-3/Week	1.41	1.13	0.9	1.5	1.28	1.0	1.7	1.13	0.9	1.5
	>=4/Week	1.52	1.20	0.7	2.1	1.32	0.8	2.3	1.20	0.7	2.1
Grilled	<1/Month	1.00	1.00	(ref)		1.00	(ref)		1.00	(ref)	
	1/Month-3/Week	1.11	1.15	0.9	1.4	1.22	0.9	1.6	1.11	0.9	1.4
	>=4/Week	2.03	2.15	1.1	4.1	2.14	1.0	4.1	1.72	0.9	3.4
Milk	<1/Month	1.00	1.00	(ref)		1.00	(ref)		---	---	---
	1/Month-3/Week	0.89	1.00	0.7	1.4	1.12	0.8	1.6	---	---	---
	>=4/Week	0.84	1.01	0.8	1.3	1.20	0.9	1.6	---	---	---
Cheese	<1/Month	1.00	1.00	(ref)		1.00	(ref)		1.00	(ref)	
	1/Month-3/Week	1.16	1.17	0.9	1.5	1.41	1.1	1.8	1.17	0.9	1.5
	>=4/Week	1.11	1.14	0.8	1.5	1.44	1.0	2.0	1.14	0.8	1.5
Eggs	<1/Month	1.00	1.00	(ref)		1.00	(ref)		1.00	(ref)	
	1/Month-3/Week	1.42	1.34	1.0	1.9	1.55	1.1	2.2	1.34	1.0	1.9
	>=4/Week	1.60	1.39	1.0	2.0	1.62	1.1	2.4	1.39	1.0	2.0
Corn	<1/Month	1.00	1.00	(ref)		1.00	(ref)		---	---	---
	1/Month-3/Week	0.93	0.88	0.7	1.1	0.85	0.7	1.1	---	---	---
	>=4/Week	1.29	1.09	0.8	1.5	0.93	0.7	1.3	---	---	---
Peppers	<1/Month	1.00	1.00	(ref)		1.00	(ref)		1.00	(ref)	
	1/Month-3/Week	1.42	1.18	0.9	1.5	1.18	0.9	1.5	1.18	0.9	1.5
	>=4/Week	1.68	1.28	1.0	1.6	1.28	1.0	1.6	1.28	1.0	1.6
Pickles	<1/Month	1.00	1.00	(ref)		1.00	(ref)		---	---	---
	1/Month-3/Week	1.28	1.07	0.8	1.4	1.01	0.8	1.4	---	---	---
	>=4/Week	1.57	1.15	0.8	1.7	1.07	0.7	1.5	---	---	---
Honey	<1/Month	1.00	1.00	(ref)		1.00	(ref)		---	---	---
	1/Month-3/Week	1.02	1.04	0.7	1.4	1.12	0.8	1.6	---	---	---
	>=4/Week	0.95	0.96	0.6	1.4	1.13	0.7	1.7	---	---	---

[1] By conditional logistic regression with matching variables: age, sex, hospital, and admission period.
[2] Adjusted additionally for all empirical confounders (see text for explanation).
[3] Adjusted only for positive or negative confounders (see text for explanation).

2.1.2. Cancer of the mouth

Table 14 shows the ORs from the crude, alcohol and tobacco adjusted, all empirical confounders adjusted, and conservatively adjusted models for the cancer of the mouth. After adjusting for smoking and alcohol consumption, inverse associations with the consumption of lemon, papaya, lettuce, and tomato to the risk of cancer of the mouth were maintained but with marginally significant ORs. Only the intake of orange presented a significantly protective effect on cancer of the mouth (OR=0.62, 95% CI: 0.4-1.0). This inverse association was also observed after controlling for all empirical confounders, however, it did not persist across all the levels of consumption.

A substantial increase in risk was seen for grilled meat intake not only after adjusting for smoking and alcohol consumption (OR=3.89, 95% CI: 1.5-9.8) but also after adjusting for all empirical confounders (OR=5.88, 95% CI: 1.9-18.0). Even in the conservatively adjusted model, the intake of grilled meat presented a significant increase in risk for cancer of the mouth (OR=3.13, 95% CI: 1.2-8.3).

While a positive association between *pinhao* intake and cancer of the mouth was not present with a significant OR when controlling for smoking and alcohol consumption, a substantial increase in risk was observed after adjusting for all empirical confounders (OR=6.60, 95% CI: 1.1-39.0). Such wide confidence interval is due to the small number of subjects in the highest level of intake category. Elevated risk levels were also seen for the intake of peppers and cheese but with marginally significant ORs after adjusting for smoking and alcohol consumption as well as all empirical confounders.

Table 14. Relative risks of cancer of the mouth associated with the intake of specific food items.

Food items	Frequency of consumption	Crude[1] OR	Adjusted for smoking & alcohol OR	95% CI		Fully adjusted[2] OR	95% CI		Conservatively Adjusted[3] OR	95% CI	
Fruits											
Lemon	<1/Month	1.00	1.00	(ref)		1.00	(ref)		---	---	---
	1/Month-3/Week	0.74	0.78	0.6	1.1	0.93	0.6	1.4	---	---	---
	>=4/Week	0.67	0.70	0.4	1.1	0.91	0.6	1.5	---	---	---
Orange	<1/Month	1.00	1.00	(ref)		1.00	(ref)		1.00	(ref)	
	1/Month-3/Week	0.46	0.53	0.4	0.8	0.60	0.4	0.9	0.60	0.4	0.9
	>=4/Week	0.46	0.62	0.4	1.0	0.73	0.5	1.2	0.73	0.5	1.2
Papaya	<1/Month	1.00	1.00	(ref)		1.00	(ref)		---	---	---
	1/Month-3/Week	0.69	0.81	0.6	1.1	0.83	0.6	1.2	---	---	---
	>=4/Week	0.48	0.59	0.3	1.1	0.53	0.3	1.1	---	---	---
Pequi	<1/Month	1.00	1.00	(ref)		1.00	(ref)		---	---	---
	1/Month-3/Week	0.85	0.65	0.3	1.3	0.63	0.3	1.3	---	---	---
	>=4/Week	1.33	1.91	0.3	13.0	2.03	0.3	13.9	---	---	---
Pinhao	<1/Month	1.00	1.00	(ref)		1.00	(ref)		1.00	(ref)	
	1/Month-3/Week	0.85	0.93	0.6	1.6	1.06	0.6	2.0	0.93	0.5	1.6
	>=4/Week	2.91	2.45	0.6	10.9	6.60	1.1	39.0	1.44	0.3	6.9
Vegetables											
Carrot	<1/Month	1.00	1.00	(ref)		1.00	(ref)		---	---	---
	1/Month-3/Week	0.79	0.85	0.6	1.2	1.01	0.7	1.5	---	---	---
	>=4/Week	0.91	0.97	0.6	1.7	1.22	0.6	2.4	---	---	---
Cauliflower	<1/Month	1.00	1.00	(ref)		1.00	(ref)		---	---	---
or Spinach	1/Month-3/Week	0.85	0.84	0.6	1.1	0.99	0.7	1.4	---	---	---
or Broccoli	>=4/Week	0.93	1.15	0.6	2.1	1.49	0.8	2.8	---	---	---
Lettuce	<1/Month	1.00	1.00	(ref)		1.00	(ref)		---	---	---
	1/Month-3/Week	0.65	0.77	0.5	1.1	0.89	0.6	1.3	---	---	---
	>=4/Week	0.58	0.67	0.4	1.1	0.70	0.4	1.2	---	---	---
Cassava	<1/Month	1.00	1.00	(ref)		1.00	(ref)		---	---	---
	1/Month-3/Week	1.15	1.07	0.7	1.6	1.02	0.7	1.5	---	---	---
	>=4/Week	1.47	1.36	0.9	2.1	1.32	0.8	2.1	---	---	---
Pumpkin	<1/Month	1.00	1.00	(ref)		1.00	(ref)		---	---	---
	1/Month-3/Week	0.78	0.84	0.6	1.2	0.81	0.6	1.2	---	---	---
	>=4/Week	0.73	0.79	0.4	1.5	0.66	0.3	1.3	---	---	---
Tomato	<1/Month	1.00	1.00	(ref)		1.00	(ref)		---	---	---
	1/Month-3/Week	0.69	0.70	0.5	1.0	0.96	0.6	1.6	---	---	---
	>=4/Week	0.62	0.66	0.4	1.1	1.06	0.6	1.9	---	---	---

Table 14 (continued): Relative risks of cancer of the mouth associated with the intake of specific food items.

Food items	Frequency of consumption	Crude[1] OR	Adjusted for smoking & alcohol OR	95% CI		Fully adjusted [2] OR	95% CI		Conservatively Adjusted [3] OR	95% CI	
Meat											
Smoked	<1/Month	1.00	1.00	(ref)		1.00	(ref)		---	---	---
	1/Month-3/Week	1.28	0.96	0.7	1.4	1.10	0.7	1.6	---	---	---
	>=4/Week	1.52	1.14	0.5	2.5	1.21	0.6	2.6	---	---	---
Grilled	<1/Month	1.00	1.00	(ref)		1.00	(ref)		1.00	(ref)	
	1/Month-3/Week	0.93	0.97	0.7	1.4	0.96	0.6	1.4	1.01	0.7	1.5
	>=4/Week	2.64	3.89	1.5	9.8	5.88	1.9	18.0	3.13	1.2	8.3
Milk	<1/Month	1.00	1.00	(ref)		1.00	(ref)		---	---	---
	1/Month-3/Week	0.95	1.20	0.8	1.9	1.47	0.9	2.4	---	---	---
	>=4/Week	0.77	1.00	0.7	1.4	1.28	0.9	1.9	---	---	---
Cheese	<1/Month	1.00	1.00	(ref)		1.00	(ref)		1.00	(ref)	
	1/Month-3/Week	1.14	1.22	0.9	1.7	1.51	1.1	2.2	1.22	0.9	1.7
	>=4/Week	1.09	1.18	0.8	1.9	1.55	0.9	2.6	1.18	0.8	1.9
Eggs	<1/Month	1.00	1.00	(ref)		1.00	(ref)		---	---	---
	1/Month-3/Week	1.08	0.98	0.6	1.5	1.26	0.8	2.1	---	---	---
	>=4/Week	1.26	1.06	0.6	1.8	1.35	0.8	2.4	---	---	---
Corn	<1/Month	1.00	1.00	(ref)		1.00	(ref)		---	---	---
	1/Month-3/Week	0.84	0.85	0.6	1.2	0.82	0.6	1.2	---	---	---
	>=4/Week	1.11	0.94	0.6	1.5	0.77	0.5	1.3	---	---	---
Peppers	<1/Month	1.00	1.00	(ref)		1.00	(ref)		1.00	(ref)	
	1/Month-3/Week	1.61	1.45	1.0	2.1	1.45	1.0	2.1	1.45	1.0	2.1
	>=4/Week	1.68	1.31	0.9	1.8	1.31	0.9	1.8	1.31	0.9	1.8
Pickles	<1/Month	1.00	1.00	(ref)		1.00	(ref)		---	---	---
	1/Month-3/Week	1.21	0.94	0.6	1.4	0.76	0.8	1.2	---	---	---
	>=4/Week	1.57	1.22	0.7	2.0	0.92	0.5	1.6	---	---	---
Honey	<1/Month	1.00	1.00	(ref)		1.00	(ref)		---	---	---
	1/Month-3/Week	1.19	1.02	0.6	1.7	1.31	0.8	2.2	---	---	---
	>=4/Week	0.72	0.82	0.4	1.7	0.85	0.4	1.8	---	---	---

[1] By conditional logistic regression with matching variables: age, sex, hospital, and admission period.
[2] Adjusted additionally for all empirical confounders (see text for explanation).
[3] Adjusted only for positive or negative confounders (see text for explanation).

2.1.3. Cancer of the pharynx

Table 15 presents the ORs from the crude, alcohol and tobacco adjusted, all empirical confounders adjusted, and conservatively adjusted models for cancer of the pharynx. The consumption of lemon, orange, papaya carrot, lettuce, and pumpkin showed protective effects against cancer of the pharynx and the intake of *pequi, pinhao*, smoking and grilled meat, eggs, corn, peppers, and pickles were associated with an increased risk in the crude model. After adjusting for smoking and alcohol consumption, a significantly inverse association was maintained for the intake of orange and papaya (OR=0.42, 95% CI: 0.2-0.7 and OR=0.41, 95% CI: 0.2-1.0). A substantial increase in risk was observed with greater consumption of eggs and peppers (OR=2.24, 95% CI: 1.1-4.6 and OR=1.93, 95% CI: 1.2-3.1). Elevated risk levels were also seen with an increased consumption of corn with a marginally significant OR. *Pequi* and *pinhao* consumption appeared to be associated with cancer risk with substantial OR but had very wide confidence intervals due to the small number of subjects in the highest level of intake category.

After additionally adjusting for all empirical confounder, the consumption of eggs and peppers showed a more pronounced positive association with the risk of cancer of the pharynx (OR=2.79, 95% CI: 1.2-6.2 and OR=2.09, 95% CI: 1.3-3.4, respectively). The increase in risk also persisted for the intake of corn but the OR remained marginally significant. A substantially increased risk was observed for the consumption of cheese (OR=1.88, 95% CI: 1.0-3.6), while such an association showed an insignificant OR when adjusting only for smoking and alcohol consumption.

In the conservatively adjusted model, the positive associations were maintained for the intake of eggs and peppers (OR=2.04, 95% CI: 1.0-4.2 and OR=1.93, 95% CI: 1.2-3.1).

Table 15. Relative risks of cancer of the pharynx associated with the intake of specific food items

Food items	Frequency of consumption	Crude[1] OR	Adjusted for smoking & alcohol			Fully adjusted[2]			Conservatively Adjusted[3]		
			OR	95% CI		OR	95% CI		OR	95% CI	
Fruits											
Lemon	<1/Month	1.00	1.00	(ref)		1.00	(ref)		---	---	---
	1/Month-3/Week	0.92	0.88	0.6	1.4	0.99	0.6	1.7	---	---	---
	>=4/Week	0.70	0.61	0.3	1.1	0.87	0.4	1.7	---	---	---
Orange	<1/Month	1.00	1.00	(ref)		1.00	(ref)		---	---	---
	1/Month-3/Week	0.70	0.69	0.4	1.1	0.88	0.5	1.5	---	---	---
	>=4/Week	0.47	0.42	0.2	0.7	0.57	0.3	1.1	---	---	---
Papaya	<1/Month	1.00	1.00	(ref)		1.00	(ref)		---	---	---
	1/Month-3/Week	0.72	0.70	0.4	1.1	0.94	0.5	1.7	---	---	---
	>=4/Week	0.43	0.41	0.2	1.0	0.63	0.2	1.8	---	---	---
Pequi	<1/Month	1.00	1.00	(ref)		1.00	(ref)		---	---	---
	1/Month-3/Week	1.00	0.76	0.3	1.8	0.36	0.1	1.3	---	---	---
	>=4/Week	2.00	2.16	0.1	63.9	0.84	0.0	83.1	---	---	---
Pinhao	<1/Month	1.00	1.00	(ref)		1.00	(ref)		---	---	---
	1/Month-3/Week	1.43	1.30	0.7	2.5	1.28	0.5	3.0	---	---	---
	>=4/Week	3.38	5.47	0.6	52.0	12.90	0.6	267.3	---	---	---
Vegetables											
Carrot	<1/Month	1.00	1.00	(ref)		1.00	(ref)		---	---	---
	1/Month-3/Week	0.85	0.86	0.6	1.3	1.51	0.9	2.5	---	---	---
	>=4/Week	0.85	0.73	0.3	1.6	1.78	0.7	4.7	---	---	---
Cauliflower	<1/Month	1.00	1.00	(ref)		1.00	(ref)		---	---	---
or Spinach	1/Month-3/Week	0.80	0.84	0.6	1.3	1.24	0.7	2.1	---	---	---
or Broccoli	>=4/Week	0.94	0.63	0.3	1.5	0.84	0.3	2.5	---	---	---
Lettuce	<1/Month	1.00	1.00	(ref)		1.00	(ref)		---	---	---
	1/Month-3/Week	0.75	0.68	0.4	1.1	0.93	0.5	1.6	---	---	---
	>=4/Week	0.64	0.65	0.3	1.3	0.91	0.4	1.8	---	---	---
Cassava	<1/Month	1.00	1.00	(ref)		1.00	(ref)		---	---	---
	1/Month-3/Week	0.96	0.97	0.6	1.6	1.11	0.7	1.9	---	---	---
	>=4/Week	0.97	0.93	0.5	1.6	0.85	0.5	1.5	---	---	---
Pumpkin	<1/Month	1.00	1.00	(ref)		1.00	(ref)		---	---	---
	1/Month-3/Week	0.81	0.78	0.5	1.2	0.92	0.5	1.6	---	---	---
	>=4/Week	0.47	0.52	0.2	1.2	0.63	0.2	1.6	---	---	---
Tomato	<1/Month	1.00	1.00	(ref)		1.00	(ref)		---	---	---
	1/Month-3/Week	0.90	0.81	0.5	1.4	1.11	0.6	2.0	---	---	---
	>=4/Week	0.92	0.81	0.4	1.5	1.44	0.7	3.1	---	---	---

Table 15 (continued): Relative risks of cancer of the pharynx associated with the intake of specific food items

Food items	Frequency of consumption	Crude[1] OR	Adjusted for smoking & alcohol OR	95% CI		Fully adjusted[2] OR	95% CI		Conservatively Adjusted[3] OR	95% CI	
Meat											
Smoked	<1/Month	1.00	1.00	(ref)		1.00	(ref)		---	---	---
	1/Month-3/Week	1.52	1.20	0.7	2.0	1.73	0.9	3.2	---	---	---
	>=4/Week	1.43	1.32	0.4	3.9	1.75	0.5	6.2	---	---	---
Grilled	<1/Month	1.00	1.00	(ref)		1.00	(ref)		---	---	---
	1/Month-3/Week	1.25	1.09	0.7	1.7	1.18	0.7	2.0	---	---	---
	>=4/Week	0.83	0.70	0.2	3.3	0.47	0.0	5.0	---	---	---
Milk	<1/Month	1.00	0.94	(ref)		1.00	(ref)		---	---	---
	1/Month-3/Week	0.98	1.03	0.5	1.7	1.05	0.5	2.0	---	---	---
	>=4/Week	0.93	1.01	0.6	1.7	1.27	0.7	2.3	---	---	---
Cheese	<1/Month	1.00	1.00	(ref)		1.00	(ref)		1.00	(ref)	
	1/Month-3/Week	1.08	1.00	0.6	1.6	1.50	0.9	2.5	1.17	0.9	1.5
	>=4/Week	1.42	1.42	0.8	2.5	1.88	1.0	3.6	1.14	0.8	1.5
Eggs	<1/Month	1.00	1.00	(ref)		1.00	(ref)		1.00	(ref)	
	1/Month-3/Week	2.09	1.93	1.0	3.7	2.23	1.1	4.6	1.68	0.9	3.2
	>=4/Week	2.86	2.24	1.1	4.6	2.79	1.2	6.2	2.04	1.0	4.2
Corn	<1/Month	1.00	1.00	(ref)		1.00	(ref)		---	---	---
	1/Month-3/Week	1.06	1.05	0.7	1.6	1.07	0.7	1.7	---	---	---
	>=4/Week	1.73	1.75	0.9	3.3	1.81	0.9	3.6	---	---	---
Peppers	<1/Month	1.00	1.00	(ref)		1.00	(ref)		1.00	(ref)	
	1/Month-3/Week	1.35	1.19	0.7	2.0	1.26	0.8	2.1	1.19	0.7	2.0
	>=4/Week	2.25	1.93	1.2	3.1	2.09	1.3	3.4	1.93	1.2	3.1
Pickles	<1/Month	1.00	1.00	(ref)		1.00	(ref)		---	---	---
	1/Month-3/Week	1.66	1.40	0.8	2.4	1.67	0.9	3.0	---	---	---
	>=4/Week	1.38	0.86	0.4	1.8	0.68	0.3	1.6	---	---	---
Honey	<1/Month	1.00	1.00	(ref)		1.00	(ref)		---	---	---
	1/Month-3/Week	0.56	0.75	0.4	1.6	0.78	0.3	1.9	---	---	---
	>=4/Week	0.96	0.94	0.5	1.8	0.98	0.4	2.3	---	---	---

[1] By conditional logistic regression with matching variables: age, sex, hospital, and admission period.
[2] Adjusted additionally for all empirical confounders (see text for explanation).
[3] Adjusted only for positive or negative confounders (see text for explanation).

2.1.4. Cancer of the larynx

Table 16 gives the ORs from the crude, smoking and alcohol adjusted, all empirical confounders adjusted, and conservatively adjusted models for cancer of the larynx.

The consumption of fruits and vegetables including lemon, orange, papaya and carrot, lettuce, and tomato presented a protective effect against cancer of the larynx, and, the intake of *pinhao*, smoking and grilled meat, egg, corn, peppers and pickles were associated with an increase in risk in the crude model.

After adjusting for smoking and alcohol consumption, the protective effect was maintained for the intake of orange and papaya but with marginally significant ORs. An inverse association with cancer risk was observed for carrot intake but the OR was only significant at the middle level of consumption. Consumption of grilled meat and eggs also showed an increased risk for laryngeal cancer, though the effects were not consistent over frequencies of intake.

After adjusting for all empirical confounders, a similar protective effect was observed for the intake of orange and papaya and the middle level of consumption of carrot. A significantly positive association with the risk of cancer of the larynx was seen for the middle level of consumption of grilled meat and cheese, while the middle level of consumption of smoked meat and eggs also showed an increase in risk but with a marginally significant OR. The most interesting finding was that eating pickles four times a week or more showed a substantially increased risk (OR=2.68, 95% CI: 1.0-7.3).

Table 16. Relative risks of cancer of the larynx associated with the intake of specific food items

Food items	Frequency of consumption	Crude[1] OR	Adjusted for smoking & alcohol OR	95% CI		Fully adjusted [2] OR	95% CI		Conservatively Adjusted [3] OR	95% CI	
Fruits											
Lemon	<1/Month	1.00	1.00	(ref)		1.00	(ref)		---	---	---
	1/Month-3/Week	0.86	1.03	0.6	1.7	1.40	0.7	2.6	---	---	---
	>=4/Week	0.86	0.95	0.5	1.7	1.34	0.6	2.8	---	---	---
Orange	<1/Month	1.00	1.00	(ref)		1.00	(ref)		1.00	(ref)	
	1/Month-3/Week	0.44	0.52	0.3	0.9	0.55	0.3	1.0	0.67	0.4	1.2
	>=4/Week	0.51	0.61	0.3	1.1	0.56	0.3	1.2	0.80	0.4	1.6
Papaya	<1/Month	1.00	1.00	(ref)		1.00	(ref)		---	---	---
	1/Month-3/Week	0.60	0.65	0.4	1.1	0.76	0.4	1.4	---	---	---
	>=4/Week	0.70	0.48	0.2	1.1	0.42	0.2	1.1	---	---	---
Pequi	<1/Month	1.00	1.00	(ref)		1.00	(ref)		---	---	---
	1/Month-3/Week	2.33	2.06	0.8	5.4	2.38	0.7	8.6	---	---	---
	>=4/Week	1.00	0.81	0.1	12.6	0.29	0.0	6.8	---	---	---
Pinhao	<1/Month	1.00	1.00	(ref)		1.00	(ref)		---	---	---
	1/Month-3/Week	1.01	0.84	0.4	1.8	0.95	0.4	2.5	---	---	---
	>=4/Week	3.34	2.95	0.5	17.5	4.13	0.4	41.3	---	---	---
Vegetables											
Carrot	<1/Month	1.00	1.00	(ref)		1.00	(ref)		1.00	(ref)	
	1/Month-3/Week	0.46	0.49	0.3	0.8	0.43	0.2	0.8	0.59	0.4	1.0
	>=4/Week	0.38	0.54	0.2	1.3	0.52	0.2	1.5	0.74	0.3	1.9
Cauliflower	<1/Month	1.00	1.00	(ref)		1.00	(ref)		---	---	---
or Spinach	1/Month-3/Week	0.63	0.66	0.4	1.0	0.71	0.4	1.2	---	---	---
or Broccoli	>=4/Week	1.14	1.37	0.6	3.3	1.49	0.5	4.1	---	---	---
Lettuce	<1/Month	1.00	1.00	(ref)		1.00	(ref)		---	---	---
	1/Month-3/Week	0.80	0.88	0.5	1.5	1.05	0.6	2.0	---	---	---
	>=4/Week	0.87	1.14	0.6	2.2	1.50	0.7	3.2	---	---	---
Cassava	<1/Month	1.00	1.00	(ref)		1.00	(ref)		---	---	---
	1/Month-3/Week	0.76	0.70	0.4	1.1	0.68	0.4	1.1	---	---	---
	>=4/Week	1.09	0.84	0.5	1.5	0.93	0.5	1.7	---	---	---
Pumpkin	<1/Month	1.00	1.00	(ref)		1.00	(ref)		---	---	---
	1/Month-3/Week	0.86	0.93	0.6	1.5	1.30	0.7	3.6	---	---	---
	>=4/Week	1.04	0.92	0.4	2.4	1.31	0.5	1.6	---	---	---
Tomato	<1/Month	1.00	1.00	(ref)		1.00	(ref)		---	---	---
	1/Month-3/Week	0.66	0.79	0.4	1.4	0.98	0.5	2.0	---	---	---
	>=4/Week	0.72	0.89	0.5	1.7	1.02	0.4	2.3	---	---	---

Table 16 (continued): Relative risks of cancer of the larynx associated with the intake of specific food items.

Food items	Frequency of consumption	Crude[1] OR	Adjusted for smoking & alcohol OR	95% CI		Fully adjusted[2] OR	95% CI		Conservatively Adjusted[3] OR	95% CI	
Meat											
Smoked	<1/Month	1.00	1.00	(ref)		1.00	(ref)		---	---	---
	1/Month-3/Week	1.61	1.45	0.8	2.6	2.00	1.0	4.0	---	---	---
	>=4/Week	1.58	1.18	0.4	3.5	1.47	0.4	5.0	---	---	---
Grilled	<1/Month	1.00	1.00	(ref)		1.00	(ref)		1.00	(ref)	
	1/Month-3/Week	1.33	1.64	1.0	2.6	2.10	1.2	3.7	1.79	1.1	3.0
	>=4/Week	1.65	1.16	0.3	4.4	0.99	0.2	4.8	1.78	0.4	7.6
Milk	<1/Month	1.00	1.00	(ref)		1.00	(ref)		---	---	---
	1/Month-3/Week	0.69	0.70	0.4	1.3	0.74	0.4	1.5	---	---	---
	>=4/Week	0.87	1.02	0.6	1.7	1.36	0.8	2.5	---	---	---
Cheese	<1/Month	1.00	1.00	(ref)		1.00	(ref)		1.00	(ref)	
	1/Month-3/Week	1.30	1.26	0.8	2.0	1.62	1.0	2.7	1.15	0.7	1.8
	>=4/Week	0.84	0.83	0.4	1.6	1.00	0.5	2.1	0.70	0.4	1.3
Eggs	<1/Month	1.00	1.00	(ref)		1.00	(ref)		---	---	---
	1/Month-3/Week	1.65	2.17	1.0	4.7	2.24	0.9	5.3	---	---	---
	>=4/Week	1.43	1.79	0.8	4.0	1.66	0.7	4.2	---	---	---
Corn	<1/Month	1.00	1.00	(ref)		1.00	(ref)		---	---	---
	1/Month-3/Week	0.98	0.84	0.5	1.3	0.91	0.6	1.5	---	---	---
	>=4/Week	1.26	1.01	0.6	1.8	0.88	0.5	1.6	---	---	---
Peppers	<1/Month	1.00	1.00	(ref)		1.00	(ref)		---	---	---
	1/Month-3/Week	1.16	0.83	0.5	1.4	0.98	0.6	1.7	---	---	---
	>=4/Week	1.22	0.83	0.5	1.3	1.10	0.7	1.8	---	---	---
Pickles	<1/Month	1.00	1.00	(ref)		1.00	(ref)		1.00	(ref)	
	1/Month-3/Week	1.04	0.98	0.5	1.8	1.43	0.7	2.9	0.86	0.5	1.6
	>=4/Week	1.76	1.40	0.6	3.1	2.68	1.0	7.3	1.23	0.5	2.8
Honey	<1/Month	1.00	1.00	(ref)		1.00	(ref)		---	---	---
	1/Month-3/Week	1.27	1.38	0.8	2.5	1.63	0.8	3.3	---	---	---
	>=4/Week	1.23	1.13	0.6	2.3	1.84	0.8	4.2	---	---	---

[1] By conditional logistic regression with matching variables: age, sex, hospital, and admission period.
[2] Adjusted additionally for all empirical confounders (see text for explanation).
[3] Adjusted only for positive or negative confounders (see text for explanation).

2.2. Associations with food groups

2.2.1 Carotene-rich foods

Table 17 shows relative risks of cancers of the UADT associated with carotene-rich foods with ORs from the crude, smoking and alcohol adjusted, fully-adjusted, and conservatively adjusted models. After adjusting for smoking and alcohol consumption, the results suggested that the consumption of carotene-rich foods decreased the risk of cancer of the larynx, the mouth as well as the pharynx. Additionally controlling for all empirical confounders, a significantly protective effect was only observed for cancer of the larynx, while an non significant OR was seen for cancer of the mouth. Such protective effect was not maintained for pharyngeal cancer. All empirical confounders identified using a 5% change-in-estimate for each food group are presented in Appendix IV.

Table 17. Relative risks of cancers of the upper aero-digestive tract associated with the intake of carotene-rich foods.

Cancer sites	Frequency of consumption	Crude[1] OR	Adjusted for smoking & alcohol OR	95% CI		Fully adjusted[2] OR	95% CI		Conservatively Adjusted[3] OR	95% CI	
All sites	<1/Month	1.00	1.00	(ref)		1.00	(ref)		1.00	(ref)	
	1/Month-3/Week	0.65	0.72	0.6	0.9	0.80	0.6	1.0	0.84	0.7	1.1
	>=4/Week	0.57	0.61	0.4	0.9	0.67	0.5	0.9	0.72	0.5	1.0
Mouth	<1/Month	1.00	1.00	(ref)		1.00	(ref)		1.00	(ref)	
	1/Month-3/Week	0.66	0.67	0.5	1.0	0.65	0.4	1.0	0.79	0.5	1.2
	>=4/Week	0.65	0.70	0.4	1.1	0.66	0.4	1.2	0.80	0.5	1.3
Pharynx	<1/Month	1.00	1.00	(ref)		1.00	(ref)		1.00	(ref)	
	1/Month-3/Week	0.72	0.84	0.5	1.3	1.32	0.7	2.4	1.37	0.8	2.5
	>=4/Week	0.46	0.52	0.3	1.0	0.86	0.4	2.0	0.96	0.4	2.2
Larynx	<1/Month	1.00	1.00	(ref)		1.00	(ref)		1.00	(ref)	
	1/Month-3/Week	0.53	0.57	0.3	1.0	0.51	0.3	1.0	0.66	0.4	1.2
	>=4/Week	0.55	0.49	0.3	1.0	0.44	0.2	1.0	0.58	0.3	1.2

[1] By conditional logistic regression with matching variables: age, sex, hospital, and admission period.
[2] Adjusted additionally for all empirical confounders (see text for explanation).
[3] Adjusted only for positive or negative confounders (see text for explanation).

2.2.2. Citric fruits

Table 18 presents relative risks of cancers of the UADT associated with the intake of citric fruits with ORs from the crude, smoking and alcohol adjusted, fully-adjusted and conservatively adjusted models. The intake of citric foods also showed an inverse association with the risk of cancers of the mouth and the pharynx. Such protective effects persisted with significant ORs after adjusting for smoking and alcohol, for all empirical confounders, as well as for all "negative confounders". However, no protective effect due to intake of citric fruits was seen for laryngeal cancer.

Table 18. Relative risks of cancers of the upper aero-digestive tract associated with the intake of citric fruits.

Cancer sites	Frequency of consumption	Crude[1] OR	Adjusted for smoking & alcohol OR	95% CI		Fully adjusted[2] OR	95% CI		Conservatively Adjusted[3] OR	95% CI	
All sites	<1/Month	1.00	1.00	(ref)		1.00	(ref)		1.00	(ref)	
	1/Month-3/Week	0.59	0.66	0.5	0.8	0.72	0.6	0.9	0.72	0.6	0.9
	>=4/Week	0.54	0.63	0.5	0.8	0.71	0.5	0.9	0.71	0.5	0.9
Mouth	<1/Month	1.00	1.00	(ref)		1.00	(ref)		1.00	(ref)	
	1/Month-3/Week	0.52	0.53	0.4	0.8	0.52	0.3	0.8	0.60	0.4	0.9
	>=4/Week	0.52	0.63	0.4	0.9	0.61	0.4	1.0	0.78	0.5	1.2
Pharynx	<1/Month	1.00	1.00	(ref)		1.00	(ref)		1.00	(ref)	
	1/Month-3/Week	0.70	0.71	0.5	1.1	0.84	0.5	1.4	0.88	0.5	1.4
	>=4/Week	0.47	0.44	0.3	0.7	0.51	0.3	0.9	0.54	0.4	1.0
Larynx	<1/Month	1.00	1.00	(ref)		1.00	(ref)		1.00	(ref)	
	1/Month-3/Week	0.62	0.82	0.5	1.4	0.92	0.5	1.8	1.13	0.6	2.0
	>=4/Week	0.68	0.82	0.5	1.4	0.82	0.4	1.6	1.25	0.7	2.3

[1] By conditional logistic regression with matching variables: age, sex, hospital, and admission period.
[2] Adjusted additionally for all empirical confounders (see text for explanation).
[3] Adjusted only for positive or negative confounders (see text for explanation).

2.2.3 Spicy foods

Table 19 lists relative risks of cancers of the UADT associated with spicy foods with ORs from the crude, smoking and alcohol adjusted, fully adjusted and conservatively adjusted models. An elevated risk of the cancer of the pharynx was found with increased consumption of spicy foods. Such trends persisted after controlling not only for smoking and alcohol consumption but also for all empirical confounders. Even in the conservatively adjusted model, these positive associations remained significant. For cancer of the mouth, a positive association was also present, but did not remain significant after controlling for all empirical confounders. However, a significant increase in risk was seen again in the conservative model. The positive association between the intake of spicy foods and the risk was not observed for laryngeal cancer.

Table 19. Relative risks of cancers of the upper aero-digestive tract associated with the intake of spicy foods.

Cancer sites	Frequency of consumption	Crude[1] OR	Adjusted for smoking & alcohol OR	95% CI		Fully adjusted[2] OR	95% CI		Conservatively Adjusted[3] OR	95% CI	
All sites	<1/Month	1.50	1.00	(ref)		1.00	(ref)		1.00	(ref)	
	1/Month-3/Week	1.50	1.29	1.0	1.7	1.29	1.0	1.7	1.29	1.0	1.7
	>=4/Week	1.77	1.31	1.0	1.7	1.31	1.0	1.7	1.31	1.0	1.7
Mouth	<1/Month	1.00	1.00	(ref)		1.00	(ref)		1.00	(ref)	
	1/Month-3/Week	1.52	1.45	1.0	2.1	1.37	0.6	3.0	1.45	1.0	2.1
	>=4/Week	1.74	1.35	1.0	1.9	1.42	0.6	3.4	1.35	1.0	1.9
Pharynx	<1/Month	1.00	1.00	(ref)		1.00	(ref)		1.00	(ref)	
	1/Month-3/Week	1.75	1.57	1.0	2.6	1.98	1.2	3.4	1.57	1.0	2.6
	>=4/Week	2.50	2.08	1.3	3.4	2.61	1.5	4.4	2.08	1.3	3.4
Larynx	<1/Month	1.00	1.00	(ref)		1.00	(ref)		1.00	(ref)	
	1/Month-3/Week	1.21	0.89	0.5	1.5	1.02	0.6	1.7	0.89	0.5	1.5
	>=4/Week	1.28	0.83	0.5	1.3	1.04	0.6	1.7	0.83	0.5	1.3

[1] By conditional logistic regression with matching variables: age, sex, hospital, and admission period.
[2] Adjusted additionally for all empirical confounders (see text for explanation).
[3] Adjusted only for positive or negative confounders (see text for explanation).

2.3. Associations with nutrients

Tables 20-23 display relative risks of cancers of the upper aero-digestive tract associated with daily nutrient intake by quartile levels of consumption according to all cancer sites combined and cancer subsites analyses. All confounders identified empirically using a 5% change- in- estimate for each of nutrient indices are presented in Appendix V.

All cancer sites combined

After adjusting for smoking and alcohol consumption, it was found that the increased intake of vitamin A, vitamin C, vitamin E, beta-carotene, and folate were significantly related to a decreased risk of cancer of the UADT. However, after adjusting for all empirical confounders in addition to alcohol drinking and tobacco smoking, the protective effects persisted only for the consumption of beta-carotene and folate (OR=0.75, 95% CI: 0.6-1.0 and OR=0.63, 95% CI: 0.5-0.9). Dietary intake of zinc and iron appeared to increase the risk of cancers of the UADT. Dietary zinc intake presented such a positive association not only after adjusting for smoking and alcohol consumption (OR=1.39, 95% CI: 1.0-1.9) but also after adjusting for all empirical confounders (OR=1.58, 95% CI: 1.2-2.2). An elevated risk with intake of iron was observed after adjusting for all empirical confounders with a marginally significant OR (OR=1.30, 95% CI: 0.9-1.8) (Table 20).

Cancer of the mouth

Besides the protective effect of the intake of vitamin C and folate against cancer of the mouth, the results did not show any significant association between intake of other nutrients and the risk of cancer of the mouth. Although the protective effect of vitamin C intake persisted after adjusting for all empirical confounders, it was not significant across all categories of consumption. Similarly, the intake of folate showed a significant OR

after adjusting for smoking and alcohol consumption (OR=0.60, 95% CI: 0.4-1.0), but it failed to present a significantly protective effect after controlling for all empirical confounders (Table 21).

Cancer of the pharynx

Table 22 shows the results of the association between nutrient intake and the risk for pharyngeal cancer. Inverse associations between the intake of vitamin C (OR=0.42, 95% CI: 0.2-0.8) and folate (OR=0.44, 95% CI: 0.2-0.9) and the risk of pharyngeal cancers were also observed after adjusting for smoking and alcohol consumption. Additionally adjusting for all empirical confounders, the protective effect was maintained significantly for the intake of vitamin C (OR=0.48, 95% CI: 0.3-0.9), but such effect was somewhat less pronounced for the intake of folate (OR=0.53, 95% CI: 0.3-1.1). Consumption of iron and zinc resulted in increased risks for pharyngeal cancer, that were not significant after adjusting for smoking and alcohol consumption, but these positive associations became more pronounced after adjusting for all empirical confounders (OR=2.30, 95% CI: 1.2-4.6) for iron intake and (OR=2.41, 95% CI: 1.2-4.8) for zinc intake.

Cancer of the larynx

A protective effect against cancer of the larynx was observed for beta-carotene intake, persisting with a marginally significant OR after adjusting for smoking and alcohol consumption and adjusting for all empirical confounders. A similar association between folate intake and laryngeal cancer was also seen after adjusting for all empirical confounders. The consumption of zinc was associated with all almost 2-fold elevated risk for laryngeal cancer after adjusting for smoking and alcohol consumption (OR=1.81, 95% CI: 1.0-3.3) and for all empirical confounders (OR=1.95, 95% CI: 1.0-3.6) (Table 23).

Table 20. Relative risks of cancers of the upper aero-digestive tract (all sites combined) associated with daily nutrient intake.

Nutrient	Frequency of daily consumption	Crude[1] OR	Adjusted for smoking & alcohol OR	95% CI		Fully adjusted[2] OR	95% CI	
Vitamin A	<228 ug	1.00	1.00	(ref)		1.00	(ref)	
	228-376 ug	0.98	0.95	0.7	1.2	0.98	0.7	1.3
	376-546 ug	0.88	0.89	0.7	1.2	0.95	0.7	1.3
	>=546 ug	0.72	0.76	0.6	1.0	0.86	0.6	1.2
Vitamin C	<37.7 mg	1.00	1.00	(ref)		1.00	(ref)	
	37.7-126 mg	1.03	1.09	0.8	1.4	1.12	0.9	1.5
	126-204mg	0.62	0.70	0.5	0.9	0.81	0.6	1.1
	>=204 mg	0.58	0.70	0.5	1.0	0.79	0.6	1.1
Vitamin E	<0.65 mg	1.00	1.00	(ref)		1.00	(ref)	
	0.65-1.02 mg	0.84	0.81	0.6	1.1	0.85	0.6	1.1
	1.02-1.49mg	0.82	0.82	0.6	1.1	0.87	0.7	1.1
	>=1.49 mg	0.70	0.76	0.6	1.0	0.83	0.6	1.1
Beta-carotene	<512 ug	1.00	1.00	(ref)		1.00	(ref)	
	512-1369 ug	0.97	1.05	0.8	1.4	1.05	0.8	1.4
	1369-2431 ug	0.66	0.74	0.6	1.0	0.74	0.6	1.0
	>=2431 ug	0.67	0.75	0.6	1.0	0.75	0.6	1.0
Folate	<41.7 ug	1.00	1.00	(ref)		1.00	(ref)	
	41.7-69.0 ug	0.87	0.86	0.7	1.1	0.90	0.7	1.2
	69.0-109 ug	0.72	0.75	0.6	1.0	0.79	0.6	1.0
	>=109 ug	0.54	0.58	0.4	0.8	0.63	0.5	0.9
Calcium	<103 mg	1.00	1.00	(ref)		1.00	(ref)	
	103-314 mg	0.92	0.99	0.8	1.3	1.09	0.8	1.4
	314-392mg	0.86	0.97	0.7	1.3	1.09	0.8	1.4
	>=392 mg	0.79	0.93	0.7	1.2	1.06	0.8	1.4
Iron	<0.72 mg	1.00	1.00	(ref)		1.00	(ref)	
	0.72-1.09 mg	0.99	0.92	0.7	1.2	0.98	0.7	1.3
	1.09-1.68mg	1.21	1.19	0.9	1.6	1.33	1.0	1.8
	>=1.68 mg	1.29	1.13	0.8	1.5	1.30	0.9	1.8
Zinc	<0.88 mg	1.00	1.00	(ref)		1.00	(ref)	
	0.88-1.55 mg	1.02	1.26	0.9	1.7	1.32	1.0	1.8
	1.55-2.34mg	1.27	1.33	1.0	1.8	1.50	1.1	2.0
	>=2.34mg	1.32	1.39	1.0	1.9	1.58	1.2	2.2

[1] By conditional logistic regression with matching variables: age, sex, hospital, and admission period.
[2] Adjusted additionally for all empirical confounders.

Table 21. Relative risks of cancers of the mouth associated with daily nutrient intake.

Nutrient	Frequency of daily consumption	Crude[1] OR	Adjusted for smoking & alcohol			Fully adjusted [2]		
			OR	95% CI		OR	95% CI	
Vitamin A	<228 ug	1.00	1.00	(ref)		1.00	(ref)	
	228-376 ug	1.01	0.94	0.6	1.4	1.04	0.7	1.6
	376-546 ug	0.93	0.93	0.6	1.4	1.01	0.7	1.6
	>=546 ug	0.74	0.80	0.5	1.2	1.01	0.6	1.6
Vitamin C	<37.7 mg	1.00	1.00	(ref)		1.00	(ref)	
	37.7-126 mg	1.01	1.01	0.7	1.5	1.11	0.7	1.7
	126-204mg	0.49	0.51	0.3	0.8	0.63	0.4	1.0
	>=204 mg	0.58	0.75	0.5	1.2	0.96	0.6	1.6
Vitamin E	<0.65 mg	1.00	1.00	(ref)		1.00	(ref)	
	0.65-1.02 mg	0.76	0.78	0.5	1.2	0.79	0.5	1.2
	1.02-1.49mg	0.76	0.72	0.5	1.1	0.82	0.5	1.3
	>=1.49 mg	0.65	0.81	0.5	1.3	0.90	0.6	1.5
Beta-carotene	<512 ug	1.00	1.00	(ref)		1.00	(ref)	
	512-1369 ug	1.16	1.16	0.8	1.7	1.22	0.8	1.8
	1369-2431 ug	0.73	0.74	0.5	1.1	0.81	0.5	1.3
	>=2431 ug	0.80	0.86	0.6	1.3	1.01	0.6	1.6
Folate	<41.7 ug	1.00	1.00	(ref)		1.00	(ref)	
	41.7-69.0 ug	0.76	0.82	0.5	1.2	0.89	0.6	1.3
	69.0-109 ug	0.51	0.56	0.4	0.8	0.64	0.4	1.0
	>=109 ug	0.48	0.60	0.4	1.0	0.74	0.5	1.2
Calcium	<103 mg	1.00	1.00	(ref)		1.00	(ref)	
	103-314 mg	0.76	0.81	0.5	1.2	0.88	0.6	1.3
	314-392mg	0.64	0.71	0.5	1.1	0.80	0.5	1.2
	>=392 mg	0.68	0.86	0.6	1.3	1.01	0.7	1.6
Iron	<0.72 mg	1.00	1.00	(ref)		1.00	(ref)	
	0.72-1.09 mg	0.94	0.86	0.6	1.3	0.94	0.6	1.4
	1.09-1.68mg	1.25	1.16	0.8	1.7	1.33	0.9	2.0
	>=1.68 mg	1.12	0.93	0.6	1.5	1.13	0.7	1.8
Zinc	<0.88 mg	1.00	1.00	(ref)		1.00	(ref)	
	0.88-1.55 mg	0.92	1.09	0.7	1.6	1.10	0.7	1.7
	1.55-2.34mg	0.94	0.91	0.6	1.4	1.08	0.7	1.7
	>=2.34mg	1.09	1.14	0.7	1.7	1.32	0.8	2.1

[1] By conditional logistic regression with matching variables: age, sex, hospital, and admission period.
[2] Adjusted additionally for all empirical confounders.

Table 22: Relative risks of cancers of the pharynx associated with daily nutrient intake.

Nutrient	Frequency of daily consumption	Crude[1] OR	Adjusted for smoking & alcohol OR	95% CI		Fully adjusted [2] OR	95% CI	
Vitamin A	<228 ug	1.00	1.00	(ref)		1.00	(ref)	
	228-376 ug	0.94	0.92	0.5	1.6	1.03	0.6	1.8
	376-546 ug	0.95	0.81	0.5	1.4	0.96	0.5	1.8
	>=546 ug	0.84	0.74	0.4	1.4	0.90	0.4	1.8
Vitamin C	<37.7 mg	1.00	1.00	(ref)		1.00	(ref)	
	37.7-126 mg	0.74	0.75	0.4	1.3	0.74	0.4	1.3
	126-204mg	0.86	0.92	0.5	1.6	0.40	0.8	2.5
	>=204 mg	0.46	0.42	0.2	0.8	0.48	0.3	0.9
Vitamin E	<0.65 mg	1.00	1.00	(ref)		1.00	(ref)	
	0.65-1.02 mg	0.87	0.77	0.5	1.3	0.88	0.5	1.5
	1.02-1.49mg	0.95	0.85	0.5	1.5	0.98	0.6	1.7
	>=1.49 mg	0.79	0.70	0.4	1.3	0.87	0.5	1.7
Beta-carotene	<512 ug	1.00	1.00	(ref)		1.00	(ref)	
	512-1369 ug	0.84	1.08	0.6	1.8	1.19	0.7	2.1
	1369-2431 ug	0.64	0.81	0.5	1.4	1.00	0.6	1.8
	>=2431 ug	0.61	0.67	0.4	1.2	0.86	0.4	1.7
Folate	<41.7 ug	1.00	1.00	(ref)		1.00	(ref)	
	41.7-69.0 ug	0.94	0.86	0.5	1.4	0.96	0.6	1.7
	69.0-109 ug	1.14	0.98	0.6	1.7	1.21	0.7	2.2
	>=109 ug	0.51	0.44	0.2	0.9	0.53	0.3	1.1
Calcium	<103 mg	1.00	1.00	(ref)		1.00	(ref)	
	103-314 mg	1.08	1.18	0.7	1.9	1.43	0.8	2.4
	314-392mg	1.05	1.22	0.7	2.1	1.38	0.8	2.4
	>=392 mg	0.89	0.95	0.6	1.6	1.17	0.7	2.1
Iron	<0.72 mg	1.00	1.00	(ref)		1.00	(ref)	
	0.72-1.09 mg	0.93	0.81	0.5	1.4	0.84	0.5	1.5
	1.09-1.68mg	1.49	1.52	0.9	2.7	2.32	1.2	4.4
	>=1.68 mg	1.68	1.29	0.7	2.4	2.30	1.2	4.6
Zinc	<0.88 mg	1.00	1.00	(ref)		1.00	(ref)	
	0.88-1.55 mg	1.10	1.42	0.8	2.5	1.74	0.9	3.2
	1.55-2.34mg	1.92	2.31	1.2	3.6	3.09	1.7	5.8
	>=2.34mg	1.58	1.60	0.9	2.9	2.41	1.2	4.8

[1] By conditional logistic regression with matching variables: age, sex, hospital, and admission period.
[2] Adjusted additionally for all empirical confounders.

Table 23: Relative risks of cancers of the larynx associated with daily nutrient intake.

Nutrient	Frequency of daily consumption	Crude[1] OR	Adjusted for smoking & alcohol			Fully adjusted[2]		
			OR	95% CI		OR	95% CI	
Vitamin A	<228 ug	1.00	1.00	(ref)		1.00	(ref)	
	228-376 ug	0.98	1.08	0.6	1.8	1.09	0.6	1.8
	376-546 ug	0.74	0.90	0.5	1.5	0.82	0.5	1.4
	>=546 ug	0.58	0.68	0.4	1.3	0.59	0.3	1.1
Vitamin C	<37.7 mg	1.00	1.00	(ref)		1.00	(ref)	
	37.7-126 mg	1.42	1.79	1.0	3.1	1.90	1.0	3.5
	126-204mg	0.59	0.73	0.4	1.4	0.65	0.3	1.3
	>=204 mg	0.73	0.96	0.5	1.8	0.83	0.4	1.7
Vitamin E	<0.65 mg	1.00	1.00	(ref)		1.00	(ref)	
	0.65-1.02 mg	0.96	1.05	0.6	1.8	1.03	0.6	1.8
	1.02-1.49mg	0.81	0.97	0.6	1.7	0.99	0.6	1.8
	>=1.49 mg	0.71	0.74	0.4	1.3	0.74	0.4	1.4
Beta-carotene	<512 ug	1.00	1.00	(ref)		1.00	(ref)	
	512-1369 ug	0.80	0.87	0.5	1.5	0.83	0.5	1.5
	1369-2431 ug	0.56	0.64	0.4	1.2	0.69	0.4	1.3
	>=2431 ug	0.51	0.59	0.3	1.1	0.61	0.3	1.1
Folate	<41.7 ug	1.00	1.00	(ref)		1.00	(ref)	
	41.7-69.0 ug	0.99	1.04	0.6	1.8	0.92	0.5	1.6
	69.0-109 ug	0.81	1.01	0.6	1.8	0.95	0.5	1.7
	>=109 ug	0.64	0.70	0.4	1.3	0.61	0.3	1.1
Calcium	<103 mg	1.00	1.00	(ref)		1.00	(ref)	
	103-314 mg	1.08	1.28	0.7	2.3	1.29	0.7	2.4
	314-392mg	1.15	1.60	0.9	2.8	1.68	0.9	3.1
	>=392 mg	0.88	1.11	0.6	2.0	1.24	0.6	2.4
Iron	<0.72 mg	1.00	1.00	(ref)		1.00	(ref)	
	0.72-1.09 mg	1.12	1.10	0.6	1.9	1.10	0.6	1.9
	1.09-1.68mg	0.93	1.07	0.6	1.9	1.01	0.6	1.8
	>=1.68 mg	1.28	1.22	0.7	2.3	1.15	0.6	2.1
Zinc	<0.88 mg	1.00	1.00	(ref)		1.00	(ref)	
	0.88-1.55 mg	1.14	1.59	0.9	2.8	1.64	0.9	2.9
	1.55-2.34mg	1.37	1.95	1.1	3.5	2.10	1.1	3.9
	>=2.34mg	1.57	1.81	1.0	3.3	1.95	1.0	3.6

[1] By conditional logistic regression with matching variables: age, sex, hospital, and admission period.
[2] Adjusted additionally for all empirical confounders.

Discussion

1. Summary of key findings

Substantially decreased risk for cancers of the mouth and pharynx were observed with greater frequency of intake of citrus fruits and these inverse associations were independent of smoking and alcohol consumption as well as of other possible confounding effects. These findings are consistent with the findings from other studies {Winn, 1984, Franco, 1989, La Vecchia, 1991}. Significantly protective effects against cancers of the mouth and the pharynx were also found for the consumption of orange and papaya. A significantly positive association with cancers of the mouth was observed for the intake of *pinhao* after adjustment for all empirical confounders, but its confidence interval was very wide due to limited study sample size. After carefully adjusting for all empirical confounders, consumption of vegetables in general were not associated with a reduction in risk for cancer of the mouth and pharynx in this study.

The protective effects of fruits and vegetables had been postulated as a result of the high concentrations of micronutrients acting as efficient antioxidants, such as beta-carotene and vitamin C {Steinmetz, 1991}. In this study, an inverse association between the intake of vitamin C and folate and risk of cancers of the mouth and the pharynx was observed after adjustment for smoking and alcohol consumption. However, data from this study

failed to support the presence of a protective effect of beta-carotene for both cancers of the mouth and the pharynx.

A substantial increase in risk of cancer of the mouth was observed with increased consumption of grilled meat after adjusting for all empirical confounders, while intake of smoked meat was not found to be significantly associated with cancer of the mouth.

Elevated but less pronounced risk levels were seen for cancer of the pharynx with the intake of cheese, eggs, and peppers. After controlling for all empirical confounders, all these positive associations with risk remained significant. Previous studies on the intake of cheese, eggs, and peppers are limited and controversial. Both an inverse association with a statistically significantly decrease (OR=0.6) {La Vecchia, 1991} and a significantly positive association of cheese consumption to cancer of the mouth and pharynx (OR=1.9) were observed {Franceschi, 1991}. For eggs consumption, a non-significant positive association (OR=1.5) {La Vecchia, 1991} and a significantly increased risk (OR=1.6) {Franceschi, 1991} for cancers of the mouth and the pharynx have been reported. There is no previous evidence relating to diets high in peppers and the risk of cancers of the UADT.

Findings from this study failed to support the protective effect of fruits and vegetables against cancer of the larynx, although many studies did suggest that intake of fruits and vegetables might decrease the risk of laryngeal cancer {Graham 1981, De Stefani 1987, La Vecchia 1990, Zheng 1992, Esteve 1996}. Inverse associations between vitamin A, beta-carotene and folate intake with the risk of laryngeal cancer were observed in this study but with statistically insignificant OR. In the literature, an earlier study conducted

in New York by Graham et al. {1981} indicated that males ingesting low amounts of vitamin A in their diet had approximately twice the risk for laryngeal cancer of those ingesting large amounts. Another study in Texas, {Mackerras 1988} demonstrated a significant protective effect of carotene with a decreased OR of 0.5. There are no studies to date reporting the effect of folate intake on laryngeal cancer. However, a case-control study by Ramasawamy et al {1996} found that mean serum levels of folate were significantly lower in cases of oral leucoplakia compared with normal controls.

It is important to note that findings of this study display differing effects for dietary factors with respect to tumour sites of cancers of the UADT. For example, the consumption of grilled meat showed a substantially increased risk for cancer of the mouth (OR=5.88, 95% CI: 1.9-18.0) but not for cancer of the pharynx (OR=0.47, 95% CI: 0.0-5.0) or larynx (OR=0.99, 95% CI: 0.2-4.8); Increased consumption of pickles was only associated with the risk of laryngeal cancer (OR=2.68, 95% CI: 1.0-7.3) but not with cancer of the mouth (OR=0.92, 95% CI: 0.5-1.6) or pharynx (OR=0.68, 95% CI: 0.3-1.6). Statistical power could be a possible explanation here. It is suggested that the effects of diet on the risk may share different underlying mechanisms along with different cancer subsets within the UADT.

2. Strengths of this study

This study was characterized by the high response rate of study participants. Also, with the exception of the head and neck surgery service in Sao Paulo, which was responsible for approximately 20% of all incident cases of the city, the cases from the other two centres represented all incident cases for their respective areas during the period of the study. All these study characteristics serve to diminish the possibility of selection bias, which could have affected the validity of the results.

The comparable catchment areas for cases and controls and the frequency matching on age, sex, and trimester of hospital administration can be seen as strengths of this study. In addition, incident rather than prevalent cases and controls were used for this study. The use of incident cases would help to reduce the possibility of information bias that could result from the differential recall of exposures for case and control subjects. The questionnaire was submitted to cases and controls by the same interviewers under similar conditions, thus further minimizing information bias. Both interviewers and interviewees were blinded to the current hypothesis of interest. With this method, if hospitalization does have an effect on recall of past dietary intake, the bias would be in the same direction for both cases and controls, thereby, tending to reduce the observed associations, not to exaggerate them. The use of both hospital cases and controls should also increase the comparability of the data derived by interview. In addition, case subjects were asked about food intake in the years prior to the diagnosis of cancer which may have reduced the possibility of recall bias due to changes in diet related to the onset or the treatment of the disease.

The approach to the examination of relationships between diet and disease conducting analyses of dietary constituents with those of foods, singly and in combination became another advantage of the study described here. In such a way, a potentially important finding is less likely to be missed. Moreover, the case for causality is strengthened when an association is observed with both overall intake of a dietary constituent and multiple food sources of that constituent, particularly when the food sources are different.

Our strategy of exhaustively controlling for confounding based on a change-in-estimate criterion {Mickey 1989, Maldonado 1993} was a distinguishing feature of our study compared to others. The advantage of this approach is best illustrated by the association between citrus fruits and UADT cancer risk. By employing an overly conservative approach that only adjusts for those confounders that always bring the OR towards one, we purposefully biased the association towards the null hypothesis. Even at such an extreme level of conservatism, the significant association between citric fruits and UADT cancer risk persisted. This would advance the claim that the protective effect observed for citrus fruits is indeed genuine and independent of other risk factors. All of these strengths supported the validity of our investigation.

3. Limitations of the study

3.1. Potential Selection Bias

As known, tobacco and alcohol consumption are major risk factors for cancers of the UADT and these two factors are also strongly associated with dietary habits as well. Thus, potential selection bias may be introduced, as this hospital-based study did not make an extra effort to avoid the inclusion of patients with any diseases related to alcohol

or tobacco consumption. However, in parallel analysis using the same data as this study to investigate the potential effect of selection bias from the inclusion of hospital controls with tobacco- and alcohol- related diseases {Nishimoto et al.}, the authors observed a minimal change in ORs for selected diet factors including consumption of beta-carotene and citrus fruits even after excluding all gastrointestinal diseases which were assigned the highest score of a causal association with alcohol. These results assuaged our concern that potential selection bias may be introduced by the inclusion of controls with diseases related tobacco and alcohol consumption.

3.2. Measurement of dietary intake

The food frequency questionnaire used in this study is a relatively crude instrument for measuring diet. Only a limited number of foods were included in the study and no information was reported on the consumption of staple foods such as rice, beans, and potatoes. The absence of these elements partly explains why the mean values of daily consumption of nutrients for both cases and controls are much lower than other reports {Zheng 1993, Esteve 1996}. In addition, there is no information on the methods regarding storage, processing, cooking, handling, or other preparation of foods. A lower degree of details in the description of foods in the questionnaire made adequately matching with the nutrient value used in food composition tables difficult. Consequently, the food-nutrient conversion is less than accurate. This in turn may have reduced our ability to detect associations. Furthermore, information about portion size of dietary factors was also not collected in this study. However, whether or not to collect additional data on portion size has been a controversial topic in the literature. Studies by Samet and colleagues {1984} and by Pickle and Hartman {1985} found that, for most foods, portion sizes vary less

among individuals than do frequencies of use. Therefore, it is not surprising that portion size data are relatively unimportant because most of the variation in consumption of any food is explained by the frequency of its use.

4. Future directions and conclusions

Like most of other cancers, UADT cancer exhibits a long preclinical phase or latency; this implies that diet and nutrition may influence cancer progression at many stages of the life cycle. In addition, the effect of some dietary components may have different impact on the risk of the different histological types of cancers of the UADT. Thus, to examine the effect of diet on different clinical stage and histopathologic types of cancers of the UADT should be the focus of future studies on the risk of cancers of the UADT.

We need to broaden our horizons when thinking about diet. While nutrient may be important determinants of cancer risk, there are many other possibilities in terms of foods, non-nutritive components of foods and food preparation practices what are important in influencing risk.

The findings from this hospital-based case-control study implicate that dietary factors may play an important role in the aetiology of cancers of the UADT. However, while this case-control study can identify the associations, it cannot explain the cause and effect relationships. Longitudinal studies or randomized controlled trials are needed to establish convincing causal relationships for selected nutrients. These efforts in turn can help us to build an effective preventive program to modify exposure of dietary factors and reduce risk for cancers of the UADT.

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Appendix I. Nutrient value for selected food items according to USDA food composition database* or Brazilian food composition table.

Food item (Portuguese name)	Weight / meal (g)	Vitamin A mcg_RE /100g (BFCT)	Vitamin C mg /100g (BFCT)	Vitamin E mg_ATE /100g (USDA)	Folate mcg /100g (USDA)	Beta-carotene mcg/100g (USDA)	Ca mg 100g (USDA)	Iron mg /100g (USDA)	Zinc mg /100g (USDA)
Fruits									
Lemon (limonada)	244	2	11.8	0.09	12.9	0	7	0.03	0.05
Orange (laranjada)	248	56	163.6	0.17	30.3	27.5	25.5	0.15	0.06
Papaya (mamao)	100	28	20.5	1.12	38	276	24	0.1	0.07
Vegetables									
Carrot (cenoura)	45	1100	26.8	0.44	14	8836	29	0.56	0.25
Cauliflower (couve) Broccoli (brocoli) Spinach (espinafre)	40	750	108	0.89	87.6	3010	68.3	1.62	0.72
Lettuce (alface)	18	425	8.7	0.44	104.5	1272	34	0.7	0.21
Cassava (mandioca)	75	2	31	0.19	27	8	16	0.27	0.34
Pumpkin (abobora)	50	100	6.2	1.06	8.5	6940	15	0.57	0.23
Tomato (tomate)	45	60	34.3	0.38	15	393	5	0.45	0.09
Meat									
Smoked meat (carne de fumadas)	100	49	0	0.08	8.27	0	7.73	2.65	5.30

Appendix I (Continued) Nutrient value for selected food items according to USDA food composition database* or Brazilian food composition table.

Food item (Portuguese name)	Weight / meal (g)	Vitamin A mcg_RE /100g (BFCT)	Vitamin C mg /100g (BFCT)	Vitamin E mg_ATE /100g (USDA)	Folate mcg /100g (USDA)	Beta-carotene mcg/100g (USDA)	Ca mg 100g (USDA)	Iron mg /100g (USDA)	Zinc mg /100g (USDA)
Grilled meat (carne de churrasco)	100	6	0	0.07	2.89	0	15.22	1.95	2.84
Milk (leite)	244	39	1.0	0.1	5	8	119.4	0.05	0.38
Cheese (queijo)	40	240	0	0.35	7	85	517	0.18	2.21
Egg (ovos)	50	500	0	1.35	41	30	52.5	1.38	1.12
Corn (milho)	40	33	6.8	0.09	45.8	50	2	0.52	0.45
Pepper (pimenta)	7	450	138	0.69	23.4	**	18	1.2	0.3
Pickles (pickles)	100	2	2.0	0.16	1	**	9	0.53	0.14
Honey (mel)	15	0	4	0	2	0	6	0.42	0.22

* US department of agriculture nutrient database, release 13.
** Value missing in USDA database.

Appendix II: Confounders for each of individual foods identified empirically using a 5% change- in-estimate for cancers of the upper aero digestive tract.

DIETS OF INTEREST	SITES	IDENTIFIED COVARIATES
Lemon	All sites	Wood stove, orange, papaya, and carrot
	Mouth	Wood stove, orange, papaya, lettuce, tomato, and cheese
	Pharynx	Schooling, income, family cancer, orange, papaya, lettuce, and pickles
	Larynx	Wood stove, marakmg*, industa*, brush teeth, orange, papaya, carrot, cauliflower, grilled meat, and cheese
Orange	All sites	Wood stove
	Mouth	Wood stove, lemon, and cheese
	Pharynx	Wood stove, lemon, papaya, lettuce, smoked meat, and eggs
	Larynx	Morakmg*, industd*, family cancer, papaya, carrot, cauliflower, smoked meat, grilled meat, and milk
Papaya	All sites	Orange, and cheese
	Mouth	Race, lemon, orange, lettuce, and cheese
	Pharynx	Schooling, income, wood stove, denture*, orange, lettuce, pumpkin, smoked meat, cheese and pickles
	Larynx	Morakmd*, industd*, family cancer, organe, pinhao, carrot, smoked meat, grilled meat, and cheese
Pequi	All sites	Family cancer
	Mouth	Morakmf*, family cancer, brush teeth, pinhao, grilled meat, and peppers
	Pharynx	Schooling, income, wood stove, morakmg*, industd, industg*, family cancer, brush teeth, chewing tobacco, cassava, pumpkin, tomato, smoked meat, grilled meat, corn, peppers, eat hot, and drink hot tea
	Larynx	Income, wood stove, refrigerator, morakmd*, industa*, industb*, industd*, induste*, industh*, bad teeth, brush teeth, orange, papaya, pinhao, cauliflower, cassava, and cheese
Pinhao	All sites	Race, wood stove, industd*, bad teeth, lemon, orange, papaya, carrot, lettuce, and drink hot café
	Mouth	Wood stove, morakmf*, industd*, family cancer, bad teeth, brush teeth, type of smoker, lemon, orange, papaya, pequi, cauliflower, lettuce, cassave, tomato, grilled meat, corn, peppers, eat hot, drink hot café, drink hot cha, drink hot chocolate
	Pharynx	Schooling, piped water, wood stove, morakmb*, morakme*, morakmh*, tonsillectomy, family cancer, denture use, bad teeth, chewing tobacco, lemon, orange, papaya, carrot, lettuce, pumpkin, grilled meat, milk, eggs, peppers, pickles, drink hot *café*, drink hot tea, drink hot chocolate
	Larynx	Race, rural resdency, morakmb*, morakmf*, industb*, induste*, industf* industh*, family cancer, bad teeth, brush teeth, chewing tobacco, orange, papaya, pequi, carrot, cauliflower, cassave, pumpkin, smoked meat, milk, cheese, corn, eat hot, drink hot *café*, drink hot *chimarrão*
Carrot	All sites	Wood stove, orange, papaya, and cheese
	Mouth	Race, wood stove, morakmd*, bad teeth, brush teeth, orange, papaya, lettuce, tomato, and cheese
	Pharynx	Schooling, income, wood stove, lemon, orange, papaya, cauliflower, lettuce
	Larynx	Schooling, wood stove, family cancer, lemon, orange, papaya, grilled meat, milk, and cheese

Appendix II (continued). Confounders for each of individual foods identified empirically using a 5% change- in- estimate for cancers of the upper aero digestive tract

DIETS OF INTEREST	SITES	IDENTIFIED COVARIATES
Cauliflower	All sites	Wood stove, orange, papaya, carrot, and lettuce
	Mouth	Wood stove, lettuce, and tomato
	Pharynx	Schooling, income, wood stove, morakmg*, industd*, orange, papaya, lettuce, eggs, and drink hot cha
	Larynx	Morakmd*, family cancer, orange, papaya, carrot, lettuce, milk, cheese, and eggs
Lettuce	All sites	Wood stove, brush teeth, lemon, orange, papaya, pinhao, carrot, and pumpkin
	Mouth	Brush teeth, orange, tomato, and drink hot chimarrã
	Pharynx	Income, wood stove, orange, and papaya
	Larynx	Wood stove, morakmd*, industd*, brush teeth, orange, papaya, carrot, cauliflower, and eggs
Cassava	All sites	Wood stove
	Mouth	Race and wood stove
	Pharynx	Wood stove, family cancer, orange, and peppers
	Larynx	Rural residence, morakmd*, industd*, chewing tobacco, and orange
Pumpkin	All sites	Orange, papaya, and carrot
	Mouth	Orange and cassava
	Pharynx	Family cancer, orange, papaya, lettuce, smoked meat, peppers, and pickles
	Larynx	Family cancer, orange, papaya, and carrot
Tomato	All sites	Wood stove, brush teeth, orange, papaya, carrot, and lettuce
	Mouth	Wood stove, brush teeth, lemon, orange, papaya, lettuce, and cheese
	Pharynx	Piped water, wood stove, industk*, orange, papaya, cauliflower, and lettuce
	Larynx	Rural residence, wood stove, morakmd*, industd*, industj*, orange, carrot, cauliflower, smoked meat, and grilled meat
Smoked meat	All sites	Orange and papaya
	Mouth	Wood stove, brush teeth, and papaya
	Pharynx	Schooling, income, family cancer, orange, papaya, cauliflower, lettuce, cheese, eggs, and drink hot cha
	Larynx	Morakmh*, industb*, family cancer, chewing tobacco, orange, papaya, carrot, grilled meat, and drink hot *chimarrã*
Grilled meat	All sites	Race, income, wood stove, industd*, denture, bad teeth, chewing tobacco, and orange
	Mouth	Income, wood stove, morakmf*, industf*, denture, bad teeth, carrot, cauliflower, smoked meat, and drink hot chimarrã
	Pharynx	Morakmb*, morakmd*, morakmh*, industd*, industh*, family cancer, denture, brush teeth, chewing tobacco, orange, papaya, pequi, pinhao, carrot, cauliflower, lettuce, smoked meat, corn, peppers, and eat hot
	Larynx	Race, morakmd*, industb*, industd*, chewing tobacco, orange, carrot, smoked meat, cheese, peppers, and pickles
Milk	All sites	Wood stove, orange, and carrot
	Mouth	Race, wood stove, brush teeth, lemon, orange, lettuce, and tomato
	Pharynx	Schooling, income, industk*, family cancer, orange, papaya, and eggs
	Larynx	Wood stove, family cancer, orange, papaya, carrot, cauliflower, and eggs

Appendix II (continued). Confounders for each of individual foods identified empirically using a 5% change- in- estimate for cancers of the upper aero digestive tract

DIETS OF INTEREST	SITES	IDENTIFIED COVARIATES
Cheese	All sites	Orange, papaya, and carrot
	Mouth	Income, wood stove, brush teeth, lemon, orange, papaya, carrot, lettuce, and tomato
	Pharynx	Schooling, income, morakmg*, orange, papaya, carrot, cauliflower, lettuce, and eggs
	Larynx	Refrigerator, orange, papaya, carrot, cauliflower, cassava, and grilled meat
Eggs	All sites	Wood stove, orange, and papaya
	Mouth	Race, wood stove, bad teeth, orange, papaya, lettuce, and tomato
	Pharynx	Income, morakmh*, brush teeth, orange, milk, and peppers
	Larynx	Rural residence, morakmd*, industd*, industj*, family cancer, papaya, cauliflower, cassava, and cheese
Core	All sites	Wood stove
	Mouth	Wood stove, family cancer, bad teeth, and tomato
	Pharynx	Schooling, wood stove, pumpkin, and drink hot *chimarrã*
	Larynx	Wood stove, morakmd*, and cassava
Peppers	All sites	None
	Mouth	None
	Pharynx	Smoked meat
	Larynx	Morakmd*, industd*, orange, and eggs
Pickles	All sites	Peppers
	Mouth	Family cancer, grilled meat, and peppers
	Pharynx	Orange, papaya, lettuce, and peppers
	Larynx	Morakmd*, industd*, industj*, papaya, pequi, carrot, cauliflower, cassava, smoked meat, eggs, and peppers
Honey	All sites	Orange, papaya, carrot, and cheese
	Mouth	Orange, papaya, lettuce, pumpkin, tomato, cheese and eat hot
	Pharynx	Income, wood stove, family cancer, denture use, orange, papaya, cauliflower, lettuce, cheese, and eggs
	Larynx	Wood stove, industd*, orange, papaya, carrot, cauliflower, and cheese

* Definitions of variables relating to living or occupational setting can be seen in table 5.

Appendix III. Confounders for each of food groups identified empirically using a 5% change- in-estimate for cancers of the upper aero digestive tract

FOOD GROUPS	SITES	IDENTIFIED CONFOUNDERS
Carotene-rich	All sites	Brush teeth, orange, and cheese
	Mouth	Race, brush teeth, orange, lettuce, tomato, grilled meat, cheese, and peppers
	Pharynx	Income, wood stove, denture use, lemon, orange, cauliflower, lettuce, smoked meat, and drink hot cha
	Larynx	Morakmg*, family cancer, orange, lettuce, milk, cheese, and eggs
Citric fruits	All sites	Wood stove and orange
	Mouth	Race, wood stove, brush teeth, cheese, and peppers
	Pharynx	Wood stove, papaya, lettuce, and pickles
	Larynx	Rural residence, wood stove, morakmg*, undusta*, brush teeth, papaya, carrot, cauliflower, cassava, grilled meat, and milk
Spicy foods	All sites	None
	Mouth	Brush teeth
	Pharynx	Denture use, orange, and milk
	Larynx	Wood stove, morakmd*, industd*, and carrot

*Variables relating to living or occupational setting, detail definitions see table.

Appendix IV. Confounders for each of nutrient indices identified empirically using a 5% change- in-estimate for cancers of the upper aero digestive tract

NUTRIENTS	SITES	IDENTIFIED CONFOUNDERS
Vitamin A	All sites	Wood stove
	Mouth	Race, wood stove, bad teeth, and brush teeth
	Pharynx	Schooling, income, wood stove, and industd*
	Larynx	Rural residence and morakmg*
Vitamin C	All sites	Wood stove
	Mouth	Wood stove and brush teeth
	Pharynx	Schooling, wood stove, and denture use
	Larynx	Race, wood stove, morakmg*, industd*, and family cancer
Vitamin E	All sites	Brush teeth
	Mouth	Race, wood stove, and brush teeth
	Pharynx	Schooling and income
	Larynx	Wood stove, morakmd*, and family cancer
Beta-carotene	All sites	None
	Mouth	Bad teeth and brush teeth
	Pharynx	Schooling, income, wood stove, and family cancer
	Larynx	Wood stove
Folate	All sites	Brush teeth
	Mouth	Wood stove and brush teeth
	Pharynx	Schooling, income, and wood stove
	Larynx	Rural residence and industa*
Calcium	All sites	Income, wood stove, and brush teeth
	Mouth	Race, wood stove, and brush teeth
	Pharynx	Schooling and income
	Larynx	Family cancer, drink hot café, and drink hot tea
Iron	All sites	Income and brush teeth
	Mouth	Income and brush teeth
	Pharynx	Schooling, income, morakmh*, denture use, bad teeth, and drink hot cha
	Larynx	Rural residence
Zinc	All sites	Income and brush teeth
	Mouth	Income, bad teeth, and brush teeth
	Pharynx	Schooling, income, bad teeth, and drink hot cha
	Larynx	Drink hot chocolate

*Variables relating to living or occupational setting, detail definitions see table.

1. NOME DO PACIENTE: _____ Nº. NO ESTUDO: _____ ..... |__|__|__|

2. LOCAL: |1| SP |2| CTB |3| GOI ..... |__|

3. REGISTRO HOSPITALAR: _____ (INSTITUIÇÃO: _____)

4. ATRIBUTO: |1| CASO |2| CONTROLE ..... |__|

********** BLOCO A (INFORMAÇÕES SOCIO-DEMOGRÁFICAS) **********

5. SEXO: |1| MASCULINO |2| FEMININO ..... |__|

6. QUAL A SUA IDADE? _____ ANOS ..... |__|__|

7. GRUPO ÉTNICO (INTERPRETAÇÃO DO ENTREVISTADOR): |1| BRANCO |2| MULATO |3| PRETO |4|AMARELO |5| OUTRO ..... |__|

8. O(A) SR.(A) É: |1| SOLTEIRO |2| CASADO |3| VIUVO |4| SEPARADO |5| VIVE MARITALMENTE ..... |__|

9. ONDE O(A) SR(A) NASCEU? CIDADE: _____ ESTADO: _____ ..... |__|__|

10. ERA ZONA RURAL OU URBANA? |1| RURAL |2| URBANA ..... |__|

11. QUANTO TEMPO VIVEU NESTE LOCAL? _____ ANOS ..... |__|__|

12. O(A) SR.(A) PODERIA ME CONTAR AS CIDADES ONDE MOROU POR MAIS DE 5 ANOS?

A) CIDADE: _____ ESTADO: _____ ..... |__|__|
ZONA: |1| RURAL |2| URBANA ..... |__|

B) CIDADE: _____ ESTADO: _____ ..... |__|__|
ZONA: |1| RURAL |2| URBANA ..... |__|

C) CIDADE: _____ ESTADO: _____ ..... |__|__|
ZONA: |1| RURAL |2| URBANA ..... |__|

13. QUAL É O SEU GRAU DE INSTRUÇÃO? (SE PRIMÁRIO INCOMPLETO, PERGUNTAR SE SABE LER/ESCREVER)
|1| ANALF. |2| PRIM. INC. |3| PRIM. COMP. |4| SECUND. INCOMP. |5| SECUND. COMP. |6| TÉCNICO-PROFIS. |7| SUPERIOR ..... |__|

14. QUAL A SUA RELIGIÃO:
|1| CATOLICA |2| CRENTE |3| PROTESTANTE |4| JUDAICA |5| ESPIRITA ..... |__|
|6| UMBANDISTA |7| NÃO TEM |8| OUTRA (QUAL? _____)

15. INCLUINDO O(A) SR.(A), QUANTAS PESSOAS VIVEM EM SUA CASA? _____ PESSOAS ..... |__|__|

16. QUAL É A SUA RENDA FAMILIAR, OU SEJA, A DO(A) SR.(A) MAIS AS DO QUE VIVEM EM SUA CASA? Cz$ _____ ..... _____

17. O(A) SR.(A) TEM GELADEIRA EM CASA? |1| SIM |2| NÃO ..... |__|

18. A RESIDENCIA ATUAL DO(A) SR.(A) É SERVIDA POR ÁGUA ENCANADA (REDE PUBLICA)? |1| SIM |2| NÃO ..... |__|

********** BLOCO B (HISTORIA DE EXPOSIÇÃO OCUPACIONAL) **********

AGORA, EU GOSTARIA DE PERGUNTAR AO(A) SR.(A) SOBRE OS LOCAIS ONDE TRABALHOU OU VIVEU:

19. NO LOCAL ONDE VIVEU MAIS TEMPO, DE QUE TIPO ERA FEITA A CASA ONDE O(A) SR.(A) MORAVA? ..... |__|
|1| ALVENARIA (TIJOLO) |2| MADEIRA |3| BARRO |4|MISTA

20. QUE TIPO DE COBERTURA TINHA ESTA MORADIA? ..... |__|

|1| TELHA DE BARRO COMUM |2| FOLHA DE ZINCO |3| BRASILIT-ETERNIT

|4| LAJE |5| SAPÉ |6| OUTRO (QUAL? _____)

21. O(A) SR.(A) PODERIA ME CONTAR SE JÁ MOROU A MENOS DE 1 KM DE UMA DAS SEGUINTES INDUSTRIAS POR MAIS DE 1 ANO?

A) INDUSTRIA TEXTIL OU TECELAGEM: |1| SIM |2| NÃO..... |__|

B) PROCESSAMENTO DE MADEIRA: |1| SIM |2| NÃO ..... |__|

C) PAPEL OU CELULOSE: |1| SIM |2| NÃO ..... |__|

D) MINERAÇÃO (SE SIM, ESPECIFICAR:_____) |1| SIM |2| NÃO ..... |__|

E) FÁBRICA DE SAPATOS OU CURTUME: |1| SIM |2| NÃO ..... |__|

F) METALURGICA (CROMAÇÃO OU NIQUELAÇÃO): |1| SIM |2| NÃO ..... |__|

G) USINA DE AÇUCAR OU ÁLCOOL: |1| SIM |2| NÃO ..... |__|

H) PLÁSTICO OU BORRACHA: |1| SIM |2| NÃO ..... |__|

22. O(A) SR.(A) PODERIA ME CONTAR SE JÁ TRABALHOU EM QUALQUER UMA DAS SEGUINTES INDUSTRIAS POR MAIS DE 6 MESES?

A) INDUSTRIA TEXTIL OU TECELAGEM: |1| SIM |2| NÃO ..... |__|

B) PROCESSAMENTO DE MADEIRA: |1| SIM |2| NÃO ..... |__|

C) PAPEL OU CELULOSE: |1| SIM |2| NÃO ..... |__|

D) MINERAÇÃO (SE SIM, ESPECIFICAR:_____) |1| SIM |2| NÃO ..... |__|

E) FÁBRICA DE SAPATOS OU CURTUME: |1| SIM |2| NÃO ..... |__|

F) METALURGICA (CROMAÇÃO OU NIQUELAÇÃO): |1| SIM |2| NÃO ..... |__|

G) USINA DE AÇUCAR OU ÁLCOOL: |1| SIM |2| NÃO ..... |__|

H) PLÁSTICO OU BORRACHA: |1| SIM |2| NÃO ..... |__|

I) GRÁFICA OU TIPOGRAFIA: |1| SIM |2| NÃO ..... |__|

J) REFINARIA DE PETROLEO: |1| SIM |2| NÃO ..... |__|

K) INDUSTRIALIZAÇÃO DE SOJA: |1| SIM |2| NÃO ..... |__|

23. O(A) SR.(A) JÁ TRABALHOU COMO LAVRADOR(A)? |1| SIM |2| NÃO (SE NÃO, IR AO BLOCO C)

24. COSTUMAVA PESSOALMENTE APLICAR PESTICIDAS OU HERBICIDAS NA LAVOURA? ..... |__|

|1| NUNCA |2| MAIS QUE 10 VEZES |3| MENOS QUE 10 VEZES

25. JÁ TEVE ALGUMA DOENÇA OU INTOXICAÇÃO CAUSADA POR ESTES PRODUTOS? |1| SIM |2| NÃO ..... |__|

********** BLOCO C (HISTORIA GERAL DE SAUDE) **********

AGORA, EU GOSTARIA DE PERGUNTAR SOBRE QUESTÕES DE SAUDE DO(A) SR.(A) E DA SUA FAMILIA:

26. O(A) SR.(A) PODERIA ME CONTAR SE ALGUÉM DE SUA FAMILIA JÁ TEVE AS SEGUINTES DOENÇAS?

A) BRONQUITE ASMÁTICA: |1| SIM |2| NÃO

B) PRESSÃO ALTA: |1| SIM |2| NÃO

C) DIABETES (AÇUCAR NO SANGUE): |1| SIM |2| NÃO

D) TUBERCULOSE: |1| SIM |2| NÃO

E) CANCER: |1| SIM |2| NÃO (SE NÃO, IR PARA Q. 29)

27. EM CASO AFIRMATIVO (DE CANCER), QUAL ERA O VINCULO DE PARENTESCO? ..... |__|__|__|

|1| PAI |2| MÃE |3| IRMÃO |4| FILHO |5| TIO(A) |6| PRIMO |7| OUTRO

28. QUAL(IS) FOI(RAM) A(S) LOCALIZAÇÃO(ÕES) DO(S) CANCER(ES)?

|1| GARGANTA |2| PULMÃO |3| ESTOMAGO |4| INTESTINO |5| GINECOLOGICO |6| MAMA |7| BOCA |8| OUTRO(QUAL?_____) |__|__|__|__|

29. E O(A) SR.(A), JÁ TEVE ALGUMA DAS SEGUINTES DOENCAS?

A) MALÁRIA OU MALEITA? |1| SIM |2| NÃO ..... |__|

B) LEPRA: |1| SIM |2| NÃO ..... |__|

C) BLASTOMICOSE (LER ABAIXO): |1| SIM |2| NÃO ..... |__|

(EXPLICAR: UMA DOENÇA DE LONGA DURAÇÃO QUE CAUSA FERIDAS NA BOCA, AS VEZES CAUSA INGUA NO PESCOÇO E ATACA OS PULMÕES. O TRATAMENTO É FEITO COM COMPRIMIDOS QUE PRECISAM SER TOMADOS POR MAIS DE UM ANO.)

30. O(A) SR.(A) JÁ OPEROU DA GARGANTA? |1| SIM |2| NÃO ..... |__|

31. (SE SIM) COM QUE IDADE? _____ ANOS (APROXIME SE NÃO PUDER PRECISAR) ..... |__|__|

********** BLOCO D (HÁBITO DE TABAGISMO) **********

AGORA, EU GOSTARIA DE SABER SOBRE ALGUNS HÁBITOS QUE O(A) SR.(A) TENHA:

32. O(A) SR.(A) FUMA OU JÁ FUMOU REGULARMENTE EM SUA VIDA? |1| SIM |2| NÃO ..... |__|

33. (SE NÃO) JÁ FUMOU MAIS DE 100 CIGARROS (5 MAÇOS) EM SUA VIDA? |1| SIM |2| NÃO (IR PARA Q. 52) ..... |__|

34. O QUE O(A) SR.(A) FUMA (OU FUMOU)? |1| CIGARRO DE PAPEL |2| CIGARRO DE PALHA |3| CHARUTO |4| CACHIMBO

--- (CIGARRO DE PAPEL) ---

35. QUANTOS CIGARROS DE PAPEL O(A) SR.(A) FUMA/FUMAVA POR DIA? ..... |__|
|1| NO MAXIMO 1 POR DIA |2| DE 2 A 5 |3| DE 6 A 10 |4| DE 11 A 20 |5| DE 21 A 40 |6| DE 41 A 60 |7| MAIS QUE 60

36. (SE AINDA FUMA, PERGUNTAR) HÁ QUANTOS ANOS O(A) SR.(A) FUMA? _____ ANOS ..... |__|__|

37. (SE PAROU, PERGUNTAR) DURANTE QUANTOS ANOS O(A) SR. (A) FUMOU? _____ ANOS ..... |__|__|

38. (HÁ QUANTOS ANOS O(A) SR.(A) PAROU? _____ ANOS ..... |__|__|

39. O(A) SR.(A) FUMAVA MAIS QUE TIPO DE CIGARRO: |1| COM FILTRO |2| SEM FILTRO ..... |__|

--- (CIGARRO DE PALHA) ---

40. QUANTOS CIGARROS DE PALHA O(A) SR.(A) FUMA/FUMAVA EM MÉDIA POR DIA? ..... |__|
|1| NO MÁXIMO 1 |2| DE 2 A 5 |3| DE 6 A 10 |4| DE 11 A 20 |5| DE 21 A 40 |6| DE 41 A 60 |7| MAIS QUE 60

41. (SE AINDA FUMA CIGARRO DE PALHA) HÁ QUANTOS ANOS O(A) SR.(A) FUMA? _____ ANOS ..... |__|__|

42. (SE PAROU, PERGUNTAR) DURANTE QUANTO TEMPO O(A) SR.(A) FUMOU? _____ ANOS ..... |__|__|

43. HÁ QUANTOS ANOS O(A) SR.(A) PAROU? _____ ANOS ..... |__|__|

--- (CHARUTO) ---

44. QUANTOS CHARUTOS O(A) SR.(A) FUMA/FUMAVA POR DIA? ..... |__|__|
|1| NO MÁXIMO 1 |2| DE 2 A 5 |3| DE 6 A 10 |4| DE 11 A 20 |5| DE 21 A 40 |6| DE 41 A 60 |7| MAIS QUE 60

45. HÁ QUANTOS ANOS O(A) SR.(A) FUMA CHARUTO? _____ ANOS ..... |__|__|

46. (SE PAROU, PERGUNTAR) DURANTE QUANTOS ANOS O(A) SR.(A) FUMOU? _____ ANOS ..... |__|__|

47. HÁ QUANTOS ANOS O(A) SR.(A) PAROU? _____ ANOS ..... |__|__|

--- (CACHIMBO) ---

48. QUANTAS VEZES O(A) SR.(A) ENCHE COM FUMO O CACHIMBO POR DIA? _____ VEZES ..... |__|__|

49. HÁ QUANTOS ANOS O(A) SR.(A) FUMA CACHIMBO? _____ ANOS ..... |__|__|

50. (SE PAROU, PERGUNTAR) DURANTE QUANTOS ANOS O(A) SR.(A) FUMOU? _____ ANOS ..... |__|__|

51. HÁ QUANTOS ANOS O(A) SR.(A) PAROU? _____ ANOS ..... |__|__|

--- (CONTINUAÇÃO TABAGISMO) ---

52. O(A) SR.(A) TEM OU TEVE O HÁBITO DE MASCAR FUMO? |1| SIM |2| NÃO (IR PARA BLOCO E) ..... |__|

53. (SE SIM, PERGUNTAR) QUANTAS VEZES POR DIA COLOCAVA FUMO NA BOCA PARA MASCAR? _____ VEZES ..... |__|__|

54. HÁ QUANTOS ANOS O(A) SR.(A) MASCA FUMO? _____ ANOS ..... |__|__|

55. (SE PAROU) HÁ QUANTOS ANOS O(A) SR.(A) PAROU? _____ ANOS ..... |__|__|

********** BLOCO E (HÁBITO DE ETILISMO) **********

56. O(A) SR.(A) CONSOME/CONSUMIU BEBIDAS ALCOOLICAS DURANTE A SUA VIDA MESMO QUE RARAMENTE? |1| SIM |2| NÃO (IR PARA Q. 74) |__|

57. QUAIS DAS SEGUINTES BEBIDAS O(A) SR.(A) JÁ CONSUMIU MAIS DE 10 VEZES:
|1| CERVEJA (CHOPP) |2| PINGA/CACHAÇA |3| VINHO |4| UISQUE/VODKA/GIN/RUM/CONHAQUE

--- (CONSUMO DE CERVEJA) ---

58. QUANTO O(A) SR.(A) COSTUMAVA BEBER POR SEMANA? ..... |__|
|1| NO MÁXIMO 1 COPO POR SEMANA |2| DE 2 A 5 |3| DE 6 A 10 |4| DE 11 A 30 |5| MAIS QUE 30

59. DURANTE A SUA VIDA, O(A) SR.(A) JÁ CONSUMIU ESTA BEBIDA DIARIAMENTE POR MAIS DE 6 MESES? |1| SIM |2| NÃO |9| IGN. |__|

60. DURANTE QUANTO TEMPO O(A) SR.(A) CONSUMIU ESTA BEBIDA? _____ ANOS ..... |__|__|

61. (SE DEIXOU, PERGUNTAR) HÁ QUANTO TEMPO O(A) SR.(A) DEIXOU DE CONSUMIR ESTA BEBIDA? _____ ANOS ..... |__|__|

--- (CONSUMO DE PINGA/CACHAÇA) ---

62. QUANTO O(A) SR.(A) COSTUMAVA BEBER POR SEMANA? ..... |__|
|1| NO MÁXIMO 1 DOSE POR SEMANA |2| DE 2 A 5 |3| DE 6 A 10 |4| DE 11 A 30 |5| MAIS QUE 30

63. DURANTE A SUA VIDA, O(A) SR.(A) JÁ CONSUMIU ESTA BEBIDA DIARIAMENTE POR MAIS DE 6 MESES? |1| SIM |2| NÃO |9| IGN. |__|

64. DURANTE QUANTO TEMPO O(A) SR.(A) CONSUMIU ESTA BEBIDA? _____ ANOS ..... |__|__|

65. (SE DEIXOU, PERGUNTAR) HÁ QUANTO TEMPO O(A) SR.(A) DEIXOU DE CONSUMIR ESTA BEBIDA? _____ ANOS ..... |__|__|

--- (CONSUMO DE VINHO) ---

66. QUANTO O(A) SR.(A) COSTUMAVA BEBER POR SEMANA? ..... |__|
|1| NO MÁXIMO 1 COPO POR SEMANA |2| DE 2 A 5 |3| DE 6 A 10 |4| DE 11 A 30 |5| MAIS QUE 30

67. DURANTE A SUA VIDA, O(A) SR.(A) JÁ CONSUMIU ESTA BEBIDA DIARIAMENTE POR MAIS DE 6 MESES? |1| SIM |2| NÃO |9| IGN. |__|

68. DURANTE QUANTO TEMPO O(A) SR.(A) CONSUMIU ESTA BEBIDA? _____ ANOS ..... |__|__|

69. (SE DEIXOU, PERGUNTAR) HÁ QUANTO TEMPO O(A) SR.(A) DEIXOU DE CONSUMIR ESTA BEBIDA? _____ ANOS ..... |__|__|

--- (CONSUMO DE OUTROS DESTILADOS) ---

70. (SE UISQUE, VODKA, GIN, PERGUNTAR) QUANTO O(A) SR.(A) COSTUMAVA BEBER POR SEMANA? ..... |__|
|1| NO MÁXIMO 1 DOSE POR SEMANA |2| DE 2 A 5 |3| DE 6 A 10 |4| DE 11 A 30 |5| MAIS QUE 30

71. DURANTE A SUA VIDA, O(A) SR.(A) JÁ CONSUMIU DIARIAMENTE ESTA BEBIDA POR MAIS DE 6 MESES? |1| SIM |2| NÃO |9| IGN. |__|

72. DURANTE QUANTO TEMPO O(A) SR.(A) CONSUMIU ESTA BEBIDA? _____ ANOS ..... |__|__|

73. (SE DEIXOU, PERGUNTAR) HÁ QUANTO TEMPO O(A) SR.(A) DEIXOU DE CONSUMIR ESTA BEBIDA? _____ ANOS ..... |__|__|

********** BLOCO F (HISTORIA DE DIETA) **********

74. QUE TIPO É O FOGÃO DE SUA CASA QUE É UTILIZADO PARA COZINHAR? |1| GÁS |2| LENHA |3| ELÉTRICO |4| OUTRO ..... |__|

75. O(A) SR.(A) TEM POR HÁBITO INGERIR ALIMENTOS MUITO QUENTES (TEMPERATURA): |1| SIM |2| NÃO ..... |__|

76. QUANTAS VEZES POR SEMANA OU MES O(A) SR.(A) COME OS ALIMENTOS QUE EU VOU FALAR A SEGUIR :

A. LARANJADA OU SUCO DE LARANJA (OU A PROPRIA FRUTA): ..... |__|
|1| NUNCA |2| <1/M |3| 1/M |4| 2-3/M |5| 1-3/S |6| 4-6/S |7| 7/S |9| IGN.

B. LIMONADA OU PRODUTO CONTENDO SUCO DE LIMÃO: ..... |__|
|1| NUNCA |2| <1/M |3| 1/M |4| 2-3/M |5| 1-3/S |6| 4-6/S |7| 7/S |9| IGN.

C. TOMATE OU PRODUTOS CONTENDO TOMATE (PASTA OU MASSA): ..... |__|
|1| NUNCA |2| <1/M |3| 1/M |4| 2-3/M |5| 1-3/S |6| 4-6/S |7| 7/S |9| IGN.

D. CENOURA (QUALQUER MODO DE PREPARO): ..... |__|
|1| NUNCA |2| <1/M |3| 1/M |4| 2-3/M |5| 1-3/S |6| 4-6/S |7| 7/S |9| IGN.

E. ABOBORA (QUALQUER MODO DE PREPARO): ..... |__|
|1| NUNCA |2| <1/M |3| 1/M |4| 2-3/M |5| 1-3/S |6| 4-6/S |7| 7/S |9| IGN.

F. MAMÃO: ..... |__|
|1| NUNCA |2| <1/M |3| 1/M |4| 2-3/M |5| 1-3/S |6| 4-6/S |7| 7/S |9| IGN.

G. PEQUI: ..... |__|
|1| NUNCA |2| <1/M |3| 1/M |4| 2-3/M |5| 1-3/S |6| 4-6/S |7| 7/S |9| IGN.

H. COUVE OU ESPINAFRE OU BROCOLI: ..... |__|
|1| NUNCA |2| <1/M |3| 1/M |4| 2-3/M |5| 1-3/S |6| 4-6/S |7| 7/S |9| IGN.

I. ALFACE: ..... |__|
|1| NUNCA |2| <1/M |3| 1/M |4| 2-3/M |5| 1-3/S |6| 4-6/S |7| 7/S |9| IGN.

J. PICLES OU CONSERVAS APIMENTADAS: ..... |__|
|1| NUNCA |2| <1/M |3| 1/M |4| 2-3/M |5| 1-3/S |6| 4-6/S |7| 7/S |9| IGN.

K. PIMENTA NA FORMA PURA OU COMO TEMPERO: ..... |__|
|1| NUNCA |2| <1/M |3| 1/M |4| 2-3/M |5| 1-3/S |6| 4-6/S |7| 7/S |9| IGN.

L. CARNES DEFUMADAS: ..... |__|
|1| NUNCA |2| <1/M |3| 1/M |4| 2-3/M |5| 1-3/S |6| 4-6/S |7| 7/S |9| IGN.

M. OVOS: ..... |__|
|1| NUNCA |2| <1/M |3| 1/M |4| 2-3/M |5| 1-3/S |6| 4-6/S |7| 7/S |9| IGN.

N. LEITE: ..... |__|
|1| NUNCA |2| <1/M |3| 1/M |4| 2-3/M |5| 1-3/S |6| 4-6/S |7| 7/S |9| IGN.

O. QUEIJO OU DERIVADOS: ..... |__|
|1| NUNCA |2| <1/M |3| 1/M |4| 2-3/M |5| 1-3/S |6| 4-6/S |7| 7/S |9| IGN.

P. MEL: ..... |__|
|1| NUNCA |2| <1/M |3| 1/M |4| 2-3/M |5| 1-3/S |6| 4-6/S |7| 7/S |9| IGN.

Q. PINHÃO: ..... |__|
|1| NUNCA |2| <1/M |3| 1/M |4| 2-3/M |5| 1-3/S |6| 4-6/S |7| 7/S |9| IGN.

R. MANDIOCA (FARINHA OU NÃO): ..... |__|
|1| NUNCA |2| <1/M |3| 1/M |4| 2-3/M |5| 1-3/S |6| 4-6/S |7| 7/S |9| IGN.

S. MILHO (QUALQUER MODO DE PREPARO): ..... |__|
|1| NUNCA |2| <1/M |3| 1/M |4| 2-3/M |5| 1-3/S |6| 4-6/S |7| 7/S |9| IGN.

T. CARNE DE QUALQUER TIPO QUE SEJA PREPARADA GRELHADA OU CHURRASQUEADA: (NÃO CONTAR OUTRO TIPO) ..... |__|
|1| NUNCA |2| <1/M |3| 1/M |4| 2-3/M |5| 1-3/S |6| 4-6/S |7| 7/S |9| IGN.

77. AGORA, GOSTARIA DE PERGUNTAR AO(A) SR.(A) A RESPEITO DE SEUS HÁBITOS DE CONSUMIR CAFÉ E CHÁ QUANTO AO NUMERO DE VEZES:

A. CAFÉ: _____ DIA _____ SEMANA _____ MES _____ ANO ..... |__|__|
B. CHÁ: _____ DIA _____ SEMANA _____ MES _____ ANO ..... |__|__|
C. CHIMARRÃO: _____ DIA _____ SEMANA _____ MES _____ ANO ..... |__|__|
C. CHOCOLATE: _____ DIA _____ SEMANA _____ MES _____ ANO ..... |__|__|

78. QUANDO TOMA QUALQUER DESTAS BEBIBAS, O(A) SR.(A) PREFERE TOMÁ-LA: |1|FRIA |2|MORNA |3|QUENTE |4|BEM QUENTE ..... |__|

********** BLOCO G (HISTORIA DE SAUDE BUCAL) **********

EU GOSTARIA AGORA DE LHE PERGUNTAR A RESPEITO DA SAUDE DOS SEUS DENTES:

79. O(A) SR.(A) USA DENTADURA OU PONTE MOVEL? |1| SIM |2| NÃO (IR PARA Q. 82) ..... |__|

80. (SE SIM) HÁ QUANTO TEMPO? _____ ANOS ..... |__|__|

81. (SE SIM) ESTA DENTADURA OU PONTE JÁ LHE CAUSOU ALGUMA FERIDA NA BOCA POR ESTAR MAL AJUSTADA? |1|SIM |2|NÃO ..... |__|

82. O(A) SR.(A) ESCOVA/ESCOVAVA OS DENTES REGULARMENTE? |1| NUNCA |2| AS VEZES |3| DIARIAMENTE ..... |__|

83. SEM CONTAR O ULTIMO ANO, QUÃO FREQUENTEMENTE O(A) SR.(A) IA AO DENTISTA? |1| NUNCA |2| <1/ANO |3| >=1/ANO ..... |__|

84. O(A) SR.(A) TEM ALGUM DENTE ESTRAGADO? |1| SIM |2|NÃO ..... |__|

85. (SE SIM) ELE(S) ESTÁ(ÃO) MACHUCANDO? |1| SIM |2| NÃO ..... |__|

****

86. (PARA O ENTREVISTADOR) QUALIDADE DAS RESPOSTAS: |1| BOA |2| REGULAR |3| MÁ ..... |__|

86a.CID-0/9: _____ ..... |__|__|__|.|__|

87. DATA DESTA ENTREVISTA: ____/____/____ ..... ____/____/