EFEITO DA SELEÇÃO DE CONTROLES EM ESTUDOS CASO-CONTROLE DE CÂNCER DE VIAS AERODIGESTIVAS SUPERIORES: UM ESTUDO METODOLÓGICO

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CI - *confidence interval*

IC – intervalo de confiança

ICD-9 – *International Classification of Diseases, version 9*

OR - *odds ratio*

ORs - *odds ratios*

RR – risco relativo

RR – *relative risk*

UADT - *upper aerodigestive tract*

VADS - vias aerodigestivas superiores

RESUMO

Nishimoto IN. **Efeito da seleção de controles em estudos caso-controle de câncer de Vias Aerodigestivas Superiores: Um estudo metodológico.** São Paulo; 2000 [Dissertação de Mestrado – Centro de Tratamento e Pesquisa Hospital do Câncer A.C. Camargo da Fundação Antonio Prudente]

O câncer das vias aerodigestivas superiores (VADS) está entre as formas mais comuns de neoplasias malignas, especialmente em países em desenvolvimento. Os hábitos de consumir tabaco e bebidas alcoólicas têm sido estabelecidos como sendo os principais fatores de risco para este tipo de neoplasia. Outros fatores, tais como os alimentares e nutricionais, bem como algumas exposições ocupacionais e ambientais, também têm sido relacionados ao câncer das Vias Aerodigestivas Superiores.

Muitas evidências identificadas, determinantes das malignidades do câncer das VADS, originam-se de estudos do tipo caso-controle, de base hospitalar ou populacional. Um aspecto que vem sendo abordado na literatura é de que os estudos caso-controle de base hospitalar, cujo delineamento determina a seleção dos indivíduos do grupo controle em hospitais, podem produzir resultados enviesados nas investigações dos fatores de risco para o câncer das VADS. Este viés pode ser causado pela seleção dos indivíduos-controle admitidos nos hospitais, portadores de doenças relacionadas ao consumo do tabaco e álcool. Como resultado, a determinação do risco devido ao consumo de tabaco e álcool pode ser subestimado, dado que o grupo-controle selecionado super-representará a distribuição do consumo de tabaco e álcool na população geral. A estimativa do risco devido a outros fatores de risco também pode estar enviesada ou causada pelo viés de seleção, ou mesmo,

dos confundimentos oriundos do imperfeito controle do efeito de confusão do consumo de tabaco e de álcool.

O presente projeto intencionou avaliar a magnitude do viés de seleção que pode ter sido originado pela indiscriminada inclusão de pacientes do grupo-controle com doenças relacionadas ao consumo de tabaco e álcool em um estudo do tipo caso-controle de base-hospitalar realizado no Brasil em câncer das VADS. Este estudo abrangeu 784 casos e 1564 pacientes-controle com ausência de diagnóstico de câncer, pareados por faixa etária com intervalo de 5 anos, sexo e hospital participante do estudo.

Os dados desse estudo original realizado no Brasil foram reanalisados, utilizando-se modelos de regressão logística condicional e empregando-se um método de eliminação cumulativa dos pacientes-controle com enfermidades segundo a classificação: certa, provável, possível ou não associação com o consumo de tabaco e/ou álcool. A princípio foram determinados os prováveis graus de associação entre as causas de hospitalização com o consumo e tabaco e álcool para cada um dos pacientes do grupo-controle; em seguida foram estimados os riscos relativos dos fatores de risco previamente identificados para o câncer das VADS antes e após a exclusão de pacientes do grupo-controle admitidos no estudo por enfermidades relacionadas ao consumo de tabaco e álcool. Também foram estimados os riscos relativos após a exclusão dos pacientes do grupo-controle com doenças do sistema cardiovascular, respiratório ou digestivo. Os fatores de risco investigados por influência do viés de seleção foram o consumo de tabaco e álcool, bem como outros fracos determinantes como consumo de chimarrão, utilização de fogão a lenha e algumas variáveis alimentares.

As estimativas dos riscos para o câncer das VADS devido ao consumo de tabaco e álcool permaneceram substancialmente as mesmas antes e após a exclusão de indivíduos com doenças associadas a essas duas principais exposições. A contínua e significante associação com elevados riscos foi encontrada entre a quantidade de tabaco (quantificada em *pack-years*), bebida alcoólica e o câncer das vias aerodigestivas superiores. A relação mais forte verificada foi entre câncer de faringe com riscos de até 27 e 13,5 vezes e laringe com 27 e 7 vezes, respectivamente para elevadas quantidades de consumo de tabaco e álcool. As análises de outros fatores de risco menos expressivos, tais como consumo de chimarrão, residências equipadas com fogão a lenha e variáveis alimentares, também revelaram estimativas sem alterações substanciais após a restrição dos indivíduos do grupo-controle. Foram revelados também riscos significativos em torno de 2 vezes para consumo freqüente de chimarrão para todas e para cada localização anatômica específica das VADS, com exceção da cavidade oral que apresentou resultados não significativos em torno de 1,5. Alimentos apimentados também mostraram associações positivas com relação às neoplasias em foco, com riscos significativos em torno de 1,5, com exceção da laringe. A utilização de fogão a lenha teve riscos 2 vezes maiores para todas e cada uma das localizações das vias aerodigestivas superiores, independentemente da cumulativa exclusão dos pacientes do grupo-controle com doenças relacionadas ao hábito de fumar tabaco e consumir bebidas alcoólicas. O freqüente consumo de frutas cítricas teve riscos negativos variados, em torno de 0,6 para o câncer de vias aerodigestivas superiores em geral, somente sendo não-significativo para a laringe; já os alimentos ricos em β-caroteno apresentam reduções de riscos marginais em torno

de 0,6 para cada e para todas as localizações anatômicas em foco, com pequenas variações de acordo com o critério de exclusão adotado.

As estimativas de risco das doenças causadas por todos os fatores de risco estudados não se alteraram substancialmente, mesmo quando foram excluídos todos os pacientes-controle com enfermidades do sistema cardiovascular, respiratório ou digestivo.

Os resultados obtidos neste estudo sugerem que a inclusão de pacientes do grupo-controle com doenças relacionadas a tabaco e álcool em estudos caso-controle de base hospitalar não é uma importante fonte de viés de seleção. Além disso, com respeito ao estudo caso-controle brasileiro de câncer das VADS conduzido em Curitiba, Goiânia e São Paulo, nossos resultados suportam conclusivamente que o viés de seleção, devido à inclusão desses controles, não é uma provável explicação para todos aqueles achados positivos dos estudos anteriormente já publicados.

SUMMARY

Cancers of the upper aero-digestive tract (UADT) are among the most common neoplasms, particularly in developing countries. Tobacco smoking and alcohol drinking have been established as the main risk factors for these neoplasms. Other factors, such as some dietary and nutritional factors, as well as occupational and environmental exposures, have also been linked to UADT cancers.

Most of the evidence identifying determinants of UADT malignancies come from case-control studies either hospital-based or population-based. It has been argued that hospital-based case-control studies, a design where control subjects are selected from hospitals, may produce biased results in the investigation of risk factors for UADT cancers. Selecting control subjects admitted to hospitals with diseases related to tobacco and alcohol consumption may cause this bias. As a result, the determination of risk due to tobacco and alcohol consumption may be underestimated, given that the selected control group will over-represent the distribution of tobacco and alcohol consumption in the general population. Estimation of risk due to other risk factors may also be biased, either due to selection bias or due to confounding caused by the incomplete control of the confounding effect of tobacco and alcohol consumption.

The purpose of the present project was to assess the magnitude of selection bias that may have arisen due to the unrestricted inclusion of control patients with tobacco and alcohol related-diseases in a hospital-based case-control study of UADT cancers in Brazil. This study comprised 784 cases, and 1564 hospital non-cancer controls matched for 5-year age-group, gender, and hospital area.

Using conditional logistic regression we reanalyzed the data from this study, using a method of cumulative elimination of controls with diseases likely to be due to tobacco and or alcohol consumption. First we determined the likelihood of association of causes of hospitalization with tobacco and alcohol consumption for each and every control patient; and then we estimated the risk of previously identified risk factors for UADT cancers before and after exclusion of control patients admitted for diseases linked to tobacco and alcohol consumption. We also estimated the risk excluding all control patients with diseases of the cardiovascular, respiratory or digestive systems. The risk factors investigated for influence from selection bias were tobacco smoking and alcohol drinking, as well as other weak determinants like *maté* (chimarrão) consumption, use of wood stoves and some dietary variables.

The estimation of risk of UADT cancer due to tobacco and alcohol consumption remained substantially the same before and after the exclusion of control subjects with diseases linked to these two main exposures. The continuing and significant associations with high risks were found with pack-years of tobacco consumption, alcohol drinking and UADT cancers. The strongest risks were found to pharyngeal cancer with 27-fold and 13.5-fold and with 25-fold and 7-fold for laryngeal cancer, respectively to high tobacco and alcohol consumption. The analysis of weak risk factors, such as *maté* drinking, use of wood stoves and dietary variables, also showed that the risk estimates did not change substantially after restriction of control subjects. Significant risks around 2-fold for frequently *maté* consumption for all and each UADT cancers anatomic site, except to oral cavity with non-significant 1.5-fold risks. Also, spicy foods revealed positive associations for all UADT and

each site cancers, with 1.5-fold risks except to larynx cancer. The use of wood stoves by all and each UADT cancers patients showed significant 2-fold risks in spite of cumulative exclusion of control group patients with tobacco and alcohol related diseases. There was varied negative risks to the various UADT cancers anatomical sites for high consumption of citric fruits with 0.6-fold, but it was a non significant risk to laryngeal cancer; and there was a marginal 0.6-fold risks resulted to β-caroteno rich foods for each and all UADT anatomic sites, risks have remained substantially the same before and after the exclusion of control subjects with diseases linked to tobacco smoking and alcohol drinking.

The estimation of risk of disease due all studied risk factors did not substantially change either even when we excluded all control subjects with diseases of the cardiovascular, respiratory or digestive system.

Our results support the hypothesis that, inclusion of controls with tobacco and alcohol related diseases in hospital-based case-control studies are not an important source of selection bias. Moreover, regarding the UADT cancer case-control study conducted in Curitiba, Goiânia, and São Paulo, our results strongly support the proposition that selection bias due to inclusion of those controls it is not a likely explanation of those positive findings from that study already published.

ÍNDICE

1. INTRODUÇÃO

1. INTRODUÇÃO

As neoplasias estão entre as principais causas de morte no Brasil, precedidas apenas por doenças do aparelho circulatório e causas externas e, em números absolutos, representam 10,2% dos óbitos em 1990 (IBGE, 1993) e 10,9% em 1994 (MINISTÉRIO DA SAÚDE, 1997). A ocorrência estimada de óbitos por neoplasias é de 104.200 mortes para 1999 em todo o território brasileiro, representando uma taxa bruta de mortalidade de 72,2/100.000 homens e 60,7/100.000 mulheres (MINISTÉRIO DA SAÚDE, 1999).

Ocorrem no mundo atualmente 197.000 mortes por cânceres da cavidade oral e faringe, das quais 74% em áreas de alto risco de países em desenvolvimento, como Melanésia, Sul e Sudeste da Ásia e em outras áreas onde o hábito de mascar tabaco e betel é popular (PISANI et al. 1999). Nessas regiões de alto risco o câncer da boca é a nona forma mais freqüente de câncer fatal entre as mulheres (MACFARLANE et al. 1994b; PISANI et al. 1993). Em termos globais, o câncer de laringe é responsável por aproximadamente 73.500 mortes por ano, sendo predominante em homens, com 64.600 óbitos estimados para 1990 (razão homem/mulher de aproximadamente 7:1). Este é um tipo raro de câncer em mulheres, representando somente 0,4% do total das mortes por neoplasias (PISANI et al. 1999).

No Sudeste Brasileiro o câncer classifica-se como a terceira causa de mortalidade, superada apenas pelas doenças cardiovasculares e causas externas (MINISTÉRIO DA SAÚDE, 1997). No Estado de São Paulo, as taxas de mortalidade por câncer de boca e de faringe foram de 6,1 por 100.000 homens e de 1,3 por 100.000 mulheres no ano de 1978 (MIRRA e FRANCO 1987).

Estima-se para o ano de 1999 um total de 261.900 casos novos de câncer no Brasil, a uma taxa específica de incidência de 162,6/100.000 homens e 170,8/100.000 mulheres (MINISTÉRIO DA SAÚDE 1999). Entre os países com as maiores incidências de câncer destaca-se o Brasil e, de acordo com o Registro de Câncer de base populacional, as mais altas taxas entre homens são encontradas em Porto Alegre, seguida de Fortaleza e Belém (MINISTÉRIO DA SAÚDE, 1995).

Segundo informações do INCa-MINISTÉRIO DA SAÚDE (1999), o câncer de boca figura como a oitava forma de neoplasia mais freqüente no Brasil em 1999, com 7.950 casos novos (3,03% de todos os casos), sendo 5.850 (7,5 por 100.000) para homens e 2.100 (2,6 por 100.000) mulheres. Nas Regiões Norte, Nordeste e Centro-Oeste, a incidência do câncer de boca apresenta-se como a oitava localização mais freqüente em 1999, com 550 (3,6%), 1850 (2,6%) e 450 (1,9%) casos novos, respectivamente. Figura entre os dez cânceres mais freqüentes da Região Sul, com estimativa de 1.450 (2,7) casos novos. No Sudeste do Brasil espera-se a ocorrência de 3.650 (3,8%) casos novos, ocupando a nona posição dentre as neoplasias dessa região (MINISTÉRIO DA SAÚDE, 1999). Conforme dados do Registro de Câncer de São Paulo, as taxas de incidência de câncer de boca, faringe e laringe no município de São Paulo em 1969 foi de 45.3/100.000 habitantes, 48/100.000 em 1973, 56.3/100.000 em 1978 (MIRRA e FRANCO 1985), 55.4/100.000 em 1983, 52.1/100.000 em 1988 e 56.6/100.000 em 1993 (MIRRA 1999).

A incidência do câncer bucal é extremamente variável. Ainda hoje é um problema de saúde pública em muitas partes do mundo, sendo prevalente na Índia e entre homens de algumas regiões da França (PARKIN et al. 1993) e o risco de mortalidade tende a aumentar entre a população masculina em vários países

(MACFARLANE et al. 1994a). As neoplasias da cavidade oral e faringe estão entre os cânceres mais freqüentes do mundo. Para 1990 estimava-se em 212.000 (2,6% do total) os casos novos de neoplasias de cavidade oral, 94.000 (1,2% de todos os casos de câncer) os casos de câncer de faringe e 57.500 (0,7% do total) os casos de câncer de nasofaringe (PARKIN et al. 1999). Em 1985 as neoplasias da cavidade oral e faringe representaram a quinta forma mais freqüente de câncer para o sexo masculino, com 270.000 (7%) casos novos, e o sétimo entre as mulheres, com 143.000 (3,8%) (PARKIN et al. 1993). Espera-se para o câncer de laringe, que é uma neoplasia predominantemente masculina, 136.000 casos novos em 1990, dos quais 118.500 em homens. O Sul da Europa, Norte da África, Ásia Ocidental e América do Sul Temperada foram registrados como áreas de alto risco para este tipo de câncer. Já para as mulheres foi estimada a ocorrência de 17.300 casos novos no mundo (PARKIN et al. 1999). A elevada incidência esperada para a América do Sul Tropical decorre das altas taxas apresentadas na região Sul do Brasil (PARKIN et al. 1993).

A maior parte dos tumores de cabeça e pescoço ocorre nas vias aerodigestivas superiores (principalmente boca, faringe e laringe), formando um grupo de neoplasmas heterogêneos que não partilham da mesma etiologia e que são caracterizados pelas diferentes freqüências relativas de incidência e mortalidade em várias partes do mundo. São geralmente estudados agrupadamente em epidemiologia, devido:

- a dois fatores de risco em comum que têm sido consistentemente identificados: tabaco e álcool (FRANCO 1987);
- à complexidade anatômica da região, que dificulta a identificação clara da origem dos tumores, principalmente quando o diagnóstico é feito em estádio avançado,

sendo semelhantes em sua apresentação clínica, histologia e tratamento (TUPCHONG e ENGIN 1999; SANGHVI et al. 1989; VOKES et al. 1993).

Fumantes em potencial têm o risco aumentado de 3 a 20 vezes para os cânceres de cabeça e pescoço, dependendo do tipo do tabaco. Para pessoas que consomem elevadas quantidades de álcool tem-se obtido aumento de risco que varia de 3 a 15 vezes, quando comparado àqueles que não bebem, dependendo da dose diária e localização do tumor (DOLL e PETO 1981; BURCH et al. 1981; DECKER e GOLDSTEIN 1982; DE STEFANI et al. 1988; BARRA et al. 1991; MUSCAT e WYNDER 1992; MUSCAT et al. 1996; KJÆRHEIM et al. 1998; SCHLECHT et al. 1999b). Para o câncer de laringe somam-se, como fatores adicionais de risco, a exposição em residências equipadas com fogão a lenha, atividade ocupacional com madeira, histórico familiar de câncer e alto consumo de chimarrão (WYNDER et al. 1956; VICTORA et al. 1987; DE STEFANI et al. 1987; SPITZ e NEWELL 1987; CATTARUZZA et al.1996; PINTOS et al. 1998). Para o câncer oral destacam-se também a higiene, os cuidados de saúde bucal e dentição pobre (GRAHAM et al. 1977; FRANCO et al. 1989; MARSHALL et al. 1992; VELLY et al. 1998).

Fatores de proteção, para os cânceres de cabeça e pescoço, têm sido associados ao consumo de frutas cítricas e vegetais, principalmente aqueles ricos em caroteno (GRAHAM et al. 1977; CANN et al. 1985; SPITZ e NEWELL 1987; FRANCO et al. 1989; RAO et al. 1994; MARSHALL e BOYLE 1996; DE STEFANI et al. 1999a,b).

A especificidade dessas associações tem sido mostrada por vários autores em muitos estudos. A devida magnitude de associação para os prováveis fatores de risco de neoplasias das vias aerodigestivas superiores é obtida através de dois tipos de

investigação epidemiológica: estudos de coortes (Risco Relativo) e estudos de casos-controles (Razão de Chances ou OR) (BRESLOW e DAY 1980, 1987). Na primeira estratégia de estudo, um grupo de indivíduos com diferentes níveis de exposição aos fatores em estudo são acompanhados até o aparecimento da neoplasia, óbito e/ou término do estudo, muitos anos após seu início. A razão entre as taxas de ocorrência ou de óbitos por câncer para indivíduos expostos e não expostos a um determinado fator mede a magnitude das associações entre os fatores de risco e a doença. Esta medida é conhecida como risco relativo ou razão entre os riscos. Nos estudos caso-controle utilizam-se informações obtidas retrospectivamente. Os casos incidentes de uma doença são avaliados ao mesmo tempo que indivíduos controles selecionados entre a população hospitalar (controles hospitalares) ou na comunidade (controles populacionais). Estudam-se os riscos relativos para cada fator de risco em investigação, obtidos por história clínica detalhada e padronizada. A razão do risco entre os indivíduos expostos e não expostos é denominada de "Odds Ratio" (OR), palavra inglesa que é comumente conhecida no nosso meio como "Razão de Chances" ou também como "Razão dos produtos cruzados". Nos últimos anos, estudos de coortes e estudos caso-controle ganharam grande impulso com o emprego de computadores e de métodos estatísticos de análise multivariada (SOARES e BARTMANN 1985; AUSTIN et al. 1994).

De acordo com WACHOLDER et al. (1992b), controles hospitalares geralmente são utilizados pelas seguintes razões:

- conveniência, pois favorece a localização dos pacientes/indivíduos nas capturas ou recapturas e/ou realização de exames;
- manter a mesma base dos casos;

- boa qualidade das informações sobre os indivíduos ou pacientes;
- altas taxas de participação para os indivíduos selecionados;
- apresentar custos reduzidos, mais baratos.

Os pareamentos reduzem a possibilidade de várias perdas de eficiência de um potencial fator de risco entre casos e controles. Entretanto, o pareamento poderia ser considerado somente para os fatores de risco cujos efeitos de confusão necessitam ser controlados, os quais não são de interesse científico como fatores de risco independentes no estudo. A idade, o sexo e/ou a raça são freqüentemente utilizados como variáveis de pareamento, pois são considerados como potenciais fatores de confusão (*confounders*) e por seus efeitos serem bem conhecidos na epidemiologia descritiva do câncer (SOARES e BARTMANN 1985; WACHOLDER et al. 1992c).

A seleção do grupo comparação apropriado é um dos aspectos mais críticos, tanto quanto problemático, já que não existe um tipo específico de controle conveniente para todos os estudos e nem há um critério sólido e aceitável para a escolha do grupo controle (AUSTIN et al. 1994; LASKY e STOLLEY 1994).

Em estudos caso-controle de base hospitalar (critério de seleção mais comum na literatura) é sugerido que os casos sejam todos pacientes portadores de neoplasia maligna e com diagnóstico confirmado. Os controles geralmente são hospitalares, pareado ou pareados a cada caso de acordo com o sexo, faixa etária (mais ou menos 5 anos) e hospital ou hospitais vizinhos ao que diagnosticou o caso (COLE 1980; SOARES e BARTMANN 1985; LASKY e STOLLEY 1994).

O delineamento do estudo caso-controle, onde é imprescindível o grupo comparação, permite abordar questões importantes de forma rápida, econômica e eficiente, justificando sua popularidade no meio médico-científico. Entretanto, existe

alguma limitação e propensão a resultados com viés nesse tipo de estudo, devido à manipulação na seleção dos grupos controle, uma vez que constituem um grupo representativo em relação à base de risco da doença (COLE 1980; SOARES e BARTMANN 1985; AUSTIN et al. 1994; LASKY e STOLLEY 1994).

Muitos fatores de riscos para cânceres de localizações anatômicas de vias respiratórias e de VADS resultam de estudos caso-controle com variadas formas de seleção de seus pacientes-controles (WYNDER and STELLMAN 1979; DE STEFANI et al. 1987; VICTORA et al. 1987; BARRA et al. 1991; SUZUKI et al. 1994; WÜNSCH-FILHO et al. 1995, 1998). Num estudo caso-controle de base-hospitalar em câncer orofaríngeo conduzido por LEVI et al. (1998) em Lausanne, Suíça, o grupo-controle hospitalar constituiu-se de pacientes com doenças que se julgavam não associadas ao consumo de tabaco, álcool ou alterações na dieta alimentar. O risco relativo ajustado que se encontrou para consumo elevado de frutas cítricas foi de 0.4 (95% CI: 0.2-0.7). Em um outro estudo caso-controle para câncer oral conduzido por FRANCO et al. (1989) no Brasil, os controles foram pacientes de várias enfermidades, excetuando-se aqueles portadores de neoplasias malignas ou distúrbios mentais. O risco relativo encontrado neste estudo brasileiro foi 0.5 (95% CI: 0.3-0.9). Observa-se que os riscos obtidos para câncer orofaríngeo (Suíça 1998) e oral (Brasil 1989) foram negativos para consumo de quantidades elevadas de frutas, independentemente da inclusão de controles com doenças associadas ou não aos fatores de riscos mais importantes para os cânceres das VADS.

Em estudos casos-controles brasileiros de câncer das VADS, com dados originalmente obtidos pelo Grupo de Estudo do Câncer das Vias Aerodigestivas Superiores do Instituto Ludwig de Pesquisa sobre Câncer *(LICR-URDS)*:

- FRANCO et al. (1989) avaliaram vários fatores de risco para o câncer oral;
- PINTOS et al. (1994) estudaram a associação entre algumas bebidas não alcoólicas (inclusive chimarrão);
- FOULKES et al. (1995) estudaram a associação com história familiar;
- PINTOS et al. (1998) avaliaram o risco em residências equipadas com fogão a lenha;
- VELLY et al. (1998) verificaram a relação entre fatores de higiene bucal e condições dentárias;
- SCHLECHT et al. (1999a) analisou o efeito da cessação do hábito de consumir tabaco e o tipo do tabaco;
- SCHLECHT et al. (1999b) estudaram a interação entre o consumo de tabaco e álcool e o câncer em foco.

Em todos estes estudos os autores sempre consideraram a inclusão indiscriminada de controles hospitalares com pacientes portadores das mais variadas enfermidades, com exceção de câncer e distúrbios mentais.

Uma monografia publicada pela IARC (1991) apontou como referência o estudo conduzido por FRANCO et al. (1989), citando um comentário feito pelo grupo de trabalho de que "aproximadamente um terço dos controles tinha doenças do aparelho digestivo". Tendo em vista a possibilidade dos resultados obtidos nesses estudos caso-controle de VADS brasileiros estarem enviesados, devido à inclusão indevida de pacientes-controle com doenças relacionadas ao consumo de tabaco e álcool, elaboramos este estudo adotando um critério de eliminação cumulativa dos controles, de acordo com a associação das doenças com o consumo desses fatores de risco.

2. OBJETIVOS

2. OBJETIVOS

O propósito do presente estudo é avaliar a magnitude do viés de seleção originado pela inclusão indiscriminada de pacientes-controle com enfermidades relacionadas ao consumo de tabaco e álcool, em um estudo epidemiológico tipo caso-controle de base hospitalar para o câncer das vias aerodigestivas superiores no Brasil. Utilizou-se um método de exclusão cumulativa dos pacientes do grupo-controle com doenças relacionadas ao consumo de tabaco e álcool. Especificamente:

a) determinar o provável grau de associação das causas de hospitalização com o consumo de tabaco e álcool para cada e todo paciente do grupo-controle;
b) estimar o risco dos prováveis e dos potenciais fatores de risco previamente identificados para o câncer das VADS e suas localizações anatômicas, considerando-se como método a exclusão cumulativa dos pacientes-controles com doenças associadas ao tabaco e álcool. Por influência do viés de seleção, os fatores de risco investigados são, principalmente, o tabaco e álcool, assim como outros determinantes menos expressivos como consumo de chimarrão, uso de fogão a lenha e algumas variáveis alimentares previamente identificadas.

3. *REPORT*

3. *REPORT*

EFFECT OF CONTROL FOR SELECTION BIAS IN A HOSPITAL-BASED CASE-CONTROL STUDY OF UPPER AERO-DIGESTIVE TRACT CANCERS

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(*Report* que, resumido em 18 páginas, 5 tabelas e 3 figuras, será submetido para publicação na Revista American Journal of Epidemiology.)

3.1 INTRODUCTION

3.1.1 *Burden of Cancer*

Carcinomas of the upper aero-digestive tract (UADT) are among the most common neoplasms, particularly in developing countries. It has been estimated that in 1990, there were nearly 500,000 new cases of head and neck cancer worldwide, 377,000 in men and 123,000 in women (PARKIN et al. 1999). In terms of mortality they rank as the third most frequent cause of death in developing countries, after lung and stomach cancer as estimated in 1985 (PISANI et al. 1993; PARKIN et al. 1993). Laryngeal cancer is the second most common respiratory cancer after lung cancer, with areas of highest risk occurring in Southern and Eastern Europe, Western Asia and South America as shown by age-standardized rates (PARKIN et al. 1999). Incidence rates in Southern Brazil are among the highest in the world. The combined annual age-standardized rates for oral, pharyngeal and laryngeal cancer are 49.7 and 36.1 per 100,000 males in São Paulo and Porto Alegre, respectively (MUIR et al. 1987; PARKIN et al. 1993). After France and India, the male population in Brazil has the highest risk worldwide for cancer of the mouth. Incidence rates for UADT cancers are increasing in São Paulo and many other areas of the world (COLEMAN et al. 1993), likely due to changes in tobacco and alcohol consumption.

UADT malignancies are relatively common cancers among men, though rarer in women. A comparison of male-to-female ratios of oral cancer incidence rates revealed that they are notably higher in São Paulo than in Bombay (India), with ratios of 3.64 (São Paulo) and 1.30 (Bombay) per 100,000 for cancer of the mouth, and

8.22 (São Paulo) and 2.76 (Bombay) for cancer of tongue. The difference has been attributed to the predominance of smoking and alcohol drinking among males in Brazil, and to widespread betel chewing among females living in India (HAMADA et al. 1991a).

Head and neck cancer is a heterogeneous group of neoplasms with similar etiology. Most epidemiological studies investigating this group of tumors include oral cavity, pharyngeal and laryngeal cancers and exclude salivary gland and nasopharyngeal tumors. Tumors at these former three sites are generally grouped together because of they share the main risk factors: tobacco and alcohol consumption, and because of the difficulty in ascertaining the anatomical subsites in some tumors at advanced stages (FRANCO 1987; SANGHVI et al. 1989; VOKES et al. 1993; TUPCHONG and ENGIN 1999).

Tobacco and alcohol consumption have been established as the main risk factors for laryngeal cancer as have been for other neoplasms of the UADT (WYNDER and STELLMAN 1977, 1979; DOLL and PETO 1981; DE STEFANI et al. 1987; DE STEFANI et al. 1988; FRANCO et al. 1989; BLOT et al. 1988; BARRA et al. 1991; DE STEFANI et al. 1992; BARON et al. 1993; KABAT et al. 1994; CATTARUZZA et al. 1996; SCHILDT et al. 1998; LEWIN et al. 1998; KJÆRHEIM et al. 1998; SCHLECHT et al. 1999a). In a recent study conducted by FRANCESCHI et al. (1999) the oral cavity cancer risk tended to be about 2-fold greater than pharyngeal neoplasm at each combined at high level of smoking and drinking habits. Several dietary and nutritional factors (VICTORA et al. 1987; SPITZ and NEWELL 1987; MARSHALL and BOYLE 1996; RAO et al. 1994; PINTOS et al. 1994; RIBOLI et al. 1996; ESTÈVE et al. 1996; EL-BAYOUMY et al. 1997;

LEVI et al. 1998; KJÆRHEIM et al. 1998; DE STEFANI et al. 1999a) as well as occupational and environmental exposures have also been identified in previous studies on UADT cancers (KEANE et al. 1981; COWLES 1983; FRANCO et al. 1989; HAMADA et al. 1991b; PINTOS et al. 1998).

3.1.2 Epidemiological Evidence

The magnitude of association between risk factors and cancer obtained from epidemiological investigations has mainly been derived from case-control studies, which estimate the relative risk of disease due to exposure via computation of odds ratio (OR).

Case-control studies are observational epidemiological investigations in which individuals with a given disease of interest (cases) are selected for comparison with a group of subjects who does not have that given disease (controls) under study. Cases and controls are then compared with respect to certain characteristics or past exposure to risk factors of interest. This study design offers a number of advantages for evaluating the association between an exposure and a disease: tend to be smaller in size, relatively rapidly completed and relatively inexpensive. In summary, case-control studies compare exposure histories of "cases" with "non-cases" from the same population and provide the strength of the association (MIETTINEN 1985; SCHLESSELMAN 1982).

Case-control studies typically use one of two types of control subjects, selected from either a hospital-based population (hospital-controls) or from the community (population controls). In the design of these types of studies, a primary challenge is the identification of the study base from which to select cases and

controls (BRESLOW 1982; WACHOLDER 1992a; LASKY and STOLLEY 1994). Such studies must be designed carefully in order to provide a true picture of the effect of the exposure on the incidence (HORWITZ and FEINSTEIN 1979; PEARCE and CHECKOWAY 1988; POOLE 1999). Three basic principles should be considered to minimize the effect of bias on the results of these studies: a) to eliminate selection bias (cases and controls should come from the population with the same base of experience); b) to control for confounding (distortions of the effect by other unmeasured risk factors associated with disease and exposure under study should be controlled), and c) to reduce information bias (an equivalent degree of accuracy in measuring the exposure of interest should be observed in the analysis) (HORWITZ and FEINSTEIN 1979; COLE 1980; BRESLOW 1982; AUSTIN et al. 1994).

In hospital based case-control studies, it can usually be assumed that control patients admitted to the same hospital as the cases are members of the same base. However, an important assumption of "representativeness of exposure" should be taken in account in diseased subjects for hospital controls (PEARCE and CHECKOWAY, 1988; WACHOLDER et al. 1992a). Control subject selection, therefore, is crucial in case-control studies, since the use of inappropriate control subjects can lead to both selection bias and information bias, and may affect the validity of a study. An important point to consider in hospital-based case-control studies is control eligibility, in particular whether "exposure-related" diseases were the cause of hospitalization for control subjects. According to many epidemiologists, subjects with conditions known to be associated with the exposure under study should not be included. One of the critical aspects is the lack of uniform criteria in the selection of the control group (COLE 1980; LASKY and STOLLEY 1994).

Case-control studies have substantially contributed to the evidence implicating several factors with elevated risk effects on the occurrence of UADT cancers. One example is a hospital-based case-control study carried out in three Brazilian regions by FRANCO et al. (1989), 232 cases with oral neoplasms admitted in three Head and Neck Surgery Departments were recruited, to which twice as many hospital controls were individually matched. Control subjects with malignant diseases were excluded. Tobacco smoking and alcohol drinking habits, coffee and *maté* consumption, oral hygiene, the use of wood stoves in the home and some dietary variables were identified as risk factors for the disease. The associations between coffee drinking, *maté* consumption and oral cancer were found to be partly due to confounding by smoking and alcohol consumption. Adjustments for these extraneous variables reduced the magnitude of the relative risk estimates for *maté* and coffee drinking (FRANCO et al. 1989). It was observed, however, that approximately one-third of the controls had digestive tract disorders (IARC 1991), a condition that could have influenced the results because of selection bias caused by over sampling tobacco and alcohol related diseases among hospital controls subjects. Risk effects for other factors identified in this study, such as nutrition, dietary habits, dental factors, family history of cancer and use of wood stoves could also have been influenced by the control selection (PINTOS et al. 1994; FOULKES et al. 1995; PINTOS et al. 1998; VELLY et al. 1998; SCHLECHT et al. 1999a).

3.1.3 *Rationale*

In these studies, the risk of developing UADT cancers was estimated using control subjects admitted to a hospital, with no attempt to exclude those with tobacco

or alcohol related diseases from the control group. As a result, the relative risk estimates for tobacco and alcohol consumption may have been underestimated, given that the selected control group may have over-represented the distribution of tobacco and alcohol consumption in the general population (PEARCE and CHECKOWAY 1988).

Little is known about risk factors for UADT cancers besides the influence of tobacco and alcohol consumption. Associations with *maté* consumption (PINTOS et al. 1994), oral hygiene (VELLY et al. 1998) and exposure to wood stoves (PINTOS et al. 1998), if confirmed, could explain a sizable proportion of all head and neck cancers occurring in Brazil.

Selection bias due to over sampling of tobacco and alcohol-related diseases among hospital controls may have affected previous findings concerning the latter variables. When assessing weak determinants, such as *maté* consumption and use of wood stoves in the home, it is important to control for the confounding effect of strong determinants such as tobacco and alcohol. If the risk due to tobacco and alcohol consumption is underestimated, this situation may lead to an overestimation of the risk from other factors caused by residual confounding.

3.2 OBJECTIVE

The purpose of the present study is to assess the magnitude of selection bias that may have arisen due to the unrestricted inclusion of control patients with tobacco and alcohol related-diseases in a hospital-based case-control study of UADT cancers in Brazil. This is accomplished using a method of cumulative elimination of controls

with diseases likely to be due to tobacco and or alcohol consumption. The specific aims are:

a) to determine the likelihood of association of causes of hospitalization with tobacco and alcohol consumption for each and every control patient;

b) to estimate the risk of previously identified risk factors for UADT cancers after exclusion of control patients admitted for diseases linked to tobacco and alcohol consumption. The risk factors investigated for influence from selection bias are primarily tobacco and alcohol consumption, as well as other weak determinants like *maté* consumption, use of wood stoves and certain previously identified dietary variables.

3.3 MATERIALS AND METHODS

In order to evaluate the influence of control selection on the magnitude of the association for primary (tobacco and alcohol) and ancillary (diet, environmental exposures) risk factors for head and neck cancers, we reanalyzed the data collected in a hospital-based case-control study conducted in Brazil applying different levels of restriction criteria to controls. From 1986 to 1989, the Ludwig Institute for Cancer Research's Upper Respiratory and Digestive System Cancer Study Group (LICR-URDS) (Principal Investigator: E.L. FRANCO; Clinical Coordinator: L.P. KOWALSKI), carried out a multi-center hospital-based case-control study, in three Head and Neck Surgery Services in São Paulo (Southwest) - Hospital Heliópolis; Curitiba (South) - Hospital Erasto Gaertner, and Goiânia (Midwest) - Hospital Araújo Jorge.

3.3.1 *Case Subjects*

A total of 784 cases with newly diagnosed carcinomas of the head and neck were recruited and coded in accordance to *International Classification of Diseases, 9th revision* (ICD-9) guidelines. All patients with a new diagnosis of oral cavity cancer (ICD-9 140-145), cancer of pharynx (ICD-9 146-149), and laryngeal cancer (ICD-9 161) were approached. Subjects with histologically confirmed squamous cell carcinomas for the respective pathological sites and with no prior treatment for cancer were eligible to participate in the study. Patients with tumors of the salivary glands (ICD-9 142) or of the nasopharynx (ICD-9 147) were not included in the investigation. It is estimated that the Head and Neck Surgery Service in São Paulo, which is a general hospital, provides treatment to approximately 20% of all incident cases in the city, while the other two centers (Cancer Hospitals) cover 100% of all incident cases in their respective areas.

3.3.2 *Control subjects*

A total of 1564 individuals were selected as controls. They were recruited at the same hospital as the index case or at the neighboring general hospital. Two control patients were matched for each case on the basis of sex, age (within five years), and trimester of hospital admission. Patients with malignant neoplasms (ICD-9 140-239) or mental disorders (ICD-9 290-319) were not eligible as controls. Of the 1568 patients originally recruited as controls, four control subjects were excluded after no diagnosis for their disease was registered in the questionnaire.

3.3.3 *Exposure assessment*

All subjects (cases and controls) were given a standardized interview conducted by specially trained nurses, blinded to all etiologic hypotheses. Information on socio-demographic variables, health conditions, environmental and occupational exposures, tobacco and alcohol consumption, diet and oral hygiene was elicited during the interviews. Each interview lasted an average 40-60 minutes and was carried out before treatment was initiated so that the patient's ability to communicate or recall information would not be adversely affected. Interviews were interrupted if patients experienced difficulty communicating due to pain or speech problems. Altogether, nine cases were excluded from the study: one subject refusal, seven interviews were terminated due to patient's poor physical conditions and one case subject was excluded after no suitable controls could be identified.

3.3.4 *Disease scores for controls*

In order to assess the impact of the selection bias from the inclusion of tobacco and alcohol related diseases in the control group, the cause of hospitalization for each control patient was classified according to the likelihood of association with tobacco and alcohol. The likelihood of association was scored as follows: certainly associated (score = 4), probably associated (score = 3), possibly associated (score = 2) and certainly not associated (score = 1). The definition of the scores used to assess the likelihood of a causal association between each diagnostic condition among hospital controls and alcohol and tobacco consumption are shown in Table 1.

Figure 1 illustrates the study protocol used to score the control subjects' diseases with respect to their relation to tobacco and alcohol. The Medical Pathologist

Table 1: Definition of scores used to assess the likelihood of a causal association between each diagnostic condition among hospital controls and tobacco and alcohol consumption

Level of Score	Interpretation	Degree of Evidence for Causal Association
1	No association	Conclusive and abundant evidence against a causal association in the published literature. Association has been investigated in multiple studies but was never credibly found
2	Possible	Quality and quantity of evidence is lacking but there is significant body of literature suggesting a possible association from clinical impression. Alternatively, association is plausible despite lack of supporting data.
3	Probable	Limited evidence from epidemiologic or laboratory studies, consensus conferences, or other peer-reviewed sources in the medical literature. The association cannot be considered conclusive because of insufficient evidence from large epidemiologic studies or because of pending controversy.
4	Certain	Conclusive evidence from epidemiologic or laboratory studies, consensus conferences, or other peer-reviewed sources in the medical literature

(MP) and an Oncologic Surgeon (OS) carried out scoring independently for each diagnostic condition, blinded to all exposure history information and all other concurrent conditions not related to hospital admission. They used the following references to classify each disease: BURNS 1992; DIAMOND 1992; PRESCOTT et al. 1998; THUN et al. 1997; HARPER 1998. Whenever there was any contradiction between the publication or there were no information the MP and the OS classified the control-patients based on their professional experience.

The MP scored all causes of hospitalization for control-patients twice (MP1 and MP2) with an interval of 15 days. In case of disagreement between the MP1 and MP2 scores, the MP scored the condition a third time blinded to the other factors (MP3). In case of disagreement among the three MP classifications, a specialist (SP) in the disease or diagnostic condition of the control in question was consulted and a final score was established. When agreement occurred between the OS's reading and at least one of the MP's readings, the agreed score was used to assess the likelihood

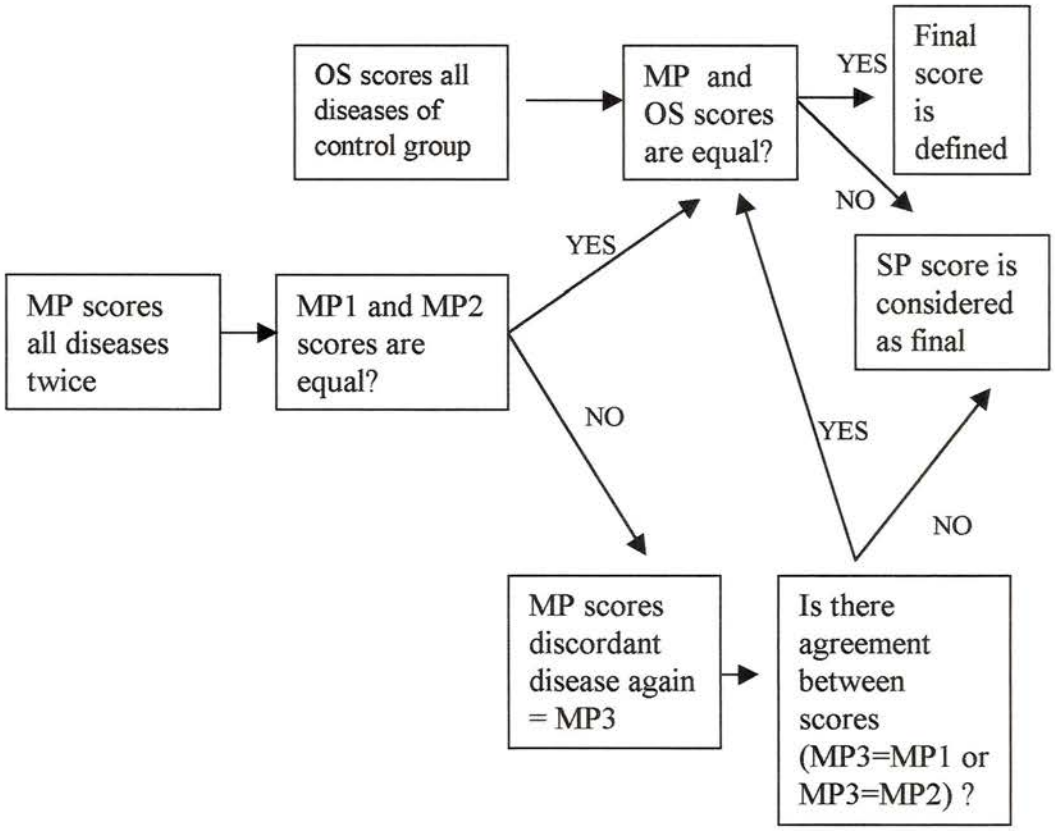


Figure 1: Study protocol used to score the control subjects' diseases with respect to their relation to tobacco and alcohol consumption.

of association. In the case of disagreement between the OS's score and both MP's scores, the score given by the specialist (SP) was used. In case of disagreement between the two scores, MP and OS, a specialist (SP) in the disease or diagnostic condition in question was again consulted to gauge the plausibility of association with tobacco and alcohol consumption for that condition.

3.3.5 *Disease class restriction criteria*

While excluding certain kinds of patients, however, we may inadvertently eliminate people with particularly high or low rates of exposure to the suspected causal agent. To verify this, we also examined the effect of excluding control patients admitted for classes of disease that are linked to tobacco and alcohol consumption (cardiovascular, respiratory or digestive systems).

3.3.6 *Statistical methods*

Derivation of ORs was done using conditional logistic regression analysis. To permit analysis after restriction of controls, matching categories were redefined on age (by five-year age group), sex and study location. ORs and their respective 95 percent confidence interval (CI) were estimated for each exposure of interest (HOSMER and LEMESHOW, 1989). The statistical software STATA release 6.0 (Stata 1999) was used to process the data analysis. Cumulative exposure to tobacco smoking was expressed in pack-years defined as the cumulative exposure equivalent of smoking one pack of cigarettes daily during one year. Cumulative alcohol exposure was expressed in kilograms of ethanol calculated from the past consumption of individual beverages over the patient's entire life. For the computation of pack-years

of tobacco consumption we assumed the following equivalence: 20 industrialized cigarettes = 4 hand-rolled, black tobacco cigarettes = 4 cigars = 5 pipefuls with pipe tobacco. Likewise, dose of ethanol consumed corresponded to 5% of beer, 10% of wine, and 50% of hard liquor and 50% of *cachaça* (a spirit distilled from sugar cane).

In addition to tobacco and alcohol consumption, the following variables were analyzed as determinants of UADT cancers or as potential confounders of the primary factors of interest: (a) Socio-demographic variables: ethnicity, rural residency, schooling level, household income; (b) Diet: past frequency of consumption of *maté*, citrus fruits (orange and lemon), β-carotene (tomato, carrot, pumpkin, papaya, and *pequi* - a fibrous fruit common in Central Brazil), spicy foods (pickles and pepper), and (c) use of a wood stove in the home.

Selection bias due to inclusion of tobacco and alcohol-related diseases in the control group was assessed using progressive exclusion from analysis of controls with admitting diseases likely to be linked to tobacco and/or alcohol consumption depending on their likelihood score. The following models were used for this assessment: i) inclusion of all controls originally recruited in the study; ii) exclusion of controls with causes of hospitalization certainly linked to tobacco and/or alcohol consumption, score 4 (tobacco = 4 and/or alcohol = 4); iii) exclusion of controls with diseases certainly or probably linked to the exposures, scores 3 and 4 (tobacco $\geq$ 3 and/or alcohol $\geq$ 3); iv) exclusion of controls with certain, probable or possible likelihood of association, scores 4, 3 and 2 (tobacco $\geq$ 2 and/or alcohol $\geq$ 2); and v) exclusion of all controls based on disease class. Controls with cardiovascular, respiratory or digestive system diseases at admission to hospital were excluded in the latter "disease class" restriction step, irrespective of their likelihood score.

3.4 RESULTS

Seven hundred and forty eight patients with UADT cancers were selected from each of the study hospitals: 213 (27.2%) from Hospital Heliópolis (São Paulo), 380 (48.5%) from Hospital Erasto Gaertner (Curitiba) and 191 (24.3%) from Hospital Araújo Jorge (Goiânia). Cases of UADT cancer included: 373 (47.6%) patients with cancer of the oral cavity (ICD-9 140-145), 217 (27.7%) with cancer of the pharynx (ICD-9, 146-149) and 194 (24.7%) with cancer of the larynx (ICD-9, 161). Table 2 illustrates the distribution of causes of hospitalization among controls originally recruited in the study as well as after progressive restriction following levels of likelihood scores: certain, probable and possible, based on their causal association with tobacco and alcohol consumption. The distribution of cases and controls according to tobacco, alcohol, diet variables and use of wood stove for cooking following restriction are shown in table 3. A similar distribution of exposure and consumption among controls as for cases was observed at each level of restriction.

Table 4 presents the frequencies of controls according to sociodemographic characteristics at each level of restriction. Around 27% of controls were selected from São Paulo, 49% from Curitiba and 24% from Goiânia. Following disease class restriction a different distribution of controls by city was observed with 13.6% coming from São Paulo. All control patients were selected from Hospital Heliópolis, which is a general hospital that has a specialized Head and Neck Surgery Department and several other medical specialties, but not all such as Gynecology, Orthopedic or Cardiac Surgery. In contrast, the Curitiba and Goiânia control patients were selected

Table 2: Distribution of reasons for hospitalization among controls as originally accrued in the study and after cumulative exclusion according to level of restriction* based on likelihood of causal association with tobacco smoking and alcohol consumption

Diagnostic Categories (ICD-9)	No Restriction	Restriction based on association with tobacco			Restriction based on association with alcohol		
		Certain	Probable	Possible	Certain	Probable	Possible
Infectious and parasitic diseases (001-139)	63 (4.0)	63 (4.6)	63 (5.4)	63 (5.9)	63 (4.2)	63 (4.6)	63 (4.7)
Neoplasms (140-239)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Endocrine, metabolic and blood disorders (240-289)	48 (3.1)	46 (3.4)	46 (4.0)	40 (3.7)	47 (3.1)	47 (3.4)	46 (3.4)
Mental disorders (290-319)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Nervous and sensory system diseases (320-389)	50 (3.2)	49 (3.6)	48 (4.1)	48 (4.5)	50 (3.3)	50 (3.6)	49 (3.6)
Cardiovascular system diseases (390-459)	400 (25.6)	230 (16.7)	113 (9.7)	97 (9.0)	377 (24.9)	359 (26.1)	357 (26.4)
Respiratory system diseases (460-519)	98 (6.3)	90 (6.6)	74 (6.4)	27 (2.5)	98 (6.5)	95 (6.9)	91 (6.7)
Digestive system diseases (520-579)	410 (26.2)	409 (29.8)	343 (29.4)	331 (30.8)	384 (25.4)	287 (20.8)	281 (20.8)
Genito-urinary tract diseases (580-629)	116 (7.4)	116 (8.4)	116 (10.0)	116 (10.8)	116 (7.7)	115 (8.4)	115 (8.5)
Pregnancy-associated diseases (630-676)	4 (0.3)	4 (0.3)	4 (0.3)	3 (0.3)	4 (0.3)	3 (0.2)	3 (0.2)
Skin diseases (680-709)	26 (1.7)	26 (1.9)	26 (2.2)	26 (2.4)	26 (1.7)	26 (1.9)	26 (1.9)
Osteo-muscular diseases (710-739)	48 (3.1)	48 (3.5)	46 (4.0)	46 (4.3)	48 (3.2)	47 (3.4)	47 (3.5)
Congenital disorders (740-759)	6 (0.4)	6 (0.4)	6 (0.5)	6 (0.6)	6 (0.4)	6 (0.4)	6 (0.4)
Ill-defined diagnostic conditions (780-799)	161 (10.3)	153 (11.1)	148 (12.7)	139 (12.9)	161 (10.6)	146 (10.6)	136 (10.1)
Trauma and poisoning (800-999)	134 (8.6)	134 (9.8)	133 (11.4)	133 (12.4)	134 (8.8)	133 (9.7)	133 (9.8)
TOTAL	1564 (100.0)	1374 (100.0)	1166 (100.0)	1075 (100.0)	1514 (100.0)	1377 (100.0)	1353 (100.0)

* Diagnostic condition scores used for exclusion: certain (=4), probable (≥ 3), possible (≥ 2)

Table 3: Distribution of cases and controls according to tobacco (t) and alcohol (a) consumption and sentinel variables, following restriction on the basis of likelihood of association with tobacco and alcohol

Variables	Levels	Cases	Controls				
			No restriction	score-based restriction*			Disease class Restriction
				a=4 and t=4	a≥3 and t≥3	a≥2 and t≥2	
		freq. (%)**	freq. (%)**	freq. (%)**	freq. (%)**	freq. (%)**	freq. (%)**
Tobacco Smoking (pack-years)	< 1	30 (3.8)	356 (22.8)	315 (23.5)	271 (25.5)	250 (25.7)	153 (23.3)
	1 - 22	142 (18.1)	362 (23.2)	309 (23.1)	245 (23.1)	225 (23.2)	154 (23.5)
	23 - 45	207 (26.4)	332 (21.2)	278 (20.8)	204 (19.2)	187 (19.2)	130 (19.8)
	46 - 91	200 (25.5)	266 (17.0)	230 (17.2)	178 (16.8)	162 (16.7)	109 (16.6)
	> 91	202 (25.8)	239 (15.3)	200 (14.9)	156 (14.7)	142 (14.6)	105 (16.0)
Alcohol Consumption (kgs)	0 - 10	95 (12.1)	413 (26.4)	367 (27.4)	299 (28.2)	275 (28.3)	152 (23.2)
	11 - 133	80 (10.2)	295 (18.9)	260 (19.4)	215 (20.3)	197 (20.3)	133 (20.3)
	134 - 793	181 (23.1)	365 (23.3)	309 (23.1)	239 (22.5)	225 (23.2)	161 (24.5)
	794 - 1248	166 (21.2)	233 (14.9)	197 (14.7)	151 (14.2)	143 (14.7)	112 (17.1)
	1249 - 9000	261 (33.3)	249 (15.9)	199 (14.9)	152 (14.3)	129 (13.3)	94 (14.3)
Mate' Consumption	Never	488 (62.2)	1091 (69.9)	925 (69.1)	738 (69.6)	677 (69.7)	426 (64.9)
	≤ 1/day	142 (18.1)	291 (18.6)	259 (19.4)	193 (18.2)	177 (18.2)	119 (18.1)
	2/day	77 (9.8)	107 (6.9)	91 (6.8)	73 (6.9)	67 (6.9)	65 (9.9)
	≥ 3/day	77 (9.8)	73 (4.7)	63 (4.7)	56 (5.3)	50 (5.2)	46(7.0)
Use of wood stove	No	386 (49.2)	1047 (66.9)	879 (65.6)	662 (62.4)	599 (61.6)	367 (56.0)
	Yes	397 (50.6)	512 (32.7)	457 (34.1)	395 (37.2)	369 (38.0)	285 (43.5)
Citric fruit Consumption	≤ 1/M	332 (42.4)	491 (31.4)	421 (31.4)	341 (32.1)	310 (31.9)	225 (34.3)
	2/M - 3/W	233 (29.7)	546 (34.9)	483 (36.0)	393 (37.0)	364 (37.5)	247 (37.7)
	≥ 4W	218 (27.8)	523 (33.4)	432 (32.2)	324 (30.5)	295 (30.4)	183 (27.9)
β-carotene Consumption	≤ 1/M	283 (36.1)	448 (28.6)	388 (29.0)	326 (30.7)	294 (30.3)	234 (35.7)
	2/M - 3/W	374 (47.7)	817 (52.2)	694 (51.8)	535 (50.4)	492 (50.6)	321 (48.9)
	≥ 4W	126 (16.1)	299 (19.1)	258 (19.3)	200 (18.9)	186 (19.1)	101 (15.4)
Spicy foods Consumption	<1/M	239 (30.5)	652 (41.7)	560 (41.8)	445 (41.9)	404 (41.6)	249 (38.0)
	1/M - 3/W	193 (24.6)	349 (22.3)	300 (22.4)	247 (23.3)	232 (23.9)	165 (25.2)
	≥ 4W	346 (44.1)	546 (34.9)	464 (34.6)	358 (33.7)	325 (33.4)	236 (36.0)

* Score cutpoints used for eliminating diagnostic condition among controls

** Frequencies do not add up to 100% due cause of missing values

from a pool of hospitals, which had a larger group of medical specialties and so of diseases under treatment. Because of the different hospital characteristics, the São Paulo control patients' distribution showed a lower level of participation after disease class restriction, which excluded cardiovascular, respiratory and digestive system diseases. A similar distribution is observed for other sociodemographic variables and each level of restriction.

3.4.1 *Tobacco smoking and alcohol drinking*

Table 5 shows ORs for UADT cancers, by site and overall, according to cumulative smoking consumption for each level of restriction by likelihood of association with tobacco. OR estimates were calculated using subjects with less than one pack-year as the reference group. Among higher tobacco consumers (more than 91 pack-years), the OR obtained for all UADT cancers was 15.3 (95% CI: 9.7-24.2) including all controls in the study. The OR obtained after restriction of all certain, probable and possible tobacco related diseases increased to 18.6 (95% CI: 11.4-30.2) and after disease class restriction to 17.6 (95% CI: 10.2-30.4). Smokers were associated with greater risks for cancer of the oral cavity compared to non-smokers after disease class restriction than for other levels of restriction. Risks for pharyngeal and laryngeal cancers were higher than for oral cancers across all levels of restriction.

Subjects consuming less than 10 kg of ethanol in their lifetime were used as the reference group to compute the OR estimates for lifetime alcohol consumption (Table 6). Although ORs for alcohol drinking increased for higher kilograms of ethanol consumption, estimates remained stable across all levels of restriction.

Table 4: Distribution of sociodemographic characteristics among controls, following restriction on the basis of likelihood of association with tobacco (t) and alcohol (a)

Sociodemographic Variables	Levels	No restriction freq. (%)**	score-based restriction* a=4 and t=4 Freq. (%)**	a≥3 and t≥3 freq. (%)**	a≥2 and t≥2 freq. (%)**	Disease class restriction freq. (%)**
Age	≤34	22 (1.4)	21 (1.6)	19 (1.8)	19 (2.0)	12 (1.8)
	35 - 44	136 (8.7)	127 (9.5)	112 (10.6)	105 (10.8)	74 (11.3)
	45 - 54	417 (26.7)	370 (27.6)	294 (27.7)	272 (28.0)	185 (28.2)
	55 - 64	551 (35.2)	460 (34.3)	362 (34.1)	329 (33.9)	216 (32.9)
	65 - 74	320 (20.5)	264 (19.7)	190 (17.9)	175 (18.0)	117 (17.8)
	>74	118 (7.5)	98 (7.3)	84 (7.9)	72 (7.4)	52 (7.9)
Gender	Female	201 (12.9)	186 (13.9)	162 (15.3)	149 (15.3)	88 (13.4)
	Male	1363 (87.2)	1154 (86.1)	899 (84.7)	823 (84.7)	568 (86.6)
City	São paulo	426 (27.2)	354 (26.4)	234 (22.1)	213 (21.9)	89 (13.6)
	Curitiba	760 (48.6)	658 (49.1)	556 (52.4)	503 (51.8)	426 (64.9)
	Goiânia	378 (24.2)	328 (24.5)	271 (25.5)	256 (26.3)	141 (21.5)
Ethnicity	White	1244 (79.5)	1063 (79.3)	832 (78.4)	761 (78.3)	533 (81.3)
	Black	312 (20.0)	269 (20.1)	222 (20.9)	204 (21.0)	117 (17.8)
Family Monthly Income (US$)	0 - 30	294 (18.8)	253 (18.9)	209 (19.7)	189 (19.4)	152 (23.2)
	31 - 60	319 (20.4)	257 (19.2)	198 (18.7)	184 (18.9)	132 (20.1)
	61 - 110	295 (18.9)	258 (19.3)	214 (20.2)	200 (20.6)	134 (20.4)
	111 - 200	299 (19.1)	262 (19.6)	202 (19.0)	184 (18.9)	111 (16.9)
	≥ 201	314 (20.1)	275 (20.5)	208 (19.6)	191 (19.7)	117 (17.8)
Schooling	Illiterate	430 (27.5)	372 (27.8)	305 (28.8)	279 (28.7)	178 (27.1)
	≤ Primary	961 (61.5)	819 (61.1)	634 (59.8)	582 (59.9)	386 (58.8)
	≤Secondary	124 (7.9)	102 (7.6)	85 (8.0)	76 (7.8)	63 (9.6)
	≤ Superior	48 (3.1)	46 (3.4)	36 (3.4)	34 (3.5)	28 (4.3)
Region	Urban	309 (19.8)	252 (18.8)	182 (17.2)	163 (16.8)	106 (16.2)
	Rural	1255 (80.2)	1088 (81.2)	879 (82.9)	809 (83.2)	550 (83.8)

* Score cutpoints used for eliminating diagnostic condition among controls

** Frequencies do not add up to 100% due cause of missing values

Table 5: Odds ratios for UADT cancers according to cumulative smoking consumption, following restriction on the basis of likelihood of association with tobacco (t)

		Level of restriction*									
	Categories	No restriction		t=4		t≥3		T≥2		Disease class restriction	
	(pack-years)	OR	95% (CI)	OR	95% (CI)	OR	95% (CI)	OR	95% (CI)	OR	95% (CI)
All Sites	< 1	1.00	(ref.)	1.00	(ref.)	1.00	(ref.)	1.00	(ref.)	1.00	(ref.)
	1 - 22	5.26	(3.4 - 8.2)	5.55	(3.5 - 8.7)	5.81	(3.7 - 9.1)	5.90	(3.7 - 9.3)	5.15	(3.1 - 8.6)
	23 - 45	9.58	(6.2 - 14.9)	10.39	(6.6 - 16.3)	11.59	(7.4 - 18.3)	11.62	(7.3 - 18.4)	10.66	(6.3 - 17.9)
	46 - 91	12.48	(8.0 - 19.5)	12.98	(8.2 - 20.5)	14.16	(8.9 - 22.5)	14.39	(9.0 - 23.0)	14.91	(8.7 - 25.4)
	> 91	15.31	(9.7 - 24.2)	16.86	(10.5 - 27.0)	18.32	(11.3 - 29.6)	18.60	(11.4 - 30.2)	17.59	(10.2 - 30.4)
Oral Cavity	< 1	1.00	(ref.)	1.00	(ref.)	1.00	(ref.)	1.00	(ref.)	1.00	(ref.)
	1 - 22	3.61	(2.1 - 6.2)	3.87	(2.2 - 6.7)	4.16	(2.4 - 7.3)	4.22	(2.4 - 7.4)	3.98	(2.1 - 7.7)
	23 - 45	7.22	(4.2 - 12.4)	8.03	(4.6 - 13.9)	9.31	(5.3 - 16.3)	9.32	(5.3 - 16.5)	9.26	(4.8 - 17.8)
	46 - 91	9.54	(5.5 - 16.5)	10.1	(5.8 - 17.7)	11.28	(6.4 - 20.0)	11.45	(6.4 - 20.4)	13.28	(6.8 - 26.0)
	> 91	12.07	(6.9 - 21.2)	13.67	(7.7 - 24.4)	15.26	(8.4 - 27.6)	15.57	(8.6 - 28.4)	16.53	(8.3 - 33.0)
Pharynx	< 1	1.00	(ref.)	1.00	(ref.)	1.00	(ref.)	1.00	(ref.)	1.00	(ref.)
	1 - 22	9.76	(3.4 - 27.6)	9.92	(3.5 - 28.1)	10.08	(3.6 - 28.6)	10.44	(3.7 - 29.7)	7.85	(2.7 - 22.6)
	23 - 45	13.14	(4.7 - 37.0)	13.87	(4.9 - 39.2)	15.02	(5.3 - 42.5)	15.23	(5.4 - 43.2)	12.23	(4.3 - 35.1)
	46 - 91	18.01	(6.4 - 51.0)	18.07	(6.4 - 51.4)	19.27	(6.8 - 54.8)	19.94	(7.0 - 56.9)	17.07	(5.9 - 49.4)
	> 91	23.72	(8.3 - 67.7)	25.43	(8.9 - 72.9)	26.95	(9.4 - 77.4)	27.14	(9.4 - 78.1)	21.76	(7.4 - 63.6)
Larynx	< 1	1.00	(ref.)	1.00	(ref.)	1.00	(ref.)	1.00	(ref.)	1.00	(ref.)
	1 - 22	8.85	(3.0 - 26.0)	9.33	(3.2 - 27.4)	9.40	(3.2 - 27.6)	9.19	(3.1 - 27.0)	6.75	(2.3 - 19.9)
	23 - 45	18.81	(6.5 - 54.2)	19.67	(6.8 - 56.9)	21.08	(7.3 - 60.9)	20.76	(7.2 - 60.0)	15.58	(5.4 - 45.1)
	46 - 91	23.27	(8.0 - 67.9)	23.77	(8.1 - 69.7)	25.03	(8.6 - 73.3)	25.00	(8.5 - 73.2)	21.76	(7.4 - 64.3)
	> 91	24.81	(8.4 - 73.0)	26.38	(8.9 - 78.1)	27.13	(9.2 - 80.2)	27.15	(9.2 - 80.3)	21.63	(7.3 - 64.4)

* Score cutpoints used for eliminating diagnostic condition among controls

Table 6: Odds ratios for UADT cancers according to cumulative alcohol consumption, following restriction on the basis of likelihood of association with alcohol (a)

				Level of restriction*							
	Categories	No restriction		a=4		a≥3		a≥2		Disease class restriction	
	(Kg)	OR	95% (CI)	OR	95% (CI)	OR	95% (CI)	OR	95% (CI)	OR	95% (CI)
All Sites	0 - 10	1.00	(ref.)	1.00	(ref.)	1.00	(ref.)	1.00	(ref.)	1.00	(ref.)
	11 - 133	1.90	(1.3 - 2.8)	1.88	(1.3 - 2.7)	1.81	(1.2 - 2.7)	1.80	(1.2 - 2.6)	1.52	(1.0 - 2.4)
	134 - 793	3.70	(2.6 - 5.3)	3.68	(2.6 - 5.2)	3.56	(2.5 - 5.1)	3.56	(2.5 - 5.1)	2.87	(1.9 - 4.4)
	794 - 1248	5.89	(4.0 - 8.6)	5.89	(4.0 - 8.6)	5.94	(4.1 - 8.7)	5.92	(4.0 - 8.7)	4.92	(3.1 - 7.7)
	1249 - 9000	8.98	(6.2 - 12.9)	9.14	(6.3 - 13.2)	9.04	(6.2 - 13.1)	9.09	(6.3 - 13.2)	9.34	(5.9 - 14.7)
Oral Cavity	0 - 10	1.00	(ref.)	1.00	(ref.)	1.00	(ref.)	1.00	(ref.)	1.00	(ref.)
	11 - 133	1.75	(1.1 - 2.9)	1.73	(1.1 - 2.9)	1.66	(1.0 - 2.7)	1.64	(1.0 - 2.7)	1.48	(0.8 - 2.6)
	134 - 793	3.55	(2.2 - 5.6)	3.54	(2.2 - 5.6)	3.40	(2.1 - 5.4)	3.38	(2.1 - 5.4)	2.87	(1.7 - 4.9)
	794 - 1248	5.19	(3.2 - 8.5)	5.22	(3.2 - 8.6)	5.28	(3.2 - 8.7)	5.21	(3.2 - 8.6)	4.83	(2.7 - 8.6)
	1249 - 9000	8.77	(5.5 - 14.1)	9.01	(5.6 - 14.5)	8.86	(5.5 - 14.3)	8.86	(5.5 - 14.3)	9.61	(5.4 - 17.1)
Pharynx	0 - 10	1.00	(ref.)	1.00	(ref.)	1.00	(ref.)	1.00	(ref.)	1.00	(ref.)
	11 - 133	2.53	(1.1 - 5.6)	2.49	(1.1 - 5.6)	2.46	(1.1 - 5.5)	2.45	(1.1 - 5.5)	1.99	(0.9 - 4.6)
	134 - 793	4.32	(2.0 - 9.1)	4.29	(2.0 – 9.0)	4.20	(2.0 - 8.9)	4.22	(2.0 - 8.9)	2.96	(1.3 - 6.5)
	794 - 1248	9.32	(4.4 - 19.7)	9.33	(4.4 - 19.8)	9.53	(4.5 - 20.2)	9.51	(4.5 - 20.2)	7.32	(3.3 - 16.3)
	1249 - 9000	13.06	(6.3 - 27.2)	13.35	(6.4 - 27.9)	13.48	(6.4 - 28.2)	13.61	(6.5 - 28.5)	12.91	(5.8 - 28.5)
Larynx	0 - 10	1.00	(ref.)	1.00	(ref.)	1.00	(ref.)	1.00	(ref.)	1.00	(ref.)
	11 - 133	1.96	(1.0 - 3.9)	1.93	(1.0 - 3.9)	1.90	(0.9 - 3.8)	1.89	(0.9 - 3.8)	1.59	(0.8 - 3.4)
	134 - 793	3.89	(2.1 - 7.4)	3.82	(2.0 - 7.3)	3.74	(2.0 - 7.1)	3.75	(2.0 - 7.1)	3.10	(1.6 - 6.2)
	794 - 1248	4.86	(2.5 - 9.5)	4.87	(2.5 - 9.5)	4.94	(2.5 - 9.7)	4.96	(2.5 - 9.7)	3.93	(1.9 - 8.1)
	1249 - 9000	6.93	(3.6 - 13.3)	7.03	(3.7 - 13.5)	7.03	(3.6 - 13.6)	7.08	(3.7 - 13.7)	7.00	(3.4 - 14.4)

* Score cutpoints used for eliminating diagnostic condition among controls

Table 7 shows the ORs for cumulative tobacco and alcohol consumption following restriction for joint levels of likelihood scores for both tobacco and alcohol-related diseases. OR estimates for smoking and alcohol drinking categories after restriction based on disease class were lower than those observed after restriction by likelihood scores, though trends were similar to that observed in previous tables for restriction based on likelihood associations with individual exposures.

Figure 2 shows the estimated risk effects due to smoking and alcohol exposure for each anatomical site, oral cavity, pharynx and larynx. There was no appreciable difference in ORs across to restriction levels.

3.4.2 *Dietary variables*

Table 8 illustrates the reduction in risks for UADT cancers due to consumption of citric fruits after adjustment for empirical confounders, tobacco and alcohol consumption, and socio-demographic variables. Little difference in risks across levels of restrictions was observed for the UADT overall or for each anatomical site. The largest change in ORs observed was for cancers of the oral cavity ranging from 0.56 (95% CI: 0.4-0.8) with no restriction to 0.65 (95% CI: 0.4-1.0) after restriction by disease class.

Table 9 presents ORs for frequency of consumption of foods containing β-carotene, adjusted for all confounding variables. The degree of reduction in risk effects was slightly smaller for all cancer sites after restriction by disease class. ORs for consumption of β-carotene more than four times per week further decreased after restriction of diseases with certain ($t=4$ and $a=4$), probable ($t\geq3$ and $a\geq3$) and possible

Table 7: Odds ratios for UADT cancers (all sites) for cumulative tobacco and alcohol consumption following restriction based on likelihood of association to tobacco (t) and alcohol (a) consumtpion

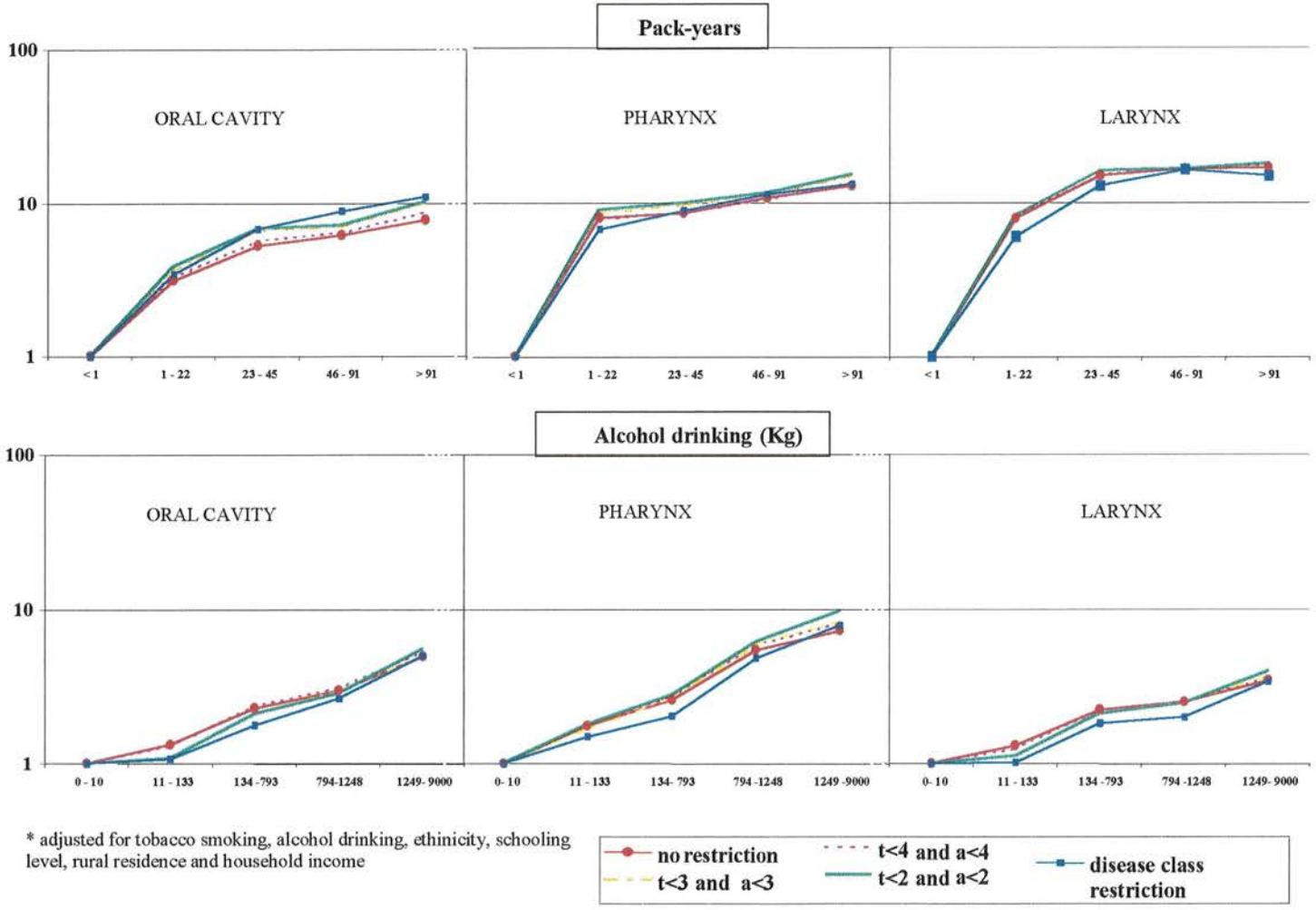
	Categories	No restriction		Level of restriction* a=4 and t=4		a≥3 and t≥3		a≥2 and t≥2		Disease class restriction	
		OR	95% (CI)	OR	95% (CI)	OR	95% (CI)	OR	95% (CI)	OR	95% (CI)
Tobacco**	< 1	1.00	(ref.)	1.00	(ref.)	1.00	(ref.)	1.00	(ref.)	1.00	(ref.)
Exposure level	1 - 22	4.37	(2.8 - 6.9)	4.46	(2.8 - 7.1)	4.74	(3.0 - 7.6)	4.96	(3.1 - 8.0)	4.30	(2.5 - 7.3)
	23 - 45	6.81	(4.3 - 10.7)	7.08	(4.5 - 11.3)	7.99	(5.0 - 12.9)	8.22	(5.1 - 13.3)	7.75	(4.5 - 13.2)
	46 - 91	8.00	(5.0 - 12.7)	8.10	(5.0 - 13.0)	8.66	(5.3 - 14.1)	8.94	(5.4 - 14.7)	10.05	(5.8 - 17.5)
	> 91	9.40	(5.9 - 15.1)	10.05	(6.2 - 16.4)	11.11	(6.7 - 18.3)	11.30	(6.8 - 18.8)	10.94	(6.2 - 19.2)
Alcohol†	0 - 10	1.00	(ref.)	1.00	(ref.)	1.00	(ref.)	1.00	(ref.)	1.00	(ref.)
Exposure level	11 - 133	1.41	(1.0 - 2.1)	1.38	(0.9 - 2.1)	1.22	(0.8 - 1.8)	1.23	(0.8 - 1.9)	1.10	(0.7 - 1.8)
	134 - 793	2.33	(1.6 - 3.4)	2.38	(1.6 - 3.5)	2.23	(1.5 - 3.3)	2.23	(1.5 - 3.3)	1.76	(1.1 - 2.8)
	794 - 1248	3.41	(2.3 - 5.0)	3.50	(2.4 - 5.2)	3.42	(2.2 - 5.2)	3.39	(2.2 - 5.2)	2.75	(1.7 - 4.5)
	1249 - 9000	4.98	(3.4 - 7.3)	5.31	(3.6 - 7.9)	5.15	(3.4 - 7.8)	5.75	(3.8 - 8.8)	4.90	(3.0 - 8.0)

* Score cutpoints used for eliminating diagnostic condition among controls

** Pack-years

† kg of alcohol consumption (lifetime)

Figure 2: Adjusted odds ratios* of anatomical sites of UADT cancers according to cumulative smoking and alcohol drinking, following restriction on the basis of likelihood of association with tobacco and alcohol consumption



* adjusted for tobacco smoking, alcohol drinking, ethinicity, schooling level, rural residence and household income

Table 8: Adjusted odds ratios* of UADT cancers for citric fruits consumption before and after cumulative exclusion of controls according to likelihood of association with tobacco (t) and alcohol (a) consumption.

	Categories**	Level of restriction†							
		No restriction		t=4 and a=4		t≥3 and a≥3		t≥2 and a≥2		Disease class restriction	
		OR	95% (CI)	OR	95% (CI)	OR	95% (CI)	OR	95% (CI)	OR	95% (CI)
All Sites	≤ 1/month	1.00	(ref.)	1.00	(ref.)	1.00	(ref.)	1.00	(ref.)	1.00	(ref.)
	2/mo-3/week	0.66	(0.5 - 0.8)	0.65	(0.5 - 0.8)	0.62	(0.5 - 0.8)	0.61	(0.5 - 0.8)	0.58	(0.4 - 0.8)
	≥ 4week	0.61	(0.5 - 0.8)	0.65	(0.5 - 0.8)	0.62	(0.5 - 0.8)	0.61	(0.5 - 0.8)	0.66	(0.5 - 0.9)
Oral Cavity	≤ 1/month	1.00	(ref.)	1.00	(ref.)	1.00	(ref.)	1.00	(ref.)	1.00	(ref.)
	2/mo-3/week	0.58	(0.4 - 0.8)	0.59	(0.4 - 0.8)	0.56	(0.4 - 0.8)	0.54	(0.4 - 0.8)	0.50	(0.3 - 0.7)
	≥ 4week	0.56	(0.4 - 0.8)	0.62	(0.4 - 0.9)	0.59	(0.4 - 0.9)	0.58	(0.4 - 0.8)	0.65	(0.4 - 1.0)
Pharynx	≤ 1/month	1.00	(ref.)	1.00	(ref.)	1.00	(ref.)	1.00	(ref.)	1.00	(ref.)
	2/mo-3/week	0.69	(0.5 - 1.0)	0.69	(0.5 - 1.0)	0.67	(0.4 - 1.0)	0.66	(0.4 - 1.0)	0.62	(0.4 - 1.0)
	≥ 4week	0.48	(0.3 - 0.7)	0.52	(0.3 - 0.8)	0.49	(0.3 - 0.8)	0.47	(0.3 - 0.8)	0.49	(0.3 - 0.8)
Larynx	≤ 1/month	1.00	(ref.)	1.00	(ref.)	1.00	(ref.)	1.00	(ref.)	1.00	(ref.)
	2/mo-3/week	0.68	(0.5 - 1.0)	0.66	(0.4 - 1.0)	0.61	(0.4 - 0.9)	0.60	(0.4 - 0.9)	0.56	(0.3 - 0.9)
	≥ 4week	0.72	(0.5 - 1.1)	0.75	(0.5 - 1.2)	0.69	(0.4 - 1.1)	0.69	(0.4 - 1.1)	0.73	(0.4 - 1.2)

* adjusted for tobacco smoking, alcohol drinking, ethnicity, schooling level, rural residence and household income

** frequency of consumption of citric fruits (see Material and Methods for details)

† Score cutpoints used for eliminating diagnostic condition among controls

(t≥2 and a≥2) likelihood scores for both tobacco and alcohol; from a 40% reduction in risk to a 43% reduction for all cancers, although this difference was minimal for cancers of the oral cavity and larynx.

OR estimates for consumption of spicy foods increased across restriction levels by likelihood scores for all sites (Table 10) and decreased after disease class restriction. The largest increase was observed for cancers of the pharynx: 1.47 (95% CI: 1.0-2.1) without restriction, to 1.64 (95% CI: 1.1-2.5) after maximum restriction of tobacco and alcohol-related control diseases.

Table 11 shows the adjusted ORs for frequency of *maté* consumption per day. Risk effects persisted across levels of restriction with little change in magnitude for all levels of consumption. Small reductions in OR were observed, however, with disease class restriction across all sites and categories of exposure.

Simple and adjusted regression analyses for tobacco and alcohol consumption were conducted and ORs computed with and without controlling for all empirical confounders and sociodemographic characteristics listed above; no appreciable differences were observed between the risks from simple and multivariate methods (data not shown).

3.4.3 *Environmental exposure*

The use of a wood stove in the home for cooking and heating was more frequently reported by cases than by controls. The excess in risk observed was not due to confounding by smoking, alcohol consumption or sociodemographic variables. Figure 3 shows the odds ratios and respective 95% CI according to wood stove use.

Table 9: Adjusted odds ratios* of UADT cancers for β-carotene consumption before and after cumulative exclusion of controls according to likelihood of association with tobacco (t) and alcohol (a) consumption.

	Categories**	No restriction		Level of restriction† t=4 and a=4		t≥3 and a≥3		t≥ and a≥2		Disease class restriction	
		OR	95% (CI)	OR	95% (CI)	OR	95% (CI)	OR	95% (CI)	OR	95% (CI)
All Sites	≤ 1/month	1.00	(ref.)	1.00	(ref.)	1.00	(ref.)	1.00	(ref.)	1.00	(ref.)
	2/mo-3/week	0.67	(0.5 - 0.9)	0.69	(0.5 - 0.9)	0.75	(0.6 - 1.0)	0.71	(0.5 - 0.9)	0.78	(0.6- 1.0)
	≥ 4week	0.60	(0.4 - 0.8)	0.59	(0.4 - 0.8)	0.58	(0.4 - 0.8)	0.57	(0.4 - 0.8)	0.66	(0.4 -1.0)
Oral Cavity	≤ 1/month	1.00	(ref.)	1.00	(ref.)	1.00	(ref.)	1.00	(ref.)	1.00	(ref.)
	2/mo-3/week	0.61	(0.4 - 0.8)	0.64	(0.5 - 0.9)	0.70	(0.5 - 1.0)	0.66	(0.5 - 0.9)	0.72	(0.5 - 1.0)
	≥ 4week	0.58	(0.4 - 0.9)	0.59	(0.4 - 0.9)	0.58	(0.4 - 0.9)	0.57	(0.4 - 0.9)	0.67	(0.4 - 1.1)
Pharynx	≤ 1/month	1.00	(ref.)	1.00	(ref.)	1.00	(ref.)	1.00	(ref.)	1.00	(ref.)
	2/mo-3/week	0.80	(0.5 - 1.2)	0.83	(0.6 - 1.2)	0.89	(0.6 - 1.3)	0.83	(0.5 - 1.3)	0.92	(0.6 - 1.4)
	≥ 4week	0.55	(0.3 - 1.0)	0.55	(0.3 - 1.0)	0.54	(0.3 - 1.0)	0.49	(0.3 - 0.9)	0.63	(0.3 - 1.2)
Larynx	≤ 1/month	1.00	(ref.)	1.00	(ref.)	1.00	(ref.)	1.00	(ref.)	1.00	(ref.)
	2/mo-3/week	0.53	(0.3 - 0.8)	0.55	(0.4 - 0.8)	0.60	(0.4 - 0.9)	0.55	(0.4 - 0.9)	0.63	(0.4 - 1.0)
	≥ 4week	0.56	(0.3 - 0.9)	0.55	(0.3 - 0.9)	0.56	(0.3 - 1.0)	0.52	(0.3 - 0.9)	0.63	(0.3 - 1.2)

* adjusted for tobacco smoking, alcohol drinking, ethnicity, schooling level, rural residence and household income

** frequency of consumption of β-carotene - rich fruits and vegetables (see Material and Methods for details)

† Score cutpoints used for eliminating diagnostic condition among controls

Table 10: Adjusted odds ratios* of UADT cancers for spicy food consumption before and after cumulative exclusion of controls according to likelihood of association with tobacco (t) and alcohol (a) consumption.

	Categories**	Level of restriction†									
		No restriction		t=4 and a=4		t≥3 and a≥3		t≥2 and a≥2		Disease class restriction	
		OR	95% (CI)	OR	95% (CI)	OR	95% (CI)	OR	95% (CI)	OR	95% (CI)
All Sites	< 1/month	1.00	(ref.)	1.00	(ref.)	1.00	(ref.)	1.00	(ref.)	1.00	(ref.)
	1/mo-3/week	1.27	(1.0 - 1.6)	1.32	(1.0 - 1.7)	1.25	(0.9 - 1.6)	1.22	(0.9 - 1.6)	1.12	(0.8 - 1.5)
	≥ 4week	1.32	(1.1 - 1.7)	1.37	(1.1 - 1.7)	1.42	(1.1 - 1.8)	1.41	(1.1 - 1.8)	1.29	(1.0 - 1.7)
Oral Cavity	< 1/month	1.00	(ref.)	1.00	(ref.)	1.00	(ref.)	1.00	(ref.)	1.00	(ref.)
	1/mo-3/week	1.38	(1.0 - 1.9)	1.47	(1.0 - 2.1)	1.39	(1.0 - 2.0)	1.36	(0.9 - 2.0)	1.30	(0.9 - 1.9)
	≥ 4week	1.49	(1.1 - 2.0)	1.55	(1.1 - 2.1)	1.60	(1.2 - 2.2)	1.61	(1.2 - 2.2)	1.45	(1.0 - 2.1)
Pharynx	< 1/month	1.00	(ref.)	1.00	(ref.)	1.00	(ref.)	1.00	(ref.)	1.00	(ref.)
	1/mo-3/week	1.42	(0.9 - 2.2)	1.49	(1.0 - 2.3)	1.39	(0.9 - 2.2)	1.37	(0.9 - 2.2)	1.33	(0.8 - 2.2)
	≥ 4week	1.47	(1.0 - 2.1)	1.56	(1.1 - 2.3)	1.64	(1.1 - 2.4)	1.64	(1.1 - 2.5)	1.48	(1.0 - 2.3)
Larynx	< 1/month	1.00	(ref.)	1.00	(ref.)	1.00	(ref.)	1.00	(ref.)	1.00	(ref.)
	1/mo-3/week	1.04	(0.7 - 1.6)	1.07	(0.7 - 1.6)	1.02	(0.7 - 1.6)	1.02	(0.6 - 1.6)	0.89	(0.5 - 1.4)
	≥ 4week	0.97	(0.7 - 1.4)	1.00	(0.7 - 1.5)	1.06	(0.7 - 1.6)	1.06	(0.7 - 1.6)	0.89	(0.6 - 1.4)

* adjusted for tobacco smoking, alcohol drinking, ethnicity, schooling level, rural residence and household income
** frequency of consumption of spicy foods (see Material and Methods for details)
† Score cutpoints used for eliminating diagnostic condition among controls

Table 11: Adjusted odds ratios* of UADT cancers for *mate'* consumption before and after cumulative exclusion of controls according to likelihood of association with tobacco (t) and alcohol (a) consumption.

	Categories**	No restriction		Level of restriction† t=4 and a=4		t≥3 and a≥3		t≥2 and a≥2		Disease class restriction	
		OR	95% (CI)	OR	95% (CI)	OR	95% (CI)	OR	95% (CI)	OR	95% (CI)
All Sites	Never	1.00	(ref.)	1.00	(ref.)	1.00	(ref.)	1.00	(ref.)	1.00	(ref.)
	≤ 1/day	0.97	(0.7 - 1.3)	0.90	(0.7 - 1.2)	0.90	(0.7 - 1.2)	0.90	(0.7 - 1.2)	0.93	(0.7 - 1.3)
	2/day	1.52	(1.1 - 2.2)	1.49	(1.0 - 2.2)	1.54	(1.0 - 2.3)	1.48	(1.0 - 2.2)	1.34	(0.9 - 2.1)
	≥ 3/day	1.98	(1.3 - 2.9)	1.93	(1.3 - 2.9)	1.86	(1.2 - 2.8)	1.99	(1.3 - 3.1)	1.81	(1.1 - 2.9)
Oral Cavity	Never	1.00	(ref.)	1.00	(ref.)	1.00	(ref.)	1.00	(ref.)	1.00	(ref.)
	≤ 1/day	0.97	(0.7 - 1.4)	0.91	(0.6 - 1.3)	0.91	(0.6 - 1.3)	0.91	(0.6 - 1.3)	1.00	(0.7 - 1.5)
	2/day	1.33	(0.8 - 2.2)	1.31	(0.8 - 2.2)	1.36	(0.8 - 2.3)	1.30	(0.8 - 2.2)	1.22	(0.7 - 2.1)
	≥ 3/day	1.58	(0.9 - 2.6)	1.50	(0.9 - 2.5)	1.47	(0.9 - 2.5)	1.60	(0.9 - 2.8)	1.44	(0.8 - 2.6)
Pharynx	Never	1.00	(ref.)	1.00	(ref.)	1.00	(ref.)	1.00	(ref.)	1.00	(ref.)
	≤ 1/day	0.94	(0.6 - 1.4)	0.88	(0.6 - 1.4)	0.88	(0.6 - 1.4)	0.90	(0.6 - 1.4)	0.87	(0.5 - 1.4)
	2/day	1.89	(1.1 - 3.3)	1.88	(1.1 - 3.3)	1.88	(1.0 - 3.4)	1.75	(1.0 - 3.2)	1.66	(0.9 - 3.0)
	≥ 3/day	2.29	(1.3 - 4.0)	2.15	(1.2 - 3.9)	2.05	(1.1 - 3.7)	2.21	(1.2 - 4.1)	1.98	(1.1 - 3.7)
Larynx	never	1.00	(ref.)	1.00	(ref.)	1.00	(ref.)	1.00	(ref.)	1.00	(ref.)
	≤ 1/day	1.12	(0.7 - 1.8)	1.02	(0.6 - 1.6)	0.95	(0.6 - 1.5)	0.94	(0.6 - 1.5)	0.90	(0.5 - 1.5)
	2/day	1.38	(0.8 - 2.5)	1.34	(0.7 - 2.5)	1.40	(0.7 - 2.6)	1.31	(0.7 - 2.5)	1.21	(0.6 - 2.3)
	≥ 3/day	2.16	(1.2 - 3.9)	2.10	(1.1 - 3.8)	1.97	(1.1 - 3.7)	2.14	(1.1 - 4.0)	2.02	(1.1 - 3.9)

* adjusted for tobacco smoking, alcohol drinking, ethnicity, schooling level, rural residence and household income

** frequency of consumption of *maté* (see details in Material and Methods for details)

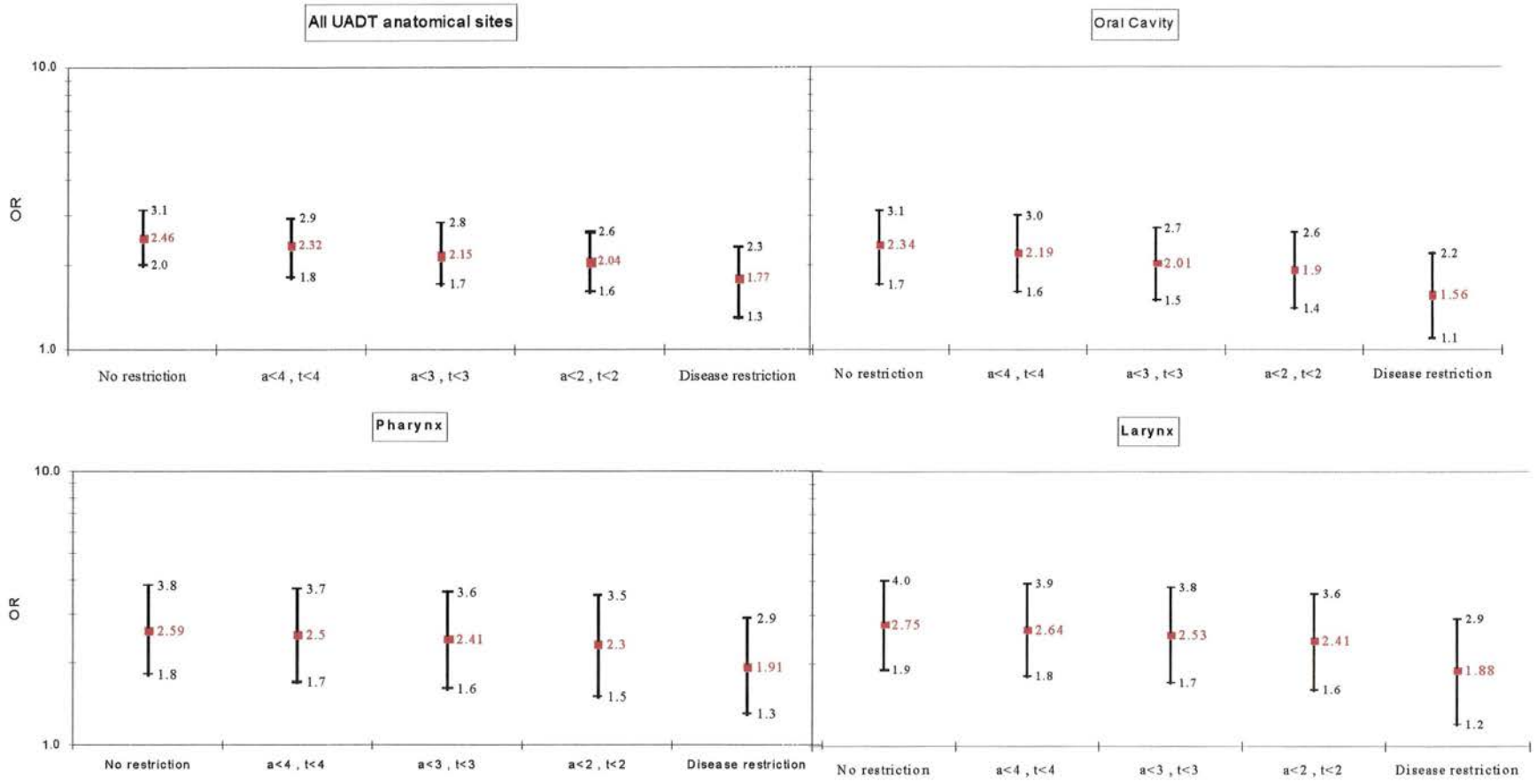
† Score cutpoints used for eliminating diagnostic condition among controls

Risk effects tended to decrease as the level of restriction increased. The crude ORs for wood stove use were also computed with similar effects being observed (Table 12). The frequency of use of wood stoves in São Paulo was 4.8% and 5.6% for cases and control-patients respectively; in Goiânia was observed 23.9% and 26.7%; in Curitiba the highest frequencies were observed: 71.3% for cases and 68.6% for control-group.

Table 12: Crude odds ratios of UADT cancers for use of wood stove before and after cumulative exclusion of controls according to likelihood of association with tobacco (t) and alcohol (a) consumption.

Level of Restriction	Categories	All Sites OR 95% (CI)	Oral Cavity OR 95% (CI)	Pharynx OR 95% (CI)	Larynx OR 95% (CI)
No restriction	other	1.0 ref.	1.0 ref.	1.0 ref.	1.0 ref.
	wood stove	2.54 (2.1 - 3.1)	2.52 (1.9 - 3.3)	2.48 (1.8 - 3.5)	2.52 (1.8 - 3.5)
a<4 and t<4	other	1.0 ref.	1.0 ref.	1.0 ref.	1.0 ref.
	wood stove	2.41 (2.0 - 3.0)	2.38 (1.8 - 3.1)	2.35 (1.7 - 3.3)	2.38 (1.7 - 3.4)
a<3 and t<3	other	1.0 ref.	1.0 ref.	1.0 ref.	1.0 ref.
	wood stove	2.21 (1.8 - 2.7)	2.16 (1.6 - 2.8)	2.17 (1.5 - 3.1)	2.16 (1.5 - 3.1)
a<2 and t<2	other	1.0 ref.	1.0 ref.	1.0 ref.	1.0 ref.
	wood stove	2.14 (1.7 - 2.7)	2.10 (1.6 - 2.8)	2.09 (1.5 -3.0)	2.08 (1.5 - 3.0)
Disease class restriction	other	1.0 ref.	1.0 ref.	1.0 ref.	1.0 ref.
	wood stove	2.03 (1.6 - 2.6)	1.89 (1.4 - 2.5)	1.97 (1.4 - 2.8)	1.86 (1.3 - 2.7)

Figure 3: Adjusted odds ratios* and respectives 95% CI of UADT for wood stove use before and after cumulative exclusion of controls according to likelihood of association with tobacco and alcohol consumption



* ajusted for tobacco smoking, alcohol drinking, ethnicity, schooling level, rural residence and household income

3.5 DISCUSSION

Many risk factors have been obtained from case-control studies. The resulting ORs may depend on the type of research design and, specifically in these studies, the manner in which cases and controls are selected. The possibility of information bias was not verified, although cases and control patients were all interviewed in a hospital setting and the same method of questioning was used for each of them. Therefore, information from cases and control subjects should be comparable and reducing the potential for information or recall bias influencing the ORs.

This hospital-based case-control study was conducted in three Brazilian regions with different lifestyle and environmental characteristics. A large sample of patients was included, 784 in the case group and 1564 in the control group. Distributed across several regions, this study could be considered akin to a population base study.

When considering the method of restriction based on disease class, it could be argued that we excluded some diseases that were not related to tobacco or alcohol consumption (PEARCE and CHECKOWAY 1988). However, five possible designs were performed to verify the effect of control group selection with levels of restriction based on increasing strength of association. When developing a new case-control study of this type, it would be difficult to apply more than one method of restriction as we have, and more often a method based on disease class would be adopted, taking account the considerable care to control the confounders.

3.5.1 *Tobacco and alcohol consumption*

In spite of the study design and sample selection methodology used in prior case-control studies, consistently high relative risks for UADT cancers due to smoking and alcohol drinking have been observed (GRAHAM et al. 1977; BARRA et al. 1991; KABAT et al. 1994; RAO et al. 1994; SCHILDT et al. 1998; JABER et al. 1998 CASTELLSAGUÉ et al. 1999). Efforts were made to avoid bias in a case-control study conducted by LEWIN et al. (1998); and the referents, or control group subjects, were selected from continuously updated population registries. For all sites of head and neck cancer, an increased relative risk (RR) for men smoking more than 25g tobacco/day was observed (RR = 6.5, 95% CI: 4.0-10.7). WYNDER and STELLMAN (1977) in a hospital-based case-control study, selected controls on the basis of absence of a history of tobacco-related disease. Subjects with cancers of the lung, oral cavity, larynx, esophagus, bladder, pancreas, liver or kidney, as well as those with myocardial infarctions, strokes, peripheral vascular disease, abdominal aortic aneurysms, chronic bronchitis or chronic obstructive pulmonary disease, gastric ulcers, or cirrhosis of the liver were not included. Cancers of the stomach, colon or rectum, prostate, breast, cervix and skin including melanoma, as well as subjects with leukemia, lymphoma, Hodgkin's disease, other cancers such as genital or reproductive organ, benign neoplastic diseases, fractures and other non non-neoplastic diseases such as burns, infections, duodenal ulcers, etc., were considered as eligible for the control group. The RRs for oral cavity and laryngeal cancers were 2.8 ($p>0.05$) and 2.9 ($p<0.05$), respectively due to more than 41 years smoking. RR for smoking more than 41 cigarettes/day, adjusted for race and age, were 5.7 ($p<0.05$) and 9.0 ($p>0.05$) for males and females, respectively.

Another hospital-based case-control study by DE STEFANI et al. (1992), showed elevated ORs for cancer of the mouth, pharynx and larynx, 2.9 (95% CI: 1.5-5.9) for smoking more than 31 cigarettes/day and 6.6 (95% CI: 2.6-16.7) for smoking longer than 50 years. This study showed increased risk effects due to hand-rolled cigarette smoking for cancers of the mouth, pharynx and larynx. To the control group subjects with malignant neoplasm diagnoses like leukemia and lymphomas were included and it would be related to tobacco consumption. In a hospital-based case-control study conducted in Korea by CHOI and KAHYO (1991), patients with cancers at the other sites and conditions due to a current diagnosis of tobacco and alcohol-related diseases were excluded as controls. For males, a significant OR for more than 40 years of cigarette smoking, adjusted for alcohol use, was 3.0 (95% CI: 1.56-5.77) for cancer of the mouth, 2.38 (95% CI: 1.17-4.82) for pharyngeal cancer and 5.62 (95% CI: 1.81-12.93) for laryngeal cancer. For smoking of more than 41 cigarettes per day the ORs were 6.11 (95% CI: 1.01-36.95), 2.89 (95% CI: 1.03-9.27), and 27.33 (95% CI: 5.27-141.85). For heavy alcohol consumption the OR was 14.82 (95% CI: 5.03-43.67) for oral cancer, 11.23 (95% CI: 4.23-29.83) for pharyngeal cancer and 11.14 (95% CI: 3.84-32.37) for laryngeal cancer, adjusted for cigarette smoking. Elevated cancer risks with increasing level of consumption of alcoholic beverages have also been reported in other studies (GRAHAM et al. 1977; ELWOOD et al. 1984; DE STEFANI et al. 1987; RAO et al. 1994; JABER et al. 1998).

In the case-control studies by WYNDER and STELLMAN (1977), DE STEFANI et al. (1992); CHOI and KAHYO et al. (1991), above mentioned, the control group was selected excluding some diseases related to tobacco or alcohol

consumption. However, in some cancers that were considered eligible to the control group, such as leukemia, have recently been found to be related to tobacco consumption (DE STEFANI et al. 1992). In order to avoid bias in a case-control study, LEWIN et al. (1998) selected the control group from continuously updated population registries. Significant ORs were observed after adjustment for different variables in the models.

BARRA et al. (1991) conducted an Italian case-control study to examine the comparability of risk estimates for tobacco smoking and alcohol drinking in oral cavity and pharyngeal cancers. Cases were hospital patients with histologically confirmed malignant neoplasms of oral and pharynx. Two different control groups were used, one selected from patients admitted to hospital for diseases (orthopaedic, trauma, surgical conditions, eye disorders and others) unrelated to tobacco and alcohol use, and the other control group were selected from subjects with cancers (colorectal, kidney, prostate, haematological and thyroid cancers) unrelated to these exposures. The ORs resulted for using either controls cancer and non-cancer for smoking and alcohol drinking habits were similars. For more than 40 years of smoking the risks were 7.4 (95% CI: 4.0-13.6) and 8.8 (95% CI: 3.9-12.1) to using cancer and non-cancer controls respectively. For more than 84 total alcohol drinks/week the ORs were 10.6 (95% CI: 5.5-20.6) and 11.4 (95% CI: 6.0-21.4), respectively. To examine the relation between alcohol intake and upper digestive tract (oropharyngeal and oesophageal) cancers a population based cohort study was carried out by GRØNBÆK et al. (1998). The results from this cohort study confirm the association between total alcohol intake, specially beer and spirits, and upper digestive tract cancers, but wine tended to reduce the risk.

In the present study an uniform restriction criteria was used for all subjects in the control group. The variability in exposure distributions was due to the exclusion of control subjects with diseases of varying degree of association with tobacco and alcohol consumption. ORs were derived for the same exposure categories and using the same adjustment methods for confounders. Criteria for creating match sets were also the same across levels of restriction. The results revealed similar risk effects for different exposures regardless of whether restriction was applied or not. The ORs calculated from this set of analysis continued to show substantial risk effects from tobacco smoking and alcohol consumption providing convincing evidence that the inclusion of diseases related to tobacco and alcohol consumption in the control group did not significantly bias previous results.

3.5.2 *Dietary variables*

3.5.2.1 *Maté consumption*

In a hospital-based case-control investigation carried out in Uruguay by DE STEFANI et al. (1987), a relationship between *maté* consumption and laryngeal cancer was observed. A significant OR of 4.9 (95% CI: 1.7-14.3) for consumption of more than 1.5 liters/day after controlling for age, smoking and alcohol drinking was found. Two hundred ninety patients with diseases considered unrelated to tobacco or alcohol exposure were included as the control group, including malignant neoplasms (colorectal, leukemia, skin, lymphoma, penis, myeloma and sarcoma).

DE STEFANI et al. (1988), in a hospital-based case-control study conducted in Uruguay, found a significant association between *maté* consumption and oropharyngeal cancer, after adjustments for age, smoking and alcohol drinking (OR =

5.2; 95% CI: 2.1-13.1). There were a total of 286 patients eligible as hospital controls that had diseases other than those associated with tobacco and alcohol consumption.

In a Brazilian hospital based case-control study conducted by FRANCO et al. (1989), a significant crude OR was observed between *maté* drinking and oral cancer, however, after adjustments for smoking and alcohol consumption, a small to moderate effect was observed (OR = 1.6; 95% CI: 0.8-3.3) for drinking more than 30 cups per month. The authors included 464 hospital controls with diseases other than cancer or mental disorders. More recently, PINTOS et al. (1994) obtained positive and significant ORs for mouth and laryngeal cancers with *maté* drinking, but no evidence of association with pharygeal cancers. Analyses were adjusted by tobacco smoking, alcohol consumption, income, rural residence, ten dietary variables and consumption of other non-alcoholic beverages.

Our findings, in spite of disease restrictions, showed significant increased risks for all UADT sites, laryngeal and pharyngeal cancer. In the study by FRANCO et al. (1989), with tobacco and alcohol consumption adjusted analysis, non-significant risk effects for oral cancer were observed, with similar ORs from this study but they were different with significative results by PINTOS et al. (1994), possibly it was resulted of the additional adjustment (tobacco, alcohol, income, rural residence, ten dietary variables and consumption of other nonalcoholic beverages) for confounders in the models. However, ORs for all UADT sites, pharyngeal and laryngeal cancers by PINTOS et al. (1994) were similar to this study except to oral cancer.

In contrast to ORs observed for alcohol consumption, there was an inconsistent relationship with *maté* consumption. It is postulated that this may be due to an interaction with the temperature at which *maté* was drunk (VASSALO et al.

1985; DE STEFANI et al. 1990; VICTORA et al. 1990; OREGGIA et al. 1991). We were not able to investigate the presence of such effect modification in our analyses, because of small numbers of controls after restriction. Nevertheless, in spite of the study design and sample selection methodology used in this hospital-based case-control study, consistently have shown associations in line with the risks reported by FRANCO et al. 1989, for oral cancers, and by PINTOS et al. 1994, for oral and laryngeal cancers, suggesting that selection bias could not be a major problem in this particular cancer sites study.

3.5.2.2 Citric fruits, foods containing β-carotene and spicy food consumption

Negative risks (protective effects) have been reported consistently for frequent intake of vegetables and citric fruits and for consumption of foods rich in micronutrients like β-carotene, vitamin C, glutathione (MCLAUGHLIN et al. 1988; GRIDLEY et al. 1990; KUNE et al. 1993; RIBOLI et al. 1996; STEINMETZ and POTTER 1996; NOMURA et al. 1997; DE STEFANI et al. 1999a) and the consumption of vegetables, fruits. In a Uruguayan study conducted by DE STEFANI et al. (1987), the results suggested a negative relationship between laryngeal cancer and frequent vegetable and fruit consumption. Again, patients who had diseases other than those associated with tobacco and alcohol consumption were considered eligible as control subjects. In another hospital-based case-control study carried out in Switzerland by LEVI et al. (1998), the authors found a similar association between oral and pharyngeal cancers and food groups including vegetables and fruits.

In a recent study, DE STEFANI et al. (1999a) found further evidence that consumption of raw vegetables, fruits and legumes, as well as overall consumption of vegetables, provided a protective effect for oral cavity, pharyngeal, laryngeal and esophageal cancers. The consumption of β-carotene was not associated to UADT cancers. The hospital control group was selected with conditions unrelated to tobacco smoking, alcohol drinking or dietary habits.

We observed similar protective associations for oral cancer with consumption of citrus fruits and β-carotene, in spite of restrictions in the control group diseases, as FRANCO et al. (1989) observed in a previous analysis without restriction. Our results have shown that the association may not have been affected by selection bias due to over sampling of tobacco and alcohol-related diseases among hospital controls.

In spite of restriction criteria positive ORs were found for consumption of spicy foods and UADT cancers, except laryngeal cancer, with meaningful risks around 1.5. Previous studies have failed to find any association between such exposure and oral cancer (FRANCO et al. 1989; MCLAUGHLIN et al.1988). Possibly it is due to "*the imprecision in the measurement of diet variables*" (MARSHALL and BOYLE 1996).

Although the restriction of control subjects was done on the basis of association with tobacco and alcohol exposure, these behaviors are likely linked with diet and may have influenced the original, unrestricted analyses through residual confounding. However, little difference in risk effect could be observed with and without restriction for any of the diet variables investigated. Again, the design used in this cancer case-control study results reassuring tobacco and alcohol related diseases in the control group not provide selection bias.

3.5.3 *Environmental exposure*

In 1989, FRANCO et al. demonstrated a significant OR between oral cancer and use of wood stoves for cooking and heating. This was later verified for all UADT sites (mouth, pharynx and larynx) in a study conducted by PINTOS et al. (1998). However, in these studies, no exclusion was done for control patient diseases, excepting for those who had other cancers or mental disorders.

Some of the products generated by the wood fires are suspected carcinogenic agents. In a study carried out in a southern Brazil region it was verified higher levels of polycyclic aromatic hydrocarbons (PAH) in kitchens and it was correlated directly with the presence of wood stoves (HAMADA et al. 1991b). A Germany head and neck case-control study, also verified that air polluted by fossil fuels from burning oil, coal, gas and wood as heating materials for more than 40 years, was associated with laryngeal cancer (DIETZ et al. 1995).

With the control group disease restrictions in the present study, significant associations between wood stove use and UADT cancers persisted. Our results have shown that the risk effects tended to decrease strongly as the level of restriction increased, however, this is based on the point of exposure measure and not cumulative exposure measure. Also, it was observed that São Paulo and Goiânia case and control patients used wood stove less frequently than those from Curitiba, a southern Brazil region. Similar to results from FRANCO et al. 1989 and by PINTOS et al. 1998, the risk effects for different exposures, regardless of whether restriction was applied or not, the magnitude of association observed in this set of analysis suggested that selection bias could not be a major problem.

3.6 CONCLUSION

Our findings indicate no appreciable difference in estimated relative risks for all variables studied following disease restrictions in the control group and support the hypothesis that inclusion of controls with tobacco and alcohol related diseases in hospital-based case-control studies is not an important source of selection bias.

However, in this study, largest changes in ORs were observed when restriction was done on the basis of disease class. This method grouped together all causes of hospitalization related to cardiovascular, respiratory and digestive system diseases but may have also excluded diseases not related to tobacco or alcohol consumption. Moreover, regarding the original UADT cancer case-control study conducted in Curitiba, Goiânia and São Paulo, our results strongly support the proposition that selection bias due to inclusion of patients in control group with tobacco and alcohol related-diseases are not a likely explanation of all those positive findings already published by the Brazilian UADT Study Group (FRANCO et al. 1989; PINTOS et al. (1994, 1998); FOULKES et al. 1995; SCHLECHT et al. (1999a, 1999b); VELLY et al. 1998).

In the present review we found an association of frequent spicy food consumption and oral and oropharyngeal cancers. This was not previously detected by the Brazilian UADT Study Group.

Hospital-based case-control study methods require improvements to help remove or avoid bias introduced by the selection of control groups for study. The methodology compiled in this study may help to improve the validity of other studies using similar designs.

4. COMENTÁRIOS

4. COMENTÁRIOS

Muitos resultados de pesquisas epidemiológicas dependem do tipo de delineamento do estudo e da forma com que os grupos de indivíduos participantes são selecionados. Este estudo caso-controle de base hospitalar de câncer de vias aerodigestivas superiores, realizado em três grandes capitais brasileiras, apresentou uma série de resultados objetivando avaliar a magnitude do efeito do viés de seleção causado pela inclusão indiscriminada de pacientes hospitalizados com doenças relacionadas ao consumo de tabaco e álcool. Foi obtida uma constante associação com elevados riscos entre a quantidade de tabaco e consumo de bebidas alcoólicas ao longo da vida e o câncer de vias aerodigestivas superiores.

No estudo sobre câncer de boca, FRANCO et al. (1989) obteve OR de 14.8 (95% CI: 4.7-47.3) para consumo acima de 100 *pack-years* de tabaco e OR de 8.5 (95% CI: 2.5-29.4) para elevadas quantidades de bebida alcoólica. Para o mesmo tipo de câncer, o presente estudo obteve riscos em torno de 9 e 5 vezes, respectivamente para tabaco e álcool. Vale ressaltar que este estudo contou com amostra maior de controles, entretanto; independentemente da magnitude, os riscos permaneceram elevados e significativos.

Para o consumo de chimarrão, FRANCO et al. (1989) obtiveram risco de 1.6 (95% IC:0.8-3.3) para câncer da cavidade oral e, no presente estudo, com restrição incluindo somente pacientes-controles com doenças não associadas ao tabaco e álcool, obtivemos risco semelhante de 1.6 (95% IC: 0.9-2.8).

O estudo realizado por FRANCO et al. (1989) para câncer da cavidade oral observou que:

- para alimentos ricos em β-caroteno, o OR foi de 0.4 (95% IC: 0.2-1.0) e, no presente estudo, o risco relativo obtido foi em torno de 0.6 vezes, independentemente do critério de restrição adotado para seleção de controles;
- para frutas cítricas, o OR foi de 0.5 (95% IC: 0.3-0.9) e de 0.6 no presente estudo;
- para consumo elevado de alimentos apimentados, o risco relativo foi de 1.3 (95% IC: 0.9-2.0) e, neste estudo, risco significativo em torno de 1.6 vezes;
- para cozinhas equipadas com fogão a lenha, OR de 2.5 (95% IC: 1.6-3.9) e, neste estudo, OR de 2 vezes.

Ao se excluir todos os pacientes do grupo-controle com doenças dos sistemas digestivo, respiratório e cardiovascular, foram verificadas maiores diferenças entre os riscos, as quais se pode atribuir ao fato de terem sido excluídos pacientes com causa de hospitalização não associadas ao consumo de tabaco e álcool.

Além dos estudos casos-controles em oncologia, as mesmas preocupações metodológicas são objeto de pesquisa em outras áreas da saúde. WÜNSCH-FILHO et al. (1993) realizaram um estudo caso-controle com objetivo de avaliar a eficácia da vacina BCG. Foram considerados três tipos de controles: hospitalar, vizinhos e crianças da mesma residência dos casos. Nesse estudo, os autores não encontram razões para sugerir a ocorrência de viés de seleção e, as diferenças entre os resultados obtidos podem ser atribuídas aos ajustes e fatores controladores.

Nossos resultados mostram que as associações não foram afetadas pelo viés de seleção, devido à inclusão de indivíduos com doenças relacionadas ao consumo de tabaco e álcool no grupo-controle. Além disso, os resultados obtidos neste estudo sustentam a proposta de que o viés de seleção, devido à inclusão desses controles,

não é uma provável explicação para todos os achados positivos anteriormente já publicados, com respeito ao estudo caso-controle de câncer das Vias Aerodigestivas Superiores conduzido em Curitiba, Goiânia e São Paulo.

5. REFERÊNCIAS BIBLIOGRÁFICAS

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