UNIVERSIDADE ESTADUAL DE CAMPINAS
FACULDADE DE ODONTOLOGIA DE PIRACICABA

ANA LETÍCIA MORES

IDADE, ESTÁGIO E CONSUMO DE ÁLCOOL NO DIAGNÓSTICO PREDIZEM A MORTALIDADE DO CÂNCER DE CABEÇA E PESCOÇO: UM ESTUDO COORTE RETROSPECTIVO PARA 3275 PACIENTES BRASILEIROS

AGE, STAGING AND ALCOHOL DRINKING AT DIAGNOSIS PREDICT MORTALITY IN HEAD AND NECK CANCER: A COHORT RETROSPECTIVE STUDY FOR 3275 BRAZILIAN PATIENTS

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Dissertação apresentada à Faculdade de Odontologia de Piracicaba da Universidade Estadual de Campinas como parte dos requisitos exigidos para a obtenção do título de Mestra em Estomatopatologia, na Área de Estomatologia.

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Orientadora: Profa. Dra. Ana Carolina Prado Ribeiro e Silva

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RESUMO

Esta dissertação de mestrado contemplou dois estudos distintos envolvendo o prognóstico e a prevenção do Câncer de Cabeça e Pescoço (CCP). O primeiro foi um estudo de coorte retrospectivo com o objetivo de determinar a Sobrevida Global (SG) dos pacientes com CCP tratados pelo Serviço de Odontologia Oncológica do Instituto do Câncer do Estado de São Paulo (ICESP), São Paulo, Brasil, entre 2011 e 2021. E identificar as interações do tabagismo, etilismo e infecção pelo Papilomavírus Humano (HPV) na determinação do risco de morte, encontrando os principais fatores prognósticos nos diferentes sítios do CCP. A análise de sobrevida foi realizada pelo método de Kaplan-Meier e comparadas pelo teste log-rank, considerou-se o tempo desde a data do diagnóstico até a data de óbito por todas as causas. Foi utilizada a regressão de Cox univariada e múltipla, calculando-se o hazard ratio (HR) e seus respectivos intervalos de confiança de 95%. Durante os 10 anos analisados, 3275 pacientes com CCP foram incluídos no estudo, sendo 832 (25,4%) de cavidade oral, 1261 (38,5%) de orofaringe, 1011 (30,8%) de laringe e 171 (5,2%) de hipofaringe. A SG em 5 anos foi de 33,7% para todos os sítios de CCP, 40,1% para a laringe, 38,5% para a cavidade oral, 28% para orofaringe e 15,5% para hipofaringe. Após os ajustes com as variáveis significativas ($p \leq 0.05$) na análise múltipla, a idade igual ou superior a 60 anos e o estágio avançado do tumor (III/IV) foram fatores prognósticos independentes desfavoráveis para a cavidade oral, orofaringe e laringe. O consumo de álcool nos sítios de orofaringe e laringe, e o gênero masculino no sítio de cavidade oral também foram fatores prognósticos independentes desfavoráveis na sobrevida do CCP. Entre os 1261 pacientes com câncer de orofaringe, apenas 356 (28,2%) tinham informações do status p16, onde 129 (36,2%) eram HPV-positivos e 227 (63,7%) HPV-negativos. A SG em 5 anos foi de 58,6% para os pacientes HPV-positivos e 35,7% para os HPV-negativos. A análise múltipla ajustada não pode ser realizada nesse grupo de pacientes, exigindo mais estudos nessa área. Por fim, a SG do CCP permanece baixa no Brasil e todos os profissionais da saúde devem incentivar o abandono do tabagismo e etilismo no momento do diagnóstico para melhorar as taxas de sobrevida. O segundo artigo apresentado nesta dissertação se trata de uma revisão sistemática que teve como objetivo analisar o impacto dos impostos e preços do cigarro sobre a prevalência do tabagismo na América Latina. Após uma busca nas bases de dados PubMed/MEDLINE, Scopus, Embase, Web of Science e LILACS, de acordo com a lista de verificação PRISMA, um total de sete estudos observacionais realizados no Brasil, México e Colômbia foram incluídos na análise qualitativa. Todos os estudos constataram que um aumento nos impostos sobre o cigarro industrializado levou a um

aumento no seu preço de varejo. Quatro estudos (57,1%) relataram que o aumento dos impostos e dos preços dos cigarros foram eficazes na diminuição da prevalência do tabagismo na América Latina, favorecendo assim, a prevenção do CCP.

Palavras-chave: Neoplasias de cabeça e pescoço. Hábito de fumar. Consumo de bebidas alcoólicas. Prognóstico. Sobrevida.

ABSTRACT

This master's dissertation included two distinct studies involving the prognosis and prevention of Head and Neck Cancer (HNC). The first was a retrospective cohort study with the objective of determining the Overall Survival (OS) of patients with HNC treated by the Oncological Dentistry Service of the Instituto do Cancer do Estado de São Paulo (ICESP), São Paulo, Brazil, between 2011 to 2021. And to identify the interactions of tobacco smoking, alcohol drinking and Human Papillomavirus (HPV) infection in determining the risk of death by finding the main prognostic factors at the different sites of HNC. Survival analysis was performed by the Kaplan-Meier method and compared by the log-rank test, considering the time from the date of diagnosis until the date of death from all causes. Univariate and multiple Cox regression were used, calculating the hazard ratio (HR) and their respective 95% confidence intervals. During the 10 years analyzed, 3275 patients with HNC were included in the study, 832 (25.4%) from oral cavity, 1261 (38.5%) from oropharynx, 1011 (30.8%) from larynx and 171 (5.2%) from hypopharynx. The 5-year OS was 33.7% for all HNC sites, 40.1% for larynx, 38.5% for oral cavity, 28% for oropharynx, and 15.5% for hypopharynx. After adjustments with the significant variables ($p \leq 0.05$) in the multiple analysis, age 60 years or older and advanced tumor stage (III/IV) were unfavorable independent prognostic factors for the oral cavity, oropharynx and larynx sites. Alcohol drinking at the oropharyngeal and laryngeal sites, and male gender at the oral cavity site were also independent unfavorable prognostic factors in the survival of HNC. Among 1261 patients with oropharyngeal cancer, only 356 (28.2%) had p16 status information, where 129 (36.2%) were HPV-positive and 227 (63.7%) were HPV-negative. The 5-year OS was 58.6% for HPV-positive and 35.7% for HPV-negative patients. The adjusted multiple analysis could not be performed in this group, requiring further studies in this area. Finally, the OS of HNC remains low in Brazil and all health professionals should encourage smoking and alcohol drinking cessation at the diagnosis to improve survival rates. The second study presented in this dissertation is a systematic review that aimed to analyze the impact of cigarette taxes and prices on the prevalence of tobacco smoking in Latin America. After a search of the PubMed/MEDLINE, Scopus, Embase, Web of Science and LILACS databases, according to the PRISMA checklist, seven observational studies conducted in Brazil, Mexico and Colombia were included in the qualitative analysis. All studies found that an increase in excise taxes of cigarette led to an increase in the retail price. Four studies (57.1%) reported that increasing cigarette taxes and prices was effective to

decrease the prevalence of tobacco smoking, thus favoring the prevention of HNC in Latin America countries.

Keywords: Head and neck neoplasms. Smoking. Alcohol drinking. Prognosis. Survivorship (Public health).

SUMÁRIO

1 INTRODUÇÃO

O câncer é considerado um dos principais problemas de saúde pública no mundo. Na maioria dos países, corresponde à primeira ou à segunda causa de morte prematura (antes dos 70 anos). O Global Cancer Observatory (GLOBOCAN), estimou para o ano de 2020 cerca de 19,3 milhões de novos casos de câncer diagnosticados (18,1 milhões sem contar os casos de câncer de pele não melanoma) e 10 milhões de mortes (9,9 milhões excluindo os cânceres de pele não melanoma) por câncer em todo o mundo. O câncer de mama feminino é o mais incidente, seguido pelo câncer de pulmão, cólon e reto, próstata e estômago (Sung et al. 2021; INCA 2023).

O Câncer de Cabeça e Pescoço (CCP) é classificado como o sexto tipo de câncer mais frequente no mundo (Ferlay et al. 2019), sendo um grupo heterogêneo de neoplasias malignas originadas no trato aero digestivo superior que acometem a cavidade oral, cavidade nasal, faringe (nasofaringe, orofaringe e hipofaringe), laringe, seios paranasais, glândulas salivares e glândula tireoide (Jethwa and Khariwala 2017; Khariwala et al. 2017; Adoga et al. 2018; Du et al. 2019). Dois terços dos casos de CCP ocorrem em países em desenvolvimento (Adoga et al., 2018), como o Brasil. O Carcinoma Espinocelular (CEC) é o tipo histopatológico mais comum do CCP, representando cerca de 90% dos casos (Adoga et al., 2018; Chin et al., 2006; Jethwa and Khariwala, 2017; Rivera, 2015).

O CCP possui vários fatores de risco associados, sendo os mais comuns a idade, o gênero, as condições socioeconômicas, o tabagismo, etilismo, sua associação, e a infecção pelo Papilomavírus Humano (HPV) (Chin et al. 2006; Boing et al. 2011; Rivera 2015; Marur and Forastiere 2016; Anantharaman et al. 2017; Jethwa and Khariwala 2017; Adoga et al. 2018; Boras et al. 2019; Madathil et al. 2020; Louredo et al. 2022a; INCA 2023).

Atualmente o CEC de cabeça e pescoço apresenta três perfis clínico patológicos distintos, a saber:

(1) Tipo clássico que afeta pacientes idosos (acima de 60 anos), com proporção homem:mulher de 2:1, baixo nível socioeconômico e fortemente associado ao tabagismo e etilismo (Chin et al. 2006; Boing et al. 2011; Rivera 2015; Marur and Forastiere 2016; Boras et al. 2019);

(2) Tumores induzidos pelo vírus HPV (em sua maioria o genótipo 16 e 18) que afetam predominantemente a orofaringe de homens por volta dos 45 anos, com proporção homem:mulher de 4:1, não tabagistas e não etilistas, alto nível socioeconômico e associado a práticas sexuais orais sem proteção (Chin et al. 2006; Rivera 2015; Marur and Forastiere 2016;

Anantharaman et al. 2017; Hussein et al. 2017; Madathil et al. 2020; Louredo et al. 2022a); e em menor proporção

(3) Tumores que afetam pacientes jovens, principalmente mulheres com menos de 40 anos, que se desenvolvem na borda lateral de língua (Adeoye et al.; Toporcov et al. 2015; Hussein et al. 2017; Dougherty et al. 2021) e tumores que afetam mulheres idosas (acima de 60 anos) que se desenvolvem em rebordo alveolar ou mucosa jugal, ambos não possuem fatores de risco associados (Adeoye et al.; Bonetti Valente et al. 2022).

Está claro que o tabagismo e o etilismo são fatores de risco para o desenvolvimento do CCP de maneira independente ou conjunta (Hashibe et al. 2007, 2009; Ferreira Antunes et al. 2013; Di Credico et al. 2019, 2020). Na fumaça do tabaco já foram identificadas mais de 5.300 componentes, dentre eles, ao menos 70 são carcinógenos (de Almeida et al. 2014; Jethwa and Khariwala 2017). O principal carcinógeno do álcool é o acetaldeído que é produzido pelo metabolismo do etanol (Lee et al. 2019). Deficiências nutricionais podem ocorrer em alcoólatras pois, o álcool ingerido age localmente como um solvente das membranas celulares, aumentando a penetração de carcinógenos na mucosa, especialmente aqueles advindos do tabaco (Rivera 2015; Di Credico et al. 2020).

Aproximadamente 75% dos CCP são atribuídos ao consumo conjunto do tabagismo e etilismo (Hashibe et al. 2007; Beynon et al. 2018). Seu efeito articular é de duas a três vezes maior do que seus efeitos individuais de fumar e beber multiplicados um pelo outro (Hashibe et al. 2009; Ferreira Antunes et al. 2013). De maneira independente, o risco de desenvolver CCP é maior entre os tabagistas comparado aos que nunca fumaram e é dose-resposta para a frequência, duração e consumo cumulativo do tabaco (Hashibe et al. 2007, 2009; Boras et al. 2019; Di Credico et al. 2019). Já para o etilismo, o risco também aumenta para o CCP comparado aos que nunca beberam, porém, é dose-resposta para o consumo de etanol diário e não sua duração (Hashibe et al. 2007, 2009; Di Credico et al. 2020).

Hashibe et al. (2009) através de estudos caso-controle advindos da International Head and Neck Cancer Epidemiology Consortium (INHANCE) determinaram a razão de chances ajustada (ORs) para o desenvolvimento do CCP, onde foi 2,37 (95%CI=1,66–3,39) para tabagistas nunca etilistas, 1,06 (95%CI=0,88–1,28) para etilistas nunca tabagistas e 5,73 (95%CI=3,62–9,06) para tabagistas e etilistas (Hashibe et al. 2009). Semelhantemente, Ferreira-Antunes et al. (2013) realizaram um estudo caso-controle no Brasil avaliando o desenvolvimento do câncer oral e de orofaringe onde encontraram ORs para fumar, beber, fumar e beber de 3,50 (95%CI=2,76–4,44), 3,60 (95%CI=2,86–4,53) e 12,60 (95%CI=7,89–20,13), respectivamente, onde estes valores foram significativos para fumantes com carga

tabágica maior de 28 maços-anos e bebedores maiores de 862 gramas-ano de etanol (Ferreira Antunes et al. 2013).

O sistema de estadiamento para o CCP mais utilizado atualmente é o TNM, preconizado pela Union for International Cancer Control (UICC), onde fornece a base para a tomada da decisão clínica e terapêutica, levando em consideração o tamanho e a profundidade de invasão do tumor primário em centímetros (T), envolvimento de linfonodos regionais (N) e presença de metástase à distância (M), variando de I à IV, sendo que estágios maiores possuem pior prognóstico (Amin et al. 2017; Beynon et al. 2018).

Os protocolos de tratamento tendem a ser multimodais, envolvendo cirurgia, quimioterapia (QT) ou radioterapia (RDT) associadas ou, mais frequentemente, combinadas (Chin et al. 2006; Epstein et al. 2014; Rivera 2015; Marur and Forastiere 2016; D'Cruz et al. 2018; Palmier et al. 2020). A cirurgia é superior a todas as outras modalidades terapêuticas, com ou sem dissecção dos linfonodos (Chin et al. 2006; Rivera 2015; Adoga et al. 2018; D'Cruz et al. 2018). A RDT conformacional tridimensional (3D) e a de intensidade modulada (IMRT) são as mais utilizadas e se baseiam em uma terapia de 60 a 70Gy no sítio primário e 50Gy nas drenagens, sendo dividido em média de 2Gy por dia, 5 dias por semana, durante 6 a 7 semanas (Chin et al. 2006; Marur and Forastiere 2016; Levi and Lalla 2018). A QT pode ser aplicada como estratégia de indução, seguida por quimiorradioterapia concomitante ou como terapia paliativa. Os agentes quimioterápicos comumente utilizados são os derivados da platina, 5-fluoruracila e taxanos (Rivera 2015; Marur and Forastiere 2016; Adoga et al. 2018).

O tratamento oncológico do paciente com CCP causa morbidades e efeitos adversos significativos tanto por danos diretos às estruturas em região de cabeça e pescoço (Chin et al. 2006) quanto por danos indiretos da toxicidade sistêmica, como mucosite, hipossalivação e xerostomia, disfagia, disgeusia, dor, infecções bacterianas, virais e fúngicas, cáries de radiação, trismo, osteorradionecrose, dentre outras. O cirurgião-dentista é extremamente necessário em todas as fases do tratamento oncológico, prevenindo e tratando as complicações decorrentes das toxicidades agudas e crônicas (Epstein et al. 2014; Marur and Forastiere 2016; Levi and Lalla 2018; de Oliveira et al. 2020; Morais-Faria et al. 2020; Palmier et al. 2020).

Apesar de um declínio nas taxas de mortalidade por CCP, a sobrevida permanece baixa. A taxa de sobrevida global em 5 anos é de cerca de 50% para todos os sítios do CCP (Chin et al. 2006; Giraldi et al. 2017; Jethwa and Khariwala 2017; Beynon et al. 2018) e varia entre 35% para hipofaringe e 72% para laringe (Giraldi et al. 2017). Pacientes com câncer orofaríngeo HPV-positivo têm melhor sobrevida comparado ao HPV-negativo, devido sua melhor resposta terapêutica (Du et al. 2019; Louredo et al. 2022a).

O tabagismo, etilismo e infecção pelo vírus HPV são fatores de risco estabelecidos para o CCP, porém a interação dessas variáveis não estão claras como fatores prognósticos na sobrevida do CCP e em seus diferentes sítios (Leoncini et al. 2015; Giraldi et al. 2017; Abrahão et al. 2018, 2020).

A presente dissertação apresenta a investigação das possíveis interações entre o tabagismo, o etilismo e o status HPV na sobrevida global de 3275 pacientes diagnosticados com CEC de cabeça e pescoço atendidos no Serviço de Odontologia Oncológica do Instituto do Câncer do Estado de São Paulo, Brasil, entre 2011 a 2021, com o objetivo de determinar os fatores prognósticos para os diferentes sítios de CCP (cavidade oral, orofaringe, laringe e hipofaringe) e auxiliar os profissionais de saúde a informar e aconselhar o paciente com CCP recém diagnosticado sobre novos estilos de vida.

Além disso, a prevenção é essencial para a diminuição de novos casos de CCP através de medidas para controle do tabagismo, etilismo, imunização contra o HPV, avaliação odontológica periódica com exame clínico intraoral sistemático, diagnóstico precoce e tratamento das lesões potencialmente malignas (Hashim et al. 2019; Louredo et al. 2022a).

A Convenção-Quadro para o Controle do Tabaco (CQCT) é o primeiro tratado negociado sob os auspícios da Organização Mundial da Saúde (OMS). Dentre uma diversidade de políticas para o controle do tabagismo, o aumento do preço dos cigarros por meio de impostos é considerado uma medida altamente eficaz e econômica. Globalmente, os impostos aplicados aos cigarros representam mais da metade do preço médio dos cigarros, variando em cerca de 65,5% em países desenvolvidos a 40,8% em países em desenvolvimento (Chaloupka et al. 2012; Gallego et al. 2021). Por meio de uma revisão sistemática da literatura, a presente dissertação avaliou também se, o impacto dos impostos sobre o preço do cigarro industrializado é eficaz na diminuição da prevalência do tabagismo nos países da América Latina.

2 ARTIGOS

2.1 ARTIGO: AGE, STAGING AND ALCOHOL DRINKING STATUS AT DIAGNOSIS PREDICT MORTALITY IN HEAD AND NECK CANCER: A COHORT RETROSPECTIVE STUDY FOR 3275 BRAZILIAN PATIENTS

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Abstract

Objective: Evaluate whether socio-demographic, clinical and lifestyle habits (tobacco smoking, alcohol drinking and human papillomavirus infection) characteristics at diagnosis of Head and Neck Cancer (HNC) are associated with the overall survival (OS) and mortality risk in the different HNC sites (oral cavity, oropharynx, larynx, and hypopharynx).

Materials and Methods: Retrospective cohort (2011-2021) at Instituto do Cancer do Estado de São Paulo, Brazil, including 3,275 HNC patients. The Kaplan-Meier method and Cox proportional hazard ratios (HRs) and the corresponding 95% confidence intervals (CIs) were estimated including variables reported significantly associated with the survival in the univariate analysis.

Results: Five-year OS was 33.7% for all HNC sites combined: 40.1% for larynx, 38.5% for oral cavity, 28.0% for oropharynx, and 15.5% for hypopharynx. In a separate analysis for oropharyngeal cancer, the five-year OS was 58.6% for HPV positive and 35.7% for HPV negative according p16 status. In a multiple analysis, we observed that older age (60 years or older), advanced tumor stages (III and IV), and alcohol drinking history at diagnosis were independent and unfavorable prognostic factors of the OS in HNC, especially in oropharynx and larynx sites. Male gender was an independent unfavorable prognostic factor in oral cavity site.

Conclusion: HNC OS remains low in Brazil. Older age, advanced tumor stages, and alcohol drinking history at diagnosis were independent and unfavorable prognostic factors, especially in oropharynx and larynx sites.

Keywords: Head and neck neoplasms, tobacco smoking, alcohol drinking, human papillomavirus, mortality, survival, prognosis, and prognostic.

Introduction

Head and Neck Cancer (HNC) is the sixth most common type of cancer worldwide and refers to a diverse group of malignancies in the upper aerodigestive tract [1,2]. In 2018, HNCs accounted for over 700,000 new cases (3.9% of all cancer cases) and over 350,000 deaths (3.8% of all cancer cases) worldwide. The overall incidence of HNC continues to rise, with a predicted 30% increase annually by 2030. Approximately 90% of HNCs are squamous cell carcinoma (HNSCC), which arise from the epithelial lining of the oral cavity, nasopharynx, oropharynx, hypopharynx, larynx, nasal cavity and paranasal sinuses. Overall, HNC affects men two to four times more than women, with estimates reaching over 20 per 100,000 [1].

The median age at diagnosis is approximately 60 years, yet the incidence of these cancers in adults younger than 45 years has been increasing in recent years, mainly due to higher numbers of oropharyngeal cancers associated with oncogenic types 16 and 18 human papillomavirus (HPV). The unprotected oral sex is the major risk factor implicated in HPV infection [3–5].

Tobacco smoking and alcohol drinking behaviors, separately and in combination, are major risk factors for HNC, accounting for 75% of cases when used in combination [6–10]. Tobacco smoking remains a major risk factor globally, with the rates continuously rising in most developing countries [11,12].

Despite an overall decline in HNC mortality rates, survival remains poor and still differs among the different HNC sites. Globally, five-year survival for HNC averages at 50% of cases, but ranges from 35% for hypopharyngeal cancers and more than 60% for laryngeal cancers [13]. About 40-60% of HNC patients develop recurrences, and around 20% of HNCs develop second primary cancer, both being associated with poorer survival [14].

Patients with HPV-positive oropharyngeal cancer have consistently demonstrated improved survival compared to their HPV-negative counterparts, even though they are frequently diagnosed at a later tumor stage [5,15–22]. This is largely due to improved therapeutic response.

There are many survival studies in the literature evaluating independent prognostic factors of HNC. However, they search for prognosis association only with tobacco smoking information [23–25], tobacco smoking and alcohol drinking [13,26–39], and tobacco smoking with HPV infection [15,17,18,40], separated. When this association is searched together (tobacco smoking, alcohol drinking and HPV infection) there are only a few studies [16,19–22,41,42], and most of them did not stratify by site (oral cavity, oropharynx, larynx and/or hypopharynx, for example) [16,19–21,42]. These factors help to explain why estimates of the effect of tobacco smoking and alcohol drinking on HNC survival have varied so considerably.

The aims of this study are to investigate the overall survival (OS) of HNC in a large retrospective cohort stratified by site (oral cavity, oropharynx, larynx, and hypopharynx) for patients treated at the Instituto do Cancer do Estado de São Paulo, Brazil, and to identify the interactions between tobacco smoking, alcohol drinking and HPV infection on oropharyngeal cancer in determining mortality risk and finding other potentially significant independent prognostic factors for oropharynx and other HNC sites. To our knowledge, this is the largest retrospective study addressing this topic at a single Cancer Center.

Materials and methods

Study design and setting

This was a 10-year cohort retrospective study that recruited 5,080 consecutive cancer patients undergoing oncologic treatment at the Instituto do Cancer do Estado de São Paulo (ICESP) in São Paulo, Brazil, from July 2011 to July 2021, by the Dental Oncology Service. This study's ethics approval was obtained from the National Human Research Ethics Committee (CAAE: 54779521.0.0000.5418). The study was conducted per the Declaration of Helsinki and performed following the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement [43,44].

Eligibility criteria

Patients were included if histologically confirmed primary squamous cell carcinoma of the head and neck (HNSCC), of oral cavity (tongue, gingiva, floor of mouth, buccal mucosa, alveolar ridge, retromolar area and hard palate), oropharynx (base of tongue, soft palate, uvula, tonsil and posterior pharyngeal wall), hypopharynx (pyriform sinus, and other hypopharynx sites), or larynx (glottis, supraglottis and subglottis). They had to be over the age of 18 and classified according to the International Classification of Diseases (ICD), version 10.

Patients with cancers outside of these head and neck regions and of the minor and major salivary glands (parotid, submandibular, or sublingual glands), of the nasal cavity/ear/paranasal sinuses, of the thyroid, or of the lip were not included.

Data collection and variables definition

After a patient was included in the study, an 18-item of socio-demographic, clinical and lifestyle characteristics were extracted from the patient's electronic medical record system Tasy (Philips Clinical Informatics) and transferred to a questionnaire made in RedCap Software, including:

Sociodemographic and clinical characteristics. Gender, age at diagnosis, marital status, race, years of education, cancer diagnosis, tumor stage, p16 protein expression (for oropharynx sites), and presence or not of comorbidities. The tumors were staged or retrospectively restaged in I-IV according to the tumor, node, metastasis (TNM) classification (American Joint Committee on Cancer (AJCC) Staging System, 8th edition) [45].

Lifestyle characteristics. With respect to tobacco smoking, patients were classified according to the smoking status (never, former, and current smokers), tobacco type (cigarette, hand-rolled straw cigarette and/or pipe), intensity of smoking (≤20 or >20 cigarettes per day), smoking duration in years (≤20 or >20 years) and pack-years. With respect to alcohol drinking, patients were classified according to the drinking status (never, former, and current drinkers),

drinking duration in years (≤20 or >20 years) and alcoholic beverage type (fermented, hard liquor or both).

The present study defined as never smokers those individuals who never smoked regularly (at least one cigarette a day), or for a very short period (less than 12 months). Likewise, former smokers and former drinkers were defined as those individuals who had abstained from any type of smoking or drinking since at least 12 months before cancer diagnosis. Never drinkers were individuals who have never had any alcohol (0g of ethanol over lifetime) or never consumed at least one drink at a regular monthly basis.

A single hand-rolled straw cigarette was considered equivalent to four cigarettes, and each pipe serve equivalent to three cigarettes. Cumulative doses of tobacco exposure were calculated in terms of pack-years (PY), the product of the number of packs of cigarette equivalents smoked per day and the number of years of tobacco use (one pack-year equals to one package of cigarettes smoked daily for one year). Subjects were categorized by PY years categories of never (≤0.05 PY), 0.06-30 PY, 30.1-49.0 PY, 49.1-75.0 PY, and ≥ 75.1 PY. When other tobacco products than cigarettes were used, established conversion criteria were applied.

The data was collected in the year 2022 by ALM and was checked by ACPR for internal consistency.

Outcome

The primary end point was the overall survival (OS), defined as the time from the date of diagnosis of HNC primary tumor until the date of death from any cause or last follow-up. One, five and ten-year survival was used. The patients that were lost to follow-up were censored at the last data in the hospital records. The secondary end point was to identify the mortality risk according to the variables and find the independent prognostic factors for the different HNC sites.

Statistical analysis

Stage-0 cancers, corresponding to carcinoma in situ were excluded because, they were not an invasive malignant neoplasia. Among smokers, their tobacco consumption was divided into smokers of cigarettes versus users of other types of tobacco like, hand-rolled straw cigarette and/or pipe.

Frequencies and percentages were used for categorical variables and means, and standard deviations were calculated for continuous variables. Survival curves were constructed using the Kaplan-Meier method to estimate 1-, 5-, and 10-year (all-cause) overall survival, compared by the long-rank test. Univariate and multiple Cox regression were also used to determine independent predictors of OS, calculating the hazard ratio (HR) of death and their

respective 95% confidence intervals (95% CI). Models evaluating the effects of smoking included adjustment for drinking, whereas models evaluating the effects of drinking included adjustment for smoking. The significance level adopted was 5% ($p \leq 0.05$). The analyses were performed in the SPSS statistical software (IBM SPSS Statistics for Windows, version 25; IBM Co., Armonk, NY).

Results

From the 5,080 patients that were referred to the Dental Oncology Service of ICESP between 2011 and 2021, 3,302 had primary HNSCC and due to differential diagnosis, 1,778 patients were excluded. Twenty-seven of primary HNSCC were carcinoma in situ, and were also excluded from the analysis. The remaining 3,275 patients were included in this study. The diagnosis of primary HNSCC comprised the years 1984 to 2021, characterizing a long follow-up period.

Among the 3,275 patients with HNSCC, 832 (25.4%) were of oral cavity, 1,261 (38.5%) of oropharynx, 1,011 (30.9%) of larynx, and 171 (5.2%) of hypopharynx. Among the 1,261 patients with oropharyngeal cancer, only 356 (28.2%) had information of the p16 status; as 71.8% (n=905) did not have this information, a separate analysis of OS and mortality risk was performed for these patients, according to their p16 status.

HNSCC patients

At the end of the follow-up period, 2,234 (68.2%) of 3,275 HNSCC patients had died, and the average follow-up time were 23.1 months. Based on Kaplan-Meier analyses, the 5-year OS was estimated in 33.7% for all sites, with the highest for larynx (40.1%), intermediate for oral cavity (38.5%) and oropharynx (28.0%), and lowest for hypopharynx (15.5%). Differences between the curves are clear (log-rank test, $p<0.001$) - **Table 1** and **Figure 1**.

Descriptive characteristics of the HNSCC sample and their mortality risk determined by univariate analysis and stratified by tumor site, are presented in **Table 2** for sociodemographic and clinical characteristics and **Table 3** for lifestyle characteristics.

The majority of HNSCC patients were male (84.1%), diagnosed after sixty years of age (51.3%), white race (54.9%), married or partnered (51.4%) and had formal education from 4 to 10 years (35.1%). They were diagnosed with advanced tumor stage (86.9% III/IV versus 12.2% I/II) and 53.3% had comorbidities at diagnosis (**Table 2**). In all sites, the advanced tumor stage was the most presented; among the 2,392 (73.0%) patients diagnosed in stage IV, 576 of 832 (69.2%) were from the oral cavity, 961 of 1,261 (76.2%) from the oropharynx, 700 of 1,011 (69.2%) from the larynx, and 155 of 171 (90.6%) from the hypopharynx.

With respect to tobacco smoking, 90.6% were ever-smokers (66.4% current and 24.2% former smokers) and 9.4% never smoked, 94.0% of these (n=2,788) smoked cigarettes and only 5.1% (n=152) smoked hand-rolled straw cigarettes and/or pipe, in an amount of ≤20 cigarettes per day (50.3%), in a period longer than 20 years (82.4%), totaling 30.1 to 49 PY (27.0%) for most patients. With respect to alcohol drinking, 79.2% were ever-drinkers (44.9% current and 34.3% former drinkers) and 20.4% never drank, 57.9% had drank for a period longer than 20 years. 67.6% of the patients had consumed predominantly hard liquors (39.2% alone and 28.4% associated with fermented beverages) (**Table 3**).

For the oral cavity, male gender, ≥50 years of age at diagnosis, black race, stages III and IV, current drinkers, >20 years of drinking hard liquor, were associated with higher mortality rates at univariate analysis. When the multiple analysis was made with the statistically significant variables, the HR for all-cause mortality were adjusted for gender, age at diagnosis and tumor stage (**Table 4)**. The male gender compared with female (HR=1.31 [CI 95% 1.02-1.69] p=0.035) had higher mortality risk, just as ≥70 years of age compared with <50 years of age at diagnosis (HR=2.22 [CI 95% 1.62-3.03] p<0.001) and stages III and IV compared with stage I (IV, HR=3.98 [CI 95% 2.58-6.14] p<0.001).

For the oropharynx, male gender, ≥50 years of age at diagnosis, brown race, stage IV, current smokers, use of hand-rolled straw cigarette and/or pipe, >20 years of smoking cigarettes daily (regardless of whether greater or less than 20), ≥30.1 PY, ever-drinkers, years of drinking (regardless of whether its quantity is greater or less than 20) and ingestion of hard liquor (with or not fermentation), were all associated with higher mortality rates at univariate analysis. Patients with 11 or more years of education were associated with lower mortality rates. In the multiple-adjusted analysis, tobacco smoking lost significance as a prognostic factor. The ≥60 years of age at diagnosis compared with <50 years of age had higher mortality risk (60-69 years, HR=1.36 [CI 95% 1.08-1.71] p=0.009; ≥70 years, HR=1.84 [CI 95% 1.41-2.39] p<0.001), just as stage IV compared with stage I (HR=2.19 [CI 95% 1.43-3.36] p<0.001) and former and current drinkers (HR=1.50 [CI 95% 1.15-1.95] p=0.002 and HR=1.55 [CI 95% 1.19-2.01] p=0.001, respectively).

For the larynx, ≥70 years of age at diagnosis, stages III and IV, ever-drinkers, years of drinking (regardless if greater or less than 20 years) and ingestion of hard liquor (with or without fermentation) were all associated with higher mortality rates at univariate analysis. Those patients with 11 or more years of education were associated with lower mortality rates. In the multiple-adjusted analysis, ≥60 years of age at diagnosis compared with <50 years of age had higher mortality risk (60-69 years, HR=1.40 [CI 95% 1.05-1.87] p=0.020; ≥70 years, HR=2.06

[CI 95% 1.51-2.80] p<0.001), just as stages III and IV compared with stage I (IV, HR=3.53 [CI 95% 2.38-5.22] p<0.001) and former and current drinkers (HR=1.42 [CI 95% 1.10-1.84] p=0.008 and HR=1.30 [CI 95% 1.00-1.69] p=0.047, respectively).

For the hypopharynx, male gender, and consumption of straw cigarette and/or pipe were associated with higher mortality rates. Stages II and III were associated with lower mortality rates compared with stage I at univariate analysis. In the multiple-adjusted analysis, the mortality risk was lower among patients with stage II (HR=0.09 [CI 95% 0.01-0.96] p=0.046) compared to stage I.

Multiple analysis showed that older age and advanced tumor stage at diagnosis are strong independents prognostic factors for HNC of the oral cavity, oropharynx, and larynx. Male gender was an independent prognostic factor in oral cavity. In other words, the risk of death can be up to 122% higher in patients with 70 years of age or older compared to those under 50, and up to 298% higher in patients with stage IV compared to those with stage I, for oral cavity cancer. Another independent prognostic factor for HNC of the oropharynx and larynx, was alcohol drinking. Current drinkers have up to 55% higher risk of death compared to never drinkers, and former drinkers have up to 50% higher risk of death compared to never drinkers.

Oropharyngeal cancer patients according p16 status

At the end of the follow-up period (2010-2021), 191 (53.7%) of 356 patients with oropharyngeal cancer had died. Based on Kaplan-Meier analyses, five-year OS was estimated at 35.7% for HPV-negative oropharyngeal cancer and 58.6% for the HPV-positive counterpart. Differences between the curves are clear (log-rank test, p<0.001). HPV-positive patients had a 49% of reduction in the risk of death compared to HPV-negative patients (HR=0.51 [95% CI 0.37-0.70] p<0.001) - **Table 5** and **Figure 2**.

Descriptive characteristics of the oropharyngeal cancer sample with the mortality risk determined by univariate analysis and stratified according p16 status (**Table 6**), and for sociodemographic and clinical characteristics (**Table 7**).

Among the 356 patients with oropharyngeal cancer who had information about p16 status, 129 (36.2%) were positive and 227 (63.7%) were negative. The HPV-positive patients were mostly males (75.2%), diagnosed until 59 years of age (62.8%), white race (57.4%), married or partnered (55.0%) and formal education for 11 years or more (37.2%). They were diagnosed with advanced tumor stages (58.9% III/IV versus 41.1% I/II) and 59.7% had comorbidities at diagnosis (**Table 6**).

With respect to tobacco smoking, 69.0% were ever-smokers (34.1% current and 34.9% former smokers) and 31.0% never smoked, 95.5% of the ever-smokers, smoked cigarettes in an amount ≤20 cigarettes per day (48.1%) for a period longer than 20 years (52.7%), totaling 0.06 to 30 pack-years (36.4%) mostly. With respect to alcohol drinking, 51.9% were ever-drinkers (35.7% current and 16.3% former drinkers) and 48.1% never drank, 37.2% had drank for a period longer than 20 years and the majority (42.6%) of patients had consumed hard liquor (20.2% alone e 22.5% associated with fermented beverages) (**Table 7**). Such as HPV-negative oropharyngeal cancer patients has similar characteristics of general profile of HNSCC, they will not be cited again, but are present in **Tables 6 and 7**.

For HPV-positive oropharyngeal cancer patients, male gender, tumor stage IV, current drinkers, >20 years of drinking and consumption of hard liquor were associated with higher mortality rates at the univariate analysis. Compared to HPV-negative patients, just the tumor stages II and III were associated with lower mortality rates compared with the stage I at the univariate analysis. The multiple-adjusted analysis was not possible to perform in this group of patients due to the few variables with statistically significant p-values. Advanced tumor stage and current drinkers at diagnosis are possible prognostic factors but an adjustment would be necessary to confirm this, as performed previously for HNSCC patients.

The not reported data for all patients was presented in **Tables 2, 3, 6 and 7** with their respective variables.

Discussion

Our results revealed that survival for head and neck cancer remains low in a tertiary cancer center in Brazil and age, stage of the tumor, and alcohol drinking at diagnosis were independents unfavorable prognostic factors.

For all HNC sites the 5-year overall survival was 33.7% with a mean of approximately 23 months after diagnosis. The hypopharynx was the site with the worst OS (15.5%) and the larynx with the best (40.1%). The OS in Brazil was reported in others studies with low rates [19,30,46] compared to developed countries that the OS for all HNC sites were more than 50% [13,21,26,29,32,39], with one exception [47]. In the same institution, treating patients of a more privileged socioeconomical status and with less advanced disease at diagnosis, the survival rates were also higher than the observed in this study [48]. On the other side, a recent epidemiological study, including preferably patients treated in the public system, conducted in the State of São Paulo, Brazil by Louredo et al. (2022)[46] found a 5-year OS for patients with oral cavity and oropharyngeal cancer in 30.9 and 22.6%, respectively. Our study obtained similar results,

38.5% for oral cavity and 28% for oropharyngeal cancer, but these rates are higher than 50% in developed countries [21,32,39]. An analysis of patients with stage III larynx tumors treated in the State of São Paulo, Brazil, also confirmed the low survival rates of patients treated, especially with non-surgical treatment options [49].

The poor survival is mainly due to older age and the advanced stage of the tumor at diagnosis, which is mostly late. The diagnosis delay is because of malignant neoplasms in their early stages do not present painful symptoms and the most patients seek medical attention when the tumor is already advanced [46,50,51]. Brazil has the "Sistema Único de Saúde (SUS)", a health and unified program, completely cost-free for the entire population, where all the patients reported in this study were initially screened in a basic health unit (primary care), biopsied, and after their definitive diagnosis of cancer were referred for treatment in tertiary care. This process often delays in the diagnosis and the initiation of treatment, thus favoring the progression of the disease [46,50] In addition, the advanced tumor stage at diagnosis can be explained by the smoking status and low education level of the patients who have less access to information about health-related issues [16,31,51–53]. This reflects the need for more effective public policies, such as primary and secondary prevention programs, aiming to increase the survival of the oncological patient.

Most patients with HNC are older and have a history of smoking and drinking for a long period in their lives. They concomitantly present with multiple comorbidities at diagnosis resulting from this lifestyle, such as cardiac and pulmonary diseases. The presence of advanced tumor stage with regional metastases and the therapeutic delay resulting from the patient's systemic condition decreases significantly the HNC survival [54]. The effect of comorbidities is remarkable, especially in older patients [55,56]. This was another factor for the poor survival in our study, since 54% of the patients had comorbidities at the time of cancer diagnosis.

The advanced tumor stage and older age of patients with HNC at diagnosis are already known unfavorable independent prognostic factors for survival [13,16,20,22,31,32,36,37,39,42] and our study agreed with this, through a multiple analysis adjusted for gender, age, stage and lifestyle, where there were higher mortality rates for patients ≥60 years and in stages III/IV mainly in the oral cavity, oropharynx and larynx HNC sites.

Tobacco smoking and alcohol drinking are well-known risk factors for HNC [6–9] but the implications of these two factors in disease prognosis are not completely clear. There are many survival studies that investigated the mortality impact of smoking and drinking at diagnosis. They describe a dose-dependent increase in mortality risk with increasing exposure to tobacco and alcohol pre-diagnosis [16,26,28,29,31,33–36,38,57]. However, not all of them

have performed this investigation through stratification into sites, since each site of HNC has a different prognosis and mortality risk.

In our study, drinking history (current or former drinkers) at the time of HNC diagnosis was also an unfavorable independent prognostic factor for the oropharynx and larynx sites. Similar to studies that found a strong relationship of current and former drinkers in the increased risk of death at the larynx/hypopharynx [13,22,30], and oropharynx sites compared with never drinkers [27], mainly were made in Latin America [13,22,30], with the exception of one that was conducted in Taiwan [27]. Most of the studies that found drinking as an unfavorable independent prognostic factor in laryngeal cancer site were performed in Brazil [13,22,30] where the alcohol consumption is higher compared to other countries [58].

Others studies that evaluated prognostic factors stratified by HNC sites, revealed that the role of smoking remains unclear. Current and former smokers with a history of ≥20 pack-years, had an increased the risk of mortality in all sites of HNC: oral cavity [22,39] oropharynx [13,22,41] and larynx associated or not with hypopharynx [39,41]. In our study, smoking was an unfavorable prognostic factor only in the univariate analysis for the oropharyngeal site. This finding lost significance after adjustments but cannot be excluded.

Black and brown races were unfavorable prognostic factors in univariate analysis, for the oral cavity and oropharynx sites, respectively. Clarke et al. (2020) [59] found that blacks, especially those living in rural areas, have lower HNC survival compared to whites living in urban areas. São Paulo has many black and brown residents who come from rural areas in search of better working conditions. Russo et al. (2020) [60] also found similar results even after controlling for socioeconomic factors.

Due to the new tumor stage classification (AJCC Staging System, 8th edition)[45] implemented in January 2018, just 28% of patients with oropharyngeal cancers had the p16 status during the period that the present study data collection was performed (2011-2021). Thus, a separate survival analysis was necessary. The OS for this group showed a high survival rate for HPV positive with oropharyngeal cancer compared with the HPV negative counterpart. This is in agreement with previously performed studies [5,15,16,18,19,21,22].

The clinicopathologic profile of HPV-positive OPC patients reveals nonsmoking and nondrinking younger men with higher schooling level and with a history of multiple oral sex partners [5]. Among the HPV-positive patients who are current smokers, the risk of death is higher compared to never smokers [15,17,18,40]. Our study reported that most HPV-positive patients were ever-smokers (69%) and ever-drinkers (52%). The univariate analysis showed that current drinkers of hard liquor in a period longer than 20 years had a higher mortality risk

compared to never drinkers. Smoking was not a prognostic factor, going against other published studies. The multiple analysis could not be performed due to the low number of significant variables among the patients with oropharyngeal cancer and this would be necessary to confirm the independent prognostic factors. Only one study conducted in 2018 [41] was able to investigate the interactions between smoking, alcohol and HPV status in determining mortality risk among patients with oropharyngeal cancer. This study, found that moderate and harmful alcohol consumption at diagnosis was an independent prognostic factor for HPV-negative patients. HPV-positive patients had no significant values after adjustments. Given the limited number of studies investigating the interactions between smoking, alcohol and HPV status, in determining mortality risk among survivors of HNSCC by subsites, more investigations are needed. And at last, every health professional should encourage tobacco smoking and alcohol drinking cessation during routine consultations in order to improve survival rates.

Limitations of the study

The participants of this study were enrolled from a single Cancer Center in Brazil, limiting their generalizability. The assessments of tobacco smoking and alcohol drinking intake were based on participants' self-reports. Prior study has shown that discrepancies between self-reported (4–7%) and biochemically verified (13–29%) rates of smoking and drinking exist [61]. Thus, data may be missing or are not true. Whilst the sample size was sufficient to detect the main effects of baseline smoking status and alcohol intake on survival, it was insufficient to examine interactions between these two exposures and HPV status in determining mortality. Moreover, we did not have data on patient's behaviors after the diagnosis, which may have affected the overall survival.

Conclusion

This study showed that older age, advanced tumor stages, alcohol drinking history at diagnosis were independent and unfavorable prognostic factors of the overall survival in head and neck cancer, especially in oropharynx and larynx sites. The analyses for oropharyngeal cancers according with HPV status were inconsistent, requiring further studies in this area.

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Authors contributions

Ana Letícia Mores: Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Validation; Visualization; Writing – Original draft preparation. **Carolina Guimarães Bonfim-Alves**: Methodology; Validation. **Rossana Verónica Mendoza López**: Formal analysis; Validation. **Leticia Rodrigues-Oliveira**: Data curation; Methodology. **Bruno Augusto Linhares Almeida Mariz**: Formal analysis. **Natália Rangel Palmier**: Writing – Review & editing. **Cesar Augusto Migliorati**: Review & editing. **Luiz Paulo Kowalski**: Review & editing. **Thaís Bianca Brandão**: Writing – Review & editing. **Alan Roger Santos-Silva**: Writing – Review & editing. **Ana Carolina Prado-Ribeiro:** Conceptualization; Data curation; Supervision; Writing – Review & editing.

Data availability

Data available within the article and its supplementary materials.

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Figures and Tables

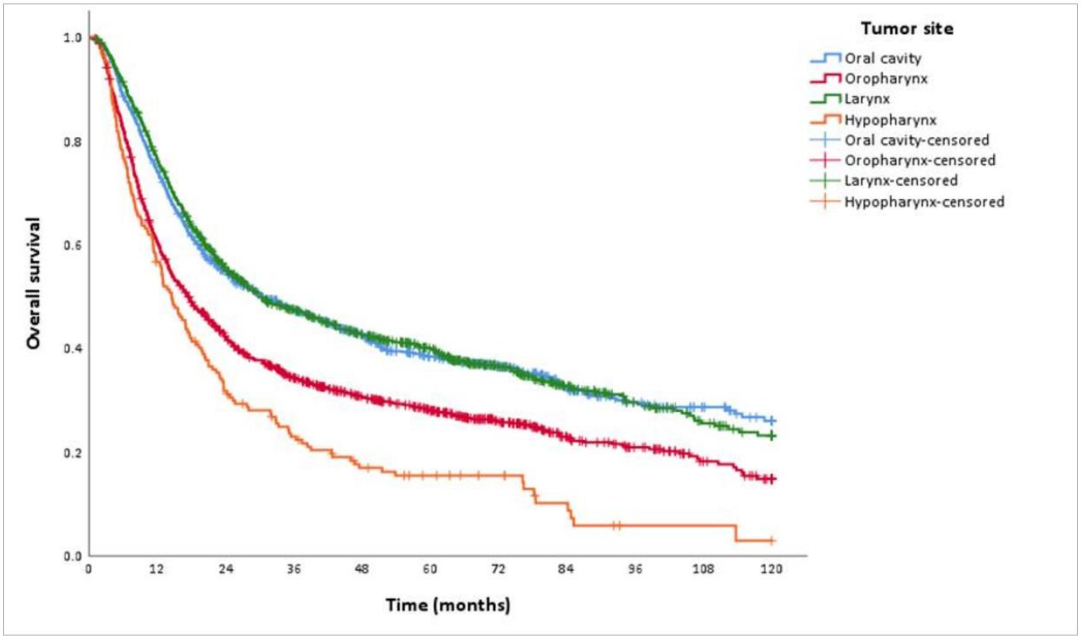

Figure 1. Ten-year overall survival head and neck cancer according tumor site (1984-2021).

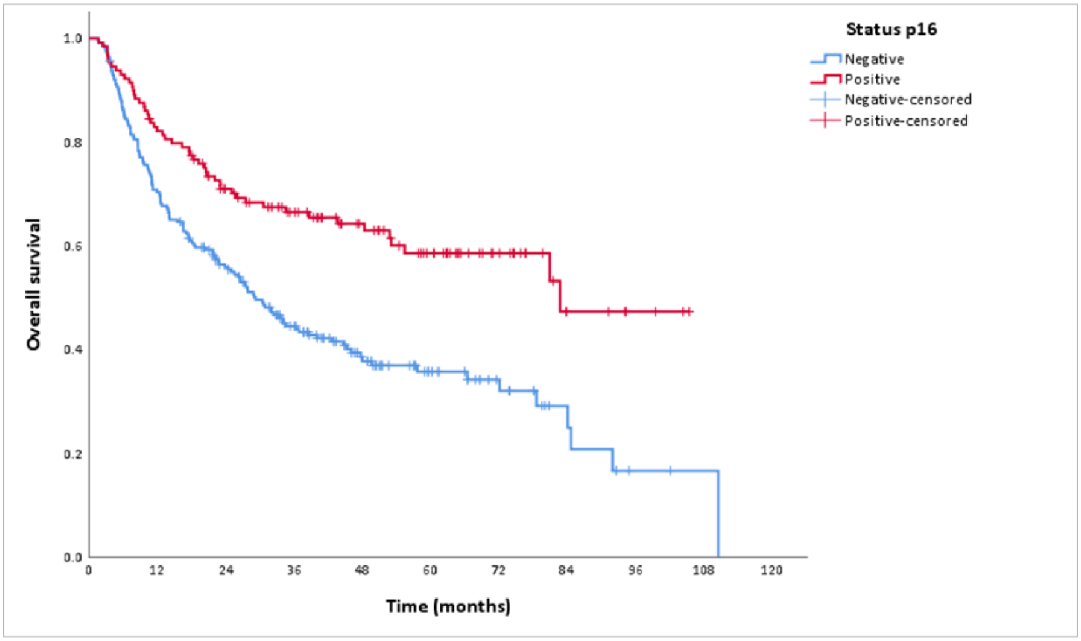

Figure 2. Ten-year overall survival oropharyngeal cancer according p16 status (2010-2021).

Table 1. Probability of overall survival at 1, 5, and 10 years for HNSCC patients by tumor site (1984-2021):

	Deaths/Total	Median (months)	Probability of survival			p-value[1]
			1-year	5-year	10-year	
All cases	2234/3275	23.1	68.8%	33.7%	19.7%	
Tumor site						<0.001
Oral cavity	527/832	30.1	74.3%	38.5%	26.0%	
Oropharynx	922/1261	17.5	60.6%	28.0%	14.8%	
Larynx	636/1011	30.5	76.5%	40.1%	23.2%	
Hypopharynx	149/171	14.6	56.7%	15.5%	2.9%	

[1] Log-rank test.

Table 2. Sociodemographic and clinical characteristics of HNSCC patients by tumor site and predictors of OS among univariate analysis (1984-2021):

Univariate	**HNSCC[a] n**	**n = 3275 %**	**Oral Cavity HR**	**n = 832 95% CI**	**Oropharynx HR**	**n = 1261 95% CI**	**Larynx HR**	**n = 1011 95% CI**	**Hypopharynx HR**	**n = 171 95% CI**
Gender										
Female	522	(15.93)	1		1		1		1	
Male	2753	(84.06)	**1.24**	**(1.01-1.53)**	**1.43**	**(1.17-1.75)**	1.24	(0.97-1.60)	**1.76**	**(1.03-3.00)**
Age at diagnosis										
<50 years	418	(12.76)	1		1		1		1	
50-59 years	1177	(35.93)	**1.36**	**(1.01-1.82)**	**1.41**	**(1.12-1.76)**	1.03	(0.78-1.37)	1.30	(0.81-2.09)
60-69 years	1114	(34.01)	**1.35**	**(1.00-1.82)**	**1.51**	**(1.20-1.89)**	1.12	(0.85-1.48)	1.04	(0.65-1.68)
≥70 years	566	(17.28)	**2.15**	**(1.58-2.91)**	**1.91**	**(1.47-2.48)**	**1.51**	**(1.12-2.03)**	1.44	(0.80-2.59)
Marriaged										
Single	735	(22.44)	1		1		1		1	
Married/partnered	1685	(51.45)	0.84	(0.68-1.05)	0.91	(0.78-1.07)	0.89	(0.72-1.10)	0.77	(0.52-1.13)
Separated/divorced	534	(16.30)	0.90	(0.67-1.21)	1.17	(0.96-1.43)	1.16	(0.90-1.51)	0.92	(0.57-1.47)
Widowed	299	(9.12)	1.17	(0.88-1.56)	1.28	(0.99-1.65)	1.14	(0.83-1.56)	0.66	(0.32-1.35)
Not reported	22	(0.67)								
Race										
White	1797	(54.87)	1		1		1		1	
Black	710	(21.67)	**1.42**	**(1.15-1.76)**	1.15	(0.98-1.35)	1.04	(0.85-1.26)	1.31	(0.86-2.01)
Brown	743	(22.68)	0.96	(0.77-1.21)	**1.21**	**(1.04-1.42)**	1.02	(0.84-1.25)	1.03	(0.70-1.52)
Yellow	14	(0.42)	0.87	(0.32-2.33)	0.36	(0.05-2.59)	1.76	(0.57-5.49)	1.89	(0.26-13.67)
Not reported	11	(0.33)								
Years of education										
0-3 years	360	(10.99)	1		1		1		1	
4-10 years	1150	(35.11)	0.96	(0.72-1.29)	0.85	(0.69-1.05)	0.88	(0.67-1.16)	0.96	(0.53-1.73)
11 or more years	446	(13.61)	0.75	(0.53-1.06)	**0.60**	**(0.46-0.79)**	**0.70**	**(0.49-0.99)**	0.80	(0.40-1.60)
Not reported	1319	(40.27)								
Stage										
Stage I	197	(6.01)	1		1		1		1	
Stage II	202	(6.16)	1.41	(0.80-2.46)	**0.51**	**(0.28-0.92)**	1.36	(0.78-2.40)	**0.08**	**(0.01-0.74)**
Stage III	455	(13.89)	**1.77**	**(1.06-2.94)**	1.10	(0.69-1.75)	**1.55**	**(1.01-2.40)**	**0.12**	**(0.01-0.96)**
Stage IV	2392	(73.03)	**4.09**	**(2.66-6.28)**	**2.51**	**(1.64-3.83)**	**3.22**	**(2.19-4.75)**	0.23	(0.03-1.67)
Not reported	29	(0.88)								
Comorbidity										
No	1474	(45.00)	1		1		1		1	
Yes	1748	(53.37)	1.01	(0.85-1.21)	0.94	(0.83-1.07)	1.00	(0.86-1.17)	1.08	(0.78-1.50)

Not reported	53	(1.61)

[a]Number of subject and percentages is referred to all HNSCC sites together;
HNSCC: Head and Neck Squamous Cell Carcinoma; HR (95%CI): hazard ratio (95% confidence interval);
Text in bold indicates statistically significant risk factors.

Table 3. Lifestyle characteristics of HNSCC patients by tumor site and predictors of OS among univariate analysis (1984-2021):

Univariate	HNSCC[a] n	n = 3275 %	Oral cavity HR	n = 832 95% CI	Oropharynx HR	n = 1261 95% CI	Larynx HR	n = 1011 95% CI	Hypopharynx HR	n = 171 95% CI
Smoking status										
Never smoker	308	(9.40)	1		1		1		1	
Former smoker	791	(24.15)	1.06	(0.81-1.40)	1.20	(0.88-1.64)	0.86	(0.60-1.21)	1.46	(0.65-3.28)
Current smoker	2176	(66.44)	1.04	(0.92-1.31)	**1.89**	**(1.43-2.51)**	1.15	(0.83-1.60)	1.62	(0.75-3.50)
Tobacco type										
Cigarette and others	2788	(85.12)	1		1		1		1	
Straw cigarette and/or pipe	152	(4.64)	1.24	(0.90-1.72)	**1.54**	**(1.15-2.06)**	0.91	(0.58-1.42)	**4.85**	**(1.94-12.11)**
Years of smoking										
Never smoker	308	(9.40)	1		1		1		1	
≤20 years	231	(7.05)	1.00	(0.69-1.46)	0.99	(0.66-1.48)	0.69	(0.44-1.10)	1.73	(0.69-4.38)
>20 years	2698	(82.38)	1.04	(0.82-1.30)	**1.75**	**(1.32-2.31)**	1.08	(0.78-1.49)	1.54	(0.72-3.30)
Not reported	38	(1.16)								
Cigarettes/day										
Never smoker	308	(9.40)	1		1		1		1	
≤20 cigarettes	1646	(50.25)	1.07	(0.84-1.36)	**1.69**	**(1.27-2.25)**	1.03	(0.74-1.43)	1.23	(0.56-2.69)
>20 cigarettes	1141	(34.83)	0.94	(0.73-1.22)	**1.58**	**(1.18-2.12)**	1.08	(0.77-1.51)	1.95	(0.89-4.25)
Not reported	180	(5.49)								
Pack-years										
Never smoker (≤0.05 PY)	308	(9.40)	1		1		1		1	
0.06-30 PY	663	(20.24)	1.05	(0.79-1.40)	1.31	(0.96-1.79)	0.82	(0.57-1.19)	1.29	(0.55-3.01)
30.1-49 PY	885	(27.02)	1.01	(0.78-1.33)	**1.88**	**(1.40-2.53)**	1.08	(0.76-1.54)	1.25	(0.56-2.79)
49.1-75 PY	671	(20.48)	0.91	(0.67-1.23)	**1.70**	**(1.25-2.30)**	1.15	(0.81-1.65)	2.01	(0.89-4.55)
>75 PY	701	(21.40)	1.13	(0.86-1.50)	**1.80**	**(1.32-2.45)**	1.12	(0.79-1.58)	1.91	(0.85-4.29)
Not reported	47	(1.43)								
Drinking status										
Never drinker	670	(20.45)	1		1		1		1	
Former drinker	1124	(34.32)	1.22	(0.97-1.54)	**1.83**	**(1.46-2.29)**	**1.54**	**(1.23-1.92)**	1.46	(0.82-2.60)
Current drinker	1471	(44.91)	**1.40**	**(1.14-1.73)**	**2.08**	**(1.68-2.59)**	**1.43**	**(1.15-1.78)**	1.45	(0.81-2.57)
Not reported	10	(0.30)								
Years of drinking										

Never drinker	670	(20.45)	1		1		1		1	
≤20 years	330	(10.07)	1.03	(0.73-1.45)	**1.57**	**(1.17-2.11)**	**1.39**	**(1.04-1.86)**	1.31	(0.65-2.60)
>20 years	1897	(57.92)	**1.26**	**(1.03-1.54)**	**2.00**	**(1.61-2.47)**	**1.45**	**(1.18-1.80)**	1.36	(0.77-2.38)
Not reported	378	(11.54)								
Type of alcoholic beverages										
Never drinker	670	(20.45)	1		1		1		1	
Fermented	251	(7.66)	0.95	(0.65-1.37)	1.34	(0.97-1.85)	1.05	(0.75-1.48)	0.93	(0.39-2.22)
Hard liquor	1283	(39.17)	**1.43**	**(1.15-1.77)**	**2.05**	**(1.64-2.57)**	**1.50**	**(1.21-1.87)**	1.29	(0.73-2.31)
Fermented + hard liquor	930	(28.39)	1.22	(0.96-1.55)	**1.94**	**(1.54-2.44)**	**1.48**	**(1.17-1.87)**	1.68	(0.92-3.07)
Not reported	141	(4.30)								

[a]Number of subject and percentages is referred to all HNSCC sites together; HNSCC:
Head and Neck Squamous Cell Carcinoma; HR (95%CI): hazard ratio (95% confidence interval);
Text in bold indicates statistically significant risk factors.

Table 4. Sociodemographic, clinical and lifestyle characteristics of HNSCC patients by tumor site and predictors of OS among multiple analysis (1984-2021):

Multiple	**HNSCC[a] n**	**n = 3275 %**	**Oral cavity HR**	**n = 832 95% CI**	**Oropharynx HR**	**n = 1261 95% CI**	**Larynx HR**	**n = 1011 95% CI**	**Hypopharynx HR**	**n = 171 95% CI**
Gender										
Female	522	(15.93)	1		1		1		1	
Male	2753	(84.06)	**1.31**	**(1.02-1.69)**	1.09	(0.88-1.34)	1.15	(0.87-1.54)	1.62	(0.78-3.34)
Age at diagnosis										
<50 years	418	(12.76)	1		1		1		1	
50-59 years	1177	(35.93)	1.25	(0.92-1.69)	1.18	(0.94-1.49)	1.09	(0.82-1.45)	1.24	(0.76-2.00)
60-69 years	1114	(34.01)	1.31	(0.96-1.77)	**1.36**	**(1.08-1.71)**	**1.40**	**(1.05-1.87)**	1.16	(0.70-1.91)
≥70 years	566	(17.28)	**2.22**	**(1.62-3.03)**	**1.84**	**(1.41-2.39)**	**2.06**	**(1.51-2.80)**	1.50	(0.82-2.74)
Stage										
Stage I	197	(6.01)	1		1		1		1	
Stage II	202	(6.16)	1.38	(0.79-2.42)	**0.48**	**(0.37-0.87)**	1.39	(0.79-2.44)	**0.09**	**(0.01-0.96)**
Stage III	455	(13.89)	**1.70**	**(1.02-2.85)**	1.00	(0.63-1.60)	**1.65**	**(1.07-2.55)**	0.13	(0.02-1.10)
Stage IV	2392	(73.03)	**3.98**	**(2.58-6.14)**	**2.19**	**(1.43-3.36)**	**3.53**	**(2.38-5.22)**	0.25	(0.03-1.82)
Smoking status										
Never	308	(9.40)	1		1		1		1	
Former	231	(7.05)	0.82	(0.58-1.16)	0.77	(0.55-1.08)	0.67	(0.46-0.97)	0.97	(0.36-2.57)
Current	2698	(82.38)	0.73	(0.52-1.01)	1.12	(0.81-1.55)	0.96	(0.67-1.38)	1.12	(0.43-2.92)
Drinking status										
Never	670	(20.45)	1		1		1		1	
Former	330	(10.07)	1.05	(0.78-1.43)	**1.50**	**(1.15-1.95)**	**1.42**	**(1.10-1.84)**	0.78	(0.35-1.72)
Current	1897	(57.92)	1.27	(0.94-1.72)	**1.55**	**(1.19-2.01)**	**1.30**	**(1.00-1.69)**	0.79	(0.351.77)

[a]Number of subject and percentages is referred to all HNSCC sites together;
HNSCC: Head and Neck Squamous Cell Carcinoma; HR (95%CI): hazard ratio (95% confidence interval);
HR adjusted by gender, age and stage at diagnosis, and smoking and drinking status;
Text in bold indicates statistically significant risk factors.

Table 5. Probability of overall survival at 1, 5, and 10 years for oropharyngeal cancer according to p16 status (2010-2021):

	Deaths/Total	Median (months)	Probability of survival			p-value[1]
			1-year	5-year	10-year	
p16 status						<0.001
Negative	141/227	3.1	70.4%	35.7%	0%	
Positive	50/129	NA	82.1%	58.6%	47.3%	

[1] Log-rank test. NA: not available.

Table 6. Sociodemographic and clinical characteristics of oropharyngeal cancer according to p16 status and predictors of OS among univariate analysis (2010-2021):

Univariate	**Oropharynx p16+[a]**		**n= 129**		**Oropharynx p16-[a]**		**n=227**	
	n	**%**	**HR**	**IC 95%**	**n**	**%**	**HR**	**IC 95%**
Gender								
Female	32	(24.80)	1		26	(11.45)	1	
Male	97	(75.19)	**2.83**	**(1.21-6.65)**	201	(88.54)	1.03	(0.61-1.74)
Age at diagnosis								
<50 years	29	(22.48)	1		21	(9.25)	1	
50-59 years	52	(40.31)	1.05	(0.50-2.20)	91	(40.08)	0.81	(0.44-1.50)
60-69 years	37	(28.68)	1.13	(0.52-2.46)	86	(37.88)	1.15	(0.63-2.09)
≥70 years	11	(8.52)	1.31	(0.46-3.78)	29	(12.77)	1.57	(0.79-3.13)
Marriaged								
Single	32	(24.80)	1		54	(23.78)	1	
Married/partnered	71	(55.03)	0.96	(0.49-1.89)	117	(51.54)	0.69	(0.45-1.04)
Separated/divorced	23	(17.82)	1.61	(0.71-3.64)	36	(15.85)	0.96	(0.57-1.61)
Widowed	3	(2.32)	NA		18	(7.92)	1.27	(0.69-2.36)
Not reported	0	0			2	(0.88)		
Race								
White	74	(57.36)	1		106	(46.69)	1	
Black	24	(18.60)	0.87	(0.39-1.93)	66	(29.07)	0.85	(0.57-1.26)
Brown	30	(23.25)	1.58	(0.84-2.99)	54	(23.78)	0.81	(0.53-1.24)
Yellow	0	0	NA		1	(0.44)	0.59	(0.08-4.33)
Not reported	1	(0.77)			0	0		
Years of education								
0-3 years	8	(6.20)	1		37	(16.29)	1	
4-10 years	40	(31.00)	0.44	(0.14-1.36)	109	(48.01)	0.86	(0.53-1.38)
11 or more years	48	(37.20)	0.41	(0.13-1.24)	38	(16.74)	0.93	(0.51-1.68)
Not reported	33	(25.58)			43	(18.94)		
Stage								
Stage I	20	(15.50)	1		4	(1.76)	1	
Stage II	33	(25.58)	0.40	(0.11-1.49)	10	(4.40)	**0.21**	**(0.05-0.86)**
Stage III	67	(51.93)	2.18	(0.85-5.61)	30	(13.21)	**0.27**	**(0.08-0.92)**
Stage IV	9	(6.97)	**9.60**	**(3.16-29-14)**	183	(80.61)	0.42	(0.13-1.32)
Comorbidity								
No	52	(40.31)	1		108	(47.57)	1	
Yes	77	(59.68)	0.62	(0.36-1.09)	119	(52.42)	1.13	(0.81-1.58)

[a]Number of subject and percentages is referred to all oropharyngeal cancer according to p16 status together;

HR (95%CI): hazard ratio (95% confidence interval);
Text in bold indicates statistically significant risk factors.

Table 7. Lifestyle characteristics of oropharyngeal cancer according to p16 status and predictors of OS among univariate analysis (2010-2021):

Univariate	**Oropharynx p16+[a]**		**n= 129**		**Oropharynx p16-[a]**		**n=227**	
	n	**%**	**HR**	**IC 95%**	**n**	**%**	**HR**	**IC 95%**
Smoking status								
Never smoker	40	(31.00)	1		7	(3.08)	1	
Former smoker	45	(34.88)	0.59	(0.27-1.28)	54	(23.78)	0.51	(0.21-1.24)
Current smoker	44	(34.10)	1.77	(0.93-3.39)	166	(73.12)	0.66	(0.29-1.50)
Tobacco type								
Cigarette and others	85	(95.50)			206	(93.63)	1	
Straw cigarette and/or pipe	4	(4.49)	NA		14	(6.36)	1.85	(0.91-3.80)
Years of smoking								
Never smoker	40	(31.00)	1		7	(3.08)	1	
≤20 years	21	(16.27)	0.72	(0.28-1.85)	12	(5.28)	0.80	(0.27-2.39)
>20 years	68	(52.71)	1.21	(0.65-2.26)	206	(90.74)	0.60	(0.27-1.37)
Not reported	0	0			2	(0.88)		
Cigarettes/day								
Never smoker	40	(31.00)	1		7	(3.08)	1	
≤20 cigarettes	62	(48.06)	1.08	(0.57-2.05)	129	(56.82)	0.66	(0.29-1.52)
>20 cigarettes	26	(20.15)	1.19	(0.54-2.66)	81	(35.68)	0.51	(0.22-1.20)
Not reported	1	(0.77)			10	(4.40)		
Pack-years								
Never smoker (≤0.05 PY)	40	(31.00)	1		7	(3.08)	1	
0.06-30 PY	47	(36.43)	1.04	(0.52-2.06)	45	(19.82)	0.67	(0.28-1.61)
30.1-49 PY	18	(13.95)	1.32	(0.58-3.01)	76	(33.48)	0.63	(0.27-1.48)
49.1-75 PY	14	(10.85)	1.05	(0.38-2.89)	48	(21.14)	0.59	(0.24-1.44)
>75 PY	10	(7.75)	0.90	(0.26-3.12)	49	(21.58)	0.55	(0.23-1.32)
Not reported	0	0			2	(0.88)		
Drinking status								
Never drinker	62	(48.06)	1		19	(8.37)	1	
Former drinker	21	(16.27)	1.90	(0.81-4.42)	87	(38.32)	0.84	(0.45-1.56)
Current drinker	46	(35.65)	**2.49**	**(1.34-4.62)**	121	(53.30)	1.13	(0.63-2.03)
Years of drinking								
Never drinker	62	(48.06)	1		19	(8.37)	1	
≤20 years	11	(8.52)	2.15	(0.79-5.85)	21	(9.25)	0.58	(0.25-1.36)
>20 years	48	(37.20)	**2.37**	**(1.27-4.42)**	176	(77.53)	1.06	(0.59-1.88)
Not reported	8	(6.20)			11	(4.84)		
Type of alcoholic beverages								

Never drinker	62	(48.06)	1		19	(8.37)	1	
Fermented	11	(8.52)	1.44	(0.48-4.29)	17	(7.48)	0.79	(0.35-1.81)
Hard liquor	26	(20.15)	**2.98**	**(1.48-5.98)**	91	(40.08)	0.90	(0.49-1.65)
Fermented + hard liquor	29	(22.48)	2.05	(0.99-4.25)	95	(41.85)	1.11	(0.61-2.02)
Not reported	1	(0.77)			5	(2.20)		

[a]Number of subject and percentages is referred to all oropharyngeal cancer according to p16 status together;
HR (95%CI): hazard ratio (95% confidence interval);
Text in bold indicates statistically significant risk factors

2.2 ARTIGO: IMPACT OF CIGARETTE TAXES AND PRICES ON THE PREVALENCE OF TOBACCO SMOKING IN LATIN AMERICA: A SYSTEMATIC REVIEW.

CAPÍTULO 2 – Artigo submetido para publicação no periódico Respiratory Medicine – Editora Elsevier (Anexo 3)

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ABSTRACT

Introduction The present systematic review (SR) aimed to analyze the impact of cigarette taxes and prices on the prevalence of tobacco smoking in Latin America countries.

Methods The methods of this SR were previously established and registered in PROSPERO (CRD42022319407) and was reported according to the PRISMA checklist. The searches were made in 5 databases (PubMed/MEDLINE, Scopus, Embase, Web of Science and LILACS) in addition to the grey literature, without limitation of year, and published in English, Spanish or Portuguese. Studies which analyzed cigarette taxes and prices on tobacco smoking prevalence in Latin America were eligible for inclusion. The study selection was conducted in two phases by two independently reviewers.

Results Seven observational studies conducted in Brazil, Mexico and Colombia were included in the qualitative analysis. The risk of bias (RoB) of each study was assessed using the Joanna Briggs Institute checklist. All studies found that an increase in excise taxes of cigarette led to an increase in the retail price. Four studies (57.1%) reported that increasing cigarette taxes and prices was effective to decrease the prevalence of tobacco smoking. The included studies were graded as having a low (57.1%) or moderate (42.8%) RoB.

Conclusions The use of cigarette taxes and prices measures are effective tools to reduce the prevalence of tobacco smoking. However, it is vital the development of further research on this topic in other countries of Latin America since the included studies were performed only in Brazil, Colombia and Mexico.

Keywords Latin America, Tobacco, Cigarette, Smoking, Price and Tax.

INTRODUCTION

There are 1.3 billion smokers in the world, and over eighty percent live in low- and middle-income countries [1,2]. Smoking is the leading risk factor for death from chronic noncommunicable diseases, accounting for more than eight million deaths a year [1,3]. This risk factor is associated with 75% of causes related to chronic obstructive pulmonary disease (COPD) and 22% and 10% of deaths in adults from cancer, and cardiovascular diseases, respectively [2]. Still, around 1.2 million of death are the result of non-smokers being exposed to second-hand smoke [1,2]. Thus, it is clear that tobacco consumption is an important public health issue, and preventive regulatory actions can substantially influence aggregate smoking in the long-term [4].

The mounting evidence of the enduring destruction caused by tobacco in the 20th century provided compelling reasons for a strong global response, which led countries to negotiate with the World Health Organization Framework Convention on Tobacco Control (WHO FCTC) in 2003 [5]. The WHO FCTC came into force in 2005 as the first public health treaty under the auspices of WHO, currently, 182 countries have ratified this treaty [1]. To facilitate its implementation at the country level, WHO packaged a set of interventions, named as MPOWER: (M) monitoring tobacco use and prevention policies; (P) protecting people with smoke-free laws; (O) offering help to quit tobacco use (cessation services); (W) warning about the dangers of tobacco; (E) enforcing bans on tobacco advertising, promotion and sponsorship; and (R) raising taxes on tobacco products [4-11].

Raising the price of cigarettes through taxation is considered as a highly cost-effective measure for controlling tobacco use and its consequences [3,5,12,13]. Higher prices encourage people to try quitting smoking, which increases the number and success of attempts. They also prevent people, especially youth, from taking up the habit, discourage former smokers from relapsing, and cause people who continue to smoke to cut back [5,14-17].

The excise taxes are overall divided into specific and ad valorem. A specific excise tax is levied based on quantity (e.g., a fixed amount per cigarette or weight of tobacco), while an ad valorem excise is levied based on value (e.g., a percentage of the factory price or retail price) [11,12,18]. Globally, taxes applied to cigarettes account for over half of the average price of cigarettes, varying from about 65.5% in high-income countries to 40.8% in low-income countries [4,12,18].

Promotion of the tobacco control agenda in public policy requires tools that simulate the impact of tax hikes. However, current exercises are based on estimates of the number of cigarettes consumed per day (intensive margin) for the total population. While such estimates are appropriate in a general sense, it is impossible to provide specific group impacts that are desirable for inequality analysis and projections [4]. Moreover, current national estimates are restricted to the intensity of consumption [4,19,20]. This scenario limits the ability of researchers to assess potential impacts on the prevalence of tobacco use (extensive margin) [4].

Therefore, this systematic review aims to analyze the impact of cigarette taxes and prices on tobacco smoking prevalence in Latin America (extensive margin) and not related about the impact of taxes and prices on the consumption of tobacco products (intensive margin), as approached by Guindon et al. (2015) [19]. Thus, we aimed to integrate the available evidence to answer the focused review question: “What is the impact of cigarette taxes and prices on the prevalence of tobacco smoking in Latin America countries?”.

METHODS

Eligibility criteria

Inclusion and exclusion criteria

The PECOS acronym (**p**opulation, **i**ntervention, **c**omparison, **o**utcome and **s**tudies design) was used to formulate the focused question and eligibility criteria of this SR, in which: **(P)** Latin America countries (Argentina, Bolivia, Brazil, Chile, Colombia, Costa Rica, Cuba, Ecuador, El Salvador, Guatemala, Haiti, Honduras, Mexico, Nicaragua, Panama, Paraguay, Peru, Dominican Republic, Uruguay, and Venezuela); **(I)** Higher cigarette taxes and prices; **(C)** Lower cigarette taxes and prices or no comparison; **(O)** Prevalence of tobacco smoking; and **(S)** Randomized/non-randomized clinical trials and observational studies (cross-sectional, cohort, case-control, ecological studies and case series with at least 10 cases).

Exclusion criteria

(1) Reviews, letters, posters, conference abstracts, study protocols, book, personal opinions, laboratory research; (2) Studies in other language than English, Spanish or Portuguese; (3) Studies that did not analyze the impact of cigarette taxes and prices on the prevalence of tobacco smoking in Latin America countries; (4) Studies that analyzed the impact of cigarette taxes and prices on tobacco smoking prevalence but not in Latin America countries; (5) Studies whose full texts were not available; (6) Studies that did not clearly report or could not be calculated the association of cigarette taxes and prices on prevalence of tobacco smoking/Poor delimitation; (7) Studies 'predicting' the impact of cigarette taxes and prices changes with prevalence simulation (economic studies).

Information sources and search strategy

Electronic search strategies were developed for each databases on April 23th, 2022: PubMed/MEDLINE, Scopus, Embase, Web of Science, and LILACS without limitation of year and published in English, Spanish or Portuguese. An additional search in grey literature including Google Scholar and ProQuest, as well as manual search across reference lists of included studies were performed (Supplementary material, **Appendix S1**). The retrieved studies were imported into the Endnote Web reference manager (Endnote Web, Clarivate Analytics, Philadelphia, PA), where duplicate references were removed.

Study selection

A two-phase process was applied to the study selection. In the first phase, two reviewers (A.L.M. and M.E.P.O.) independently selected articles based on reading titles and abstracts retrieved from databases, using an on-line software (Rayyan®, Qatar Computing Research

Institute) [21]. In the second phase, the same reviewers applied the eligibility criteria to the full text of studies. A third reviewer (A.R.S.S.) was consulted in case of disagreement.

Data collection process and data items

The data collection was performed by one reviewer (A.L.M.) and cross-checked by a second reviewer (M.E.P.O.). Information regarding author, year of publication, country, study design, sample size, age range, study period and follow-up, year of the tax reform, values, taxes and retail prices of cigarettes, tobacco smoking prevalence and main conclusion were collected from the included studies.

Risk of bias assessment

The risk of bias (RoB) assessment of selected studies was evaluated independently by two reviewers (A.L.M. and M.E.P.O.) using the Joanna Briggs Institute Critical Appaisal Checklist for Analytical Cross-Sectional Studies and Cohort Studies [22]. The RoB of each study was characterized according to the following: “high” when the study reached up to 49% score “yes”; “moderate” when the study reached 50% to 69% score “yes”; and “low” when the study reached at least 70% score “yes”. Divergences were resolved by mutual agreement. A third reviewer (A.R.S.S.) was consulted in case of disagreements.

Summary measures

The primary outcome of this study was to assess the impact of the increase cigarette taxes and prices on decrease tobacco smoking prevalence in Latin America. The prevalence of tobacco smoking, expressed by means of relative or absolute frequencies and its 95% confidence intervals (CI) in included studies, was considered and analyzed as the main outcome.

Synthesis of results

The data were analyzed only qualitatively due to the heterogeneity of the results obtained from the included studies. A qualitative synthesis was performed by grouping the data from all included studies according to feature similarity to obtain frequency data for each of the characteristics of interest.

RESULTS

Study selection

From main electronic database searches, a total of 2,466 references were identified. After duplicates removal, 1,559 records remained. No papers from the grey literature were included because identified references were already within main databases. In phase-one 74 studies were considered eligible for full-text reading. In phase-two, seven papers met the

inclusion criteria [4,6,10,17,23-25] and were included in the qualitative synthesis. The complete process of selection of studies is provided in **Figure 1**. Further information concerning reasons for exclusion of studies evaluated in phase-two is available in Supplementary material (**Appendix 2**).

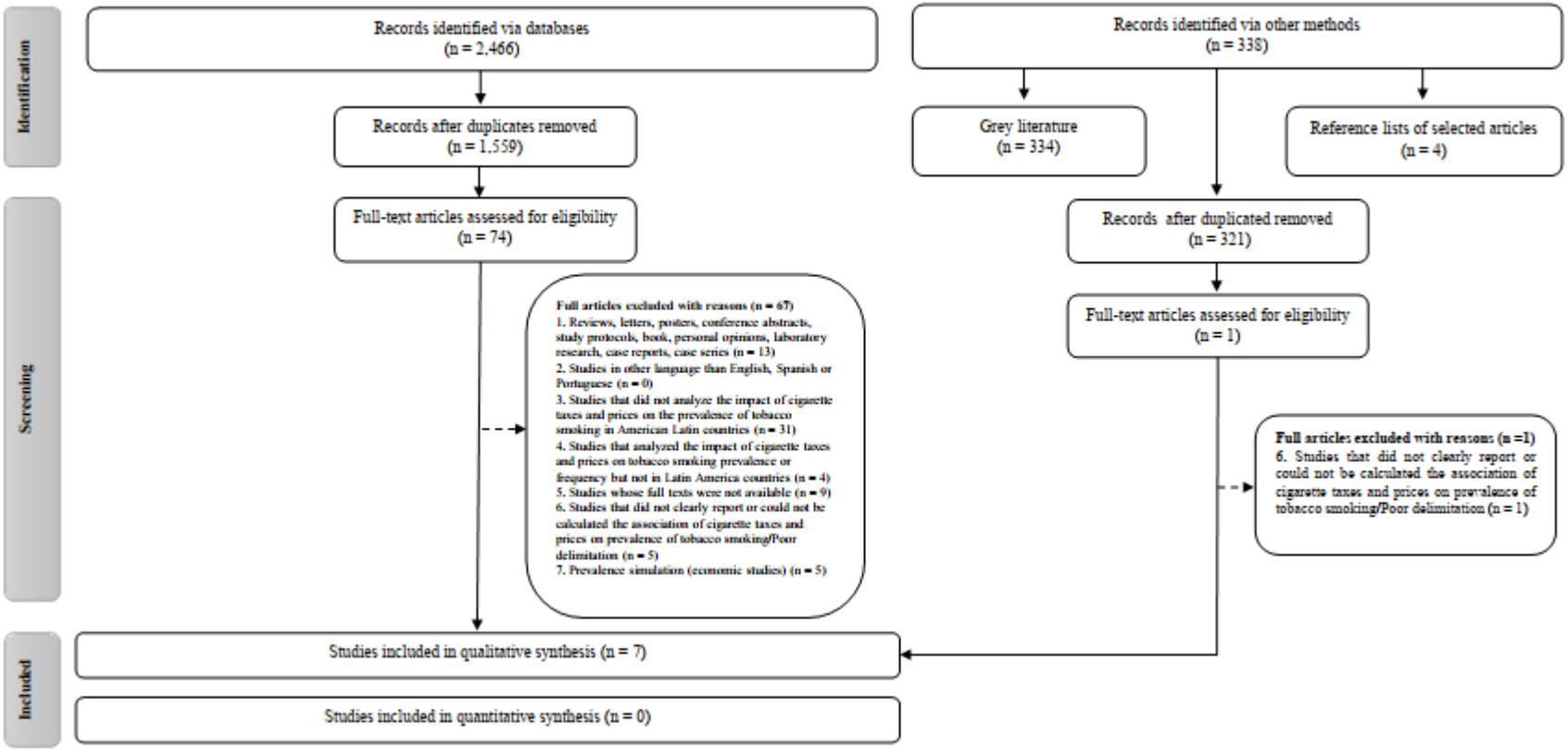

Figure 1. Flow diagram of the literature search and selection criteria, which were adapted from PRISMA [26].

Study characteristics

Out of seven included studies, one was classified as prospective cohort study [17] and six as cross-sectional studies [4,6,10,23-25], of which five of them were a national representative from two or three waves of cross-sectional surveys (secondary quantitative data analysis) [4,6,10,23,25]. Six included studies were published in English and one in Spanish. Studies were conducted in Colombia (n=2), Brazil (n=3) and Mexico (n=2) and were published between the years of 2010 to 2021. Moreover, five studies evaluated populations younger than 18 years old [4,10,23,24] and all considered smokers who smoke 100 or more cigarettes in a lifetime and smoking frequency was considered as the proportion of individuals self-reporting as daily smokers [8,11,24].

The total sample size was 288,634 participants, and the sample sizes ranged from 1,079 [17] to 46,277 [10] participants among the studies, although it has been reported only by four studies (57.1%) [10,17,23,24]. The included participants were aged ranging from 10 to ≥ 65 years old and some of the included articles (n=3) had the follow-up after of the tax reform with five years [4,6,25], two studies (28.57%) had a mean of 15.5 years of follow-up [10,23] and the other two studies had about one year of follow-up [17,24]. Five of the included papers reported the values in their national currency per stick or per pack (20 sticks of cigarette) [4,6,17,24,25], and all included papers reported an increase in cigarette tax and price of retail price impacting on the prevalence of tobacco smoking. Detailed information of study characteristics is provided in **Table 1**.

Table 1 - Summary of qualitative synthesis of included studies (n = 7)

Author, Year,	Country	Study design	Sample size (n)	Range age	Period (follow-up)	Year of Tax reform	Tax and Retail price	Cigarettes Values	Tobacco smoking *Prevalence or Frequency*	Main Conclusion	Quality
Guerrero-López et al., 2013 [10]	Mexico	Nationally representative from three cross-sectional surveys[A]	Adolescents 2000: 21,390 2006: 25,056 2012: 21,509 Adults 2000: 45,294 2006: 45,241 2012: 46,277	Adolescents ≥10–19 Adults ≥20	2000 2006 2012 (12 years)	2011	Special Tax on Production and Services (IEPS): cigarettes were subject to an excise tax of 160% on the retail price and 35 cents per cigarette; the two components represented 55% of the retail price for the most consumed brand	NR	*Prevalence/Frequency* Adolescents 2000: 9.7% / 4.8% 2006: 7.6% / 3.6% 2012: 9.2% / 2.6% Adults 2000: 22.3%/12.4% 2006: 19%/13.3% 2012: 19.9%/11.8%	The results showed that smoking prevalence had remained stable between 2000 and 2012 but had decreased in some population groups such as adolescents daily smokers and adults smokers	Moderate
Szklo et al., 2012 [23]	Brazil	Nationally representative from two cross-sectional surveys[A]	1989: 39,969 2008: 38,461	≥15	1989 2008 (19 years)	1990 2003 2006	1990: Creation of a specific tax for tobacco-drived products (“IPI-Fumo”), the tax rate was 41.3% of the retail price; 2003: Cigarette prices incresead to a level at 1.65 times their 1989 level; 2006: Cigarette prices increased to a level at 2.1 timestheir 1989 level. The tax rate was 60% of the retail price (2003 and 2006 irrespective of general price inflation)	NR	*Prevalence* 1989: 32.4% 2008: 17% (Adjusted absolute difference -12.4%)	The estimated annual average decline in current smoking prevalence between 1989 and 2008 in Brazil was approximately 0.8%	Low

Gallego et al., 2021 [4]	Colombia	Nationally representative from two waves of cross-sectional studies[A]	NR	12–65	2008 2013 (5 years)	2010	The change in taxation increase of the real inflation adjusted average price per cigarette of nearly 60%	Per pack 2008: US$1.2 2013: US$1.7 Per stick 2008:US$0.06 2013:US$0.08	*Prevalence* 2008: 17.3% (M:24.3%; F:11.2%) 2013: 13.5%	In terms of prevalence, large decreases occur in all states, especially in Bogotá, Caldas, Nariño and Valle	Moderate
Divino et al., 2021 [6]	Brazil	Nationally representative from two cross sectional surveys[A]	NR	(a) 15–29 (b) 30–39 (c) 40–49 (d) 50–59 (e) ≥60	2008 2013 (5 years)	2013	Cigarette prices increased by 50% and more, while the general price level increased by 28.5%	Avarage price per pack (BRL$) 2008 / 2013 (a) 2.5 / 4.2 (b) 2.4 / 4.2 (c) 2.3 / 4.2 (d) 2.4 / 4.2 (e) 2.3 / 3.9	*Share of smokers* 2008 / 2013 (a) 14.1% / 11.8% (b) 18.4% / 13.1% (c) 22.8% / 17.4% (d) 24.0% / 20.5% (e) 14.5% / 12.4%	The data confirm that, independent of the characteristics, there is an overall tendency to reduce smoking	Moderate
Saenz-de-Miera et al., 2010 [17]	Mexico	Prospective study (Cohort)	2006: 1,079 (100%) 2007: 756 (70.1%)	≥18	2006 to 2007 (1 year and 3 months)	2007	Two ad valorem taxes: 1)The special production and services tax (SPST); 2006: 110% of the price to the retailer; 2007: 140% of the price to the retailer; 2) Value added tax (VAT): 2006 and 2007: 15% of the price to the consumer Self reported price: Geral percentage change 12.7% (p<0.01)	Self-reported price of last pack purchased (November 2007) Per pack 2006: MX$20.15 2007: MX$22.70	*Prevalence* A total of 98 baseline smokers (13.1%; 95% CI 9.7%,16.5%) reported being quit for at least 30 days at follow-up	No statiscally significant differences were found between the entire baseline sample and the sample that was followed-up	Low
Maldonado et al., 2020 [24]	Colombia	Nationally representative from two	2016: 1,697 2017: 1,697 Total: 3,394	12–65	2016 2017 (1 year)	2016	Increase in the specific component of the excise tax	Per pack 2016: COP$189.2	*Frequency* 2016: 85.1% 2017: 79.5%	Smoking frequency remained	Low

		waves of cross-sectional studies					from COP$700 in 2016 to COP$1,400 in 2017, the ad valorem component of the excise tax of 10%, the increase in value added tax for all goods from 16% to 19%, and a 20% margin before taxes. Per pack Real increased of 28.2% Per stick Real increased of 23.1% (were used a 3.97% inflation for the period)	2017: COP$250.1 Per stick 2016: COP$337.3 2017: COP$428.6 (average price)			stable over time. The proportion of daily smokers went down from 85.1% in 2016 to 79.5% in 2017, and the difference is not statistically significant	
Iglesias et al., 2017 [25]	Brazil	Nationally representative from two cross-sectional surveys[A]	2008: 37,317 2013: 60,237	≥18	2008 2013 (5 years)	2008	Per pack Specific tax rates 2008: BRL$0.652 2013: BRL$1.086 Ad valorem tax rates 2008: BRL$0.566 2013: BRL$1.474 The average price for legal cigarettes grew 101.5% between 2008 and 2013	Per pack 2008: BRL$1.668 2013: BRL$3.236	*Prevalence* 2008: 13.3% (M: 16.5%; F: 10.4%) 2013: 10.8% (M: 13.7%; F: 8.2%)	Daily manufactured cigarette smoking prevalence rates decreased between 2008 and 2013 from 13.3% to 10.8%	Low

Abbreviations: **A**: Secondary quantitative data analysis; **NR**= Not reported;
BRL=US$0.547 in 2008 and US$0.446 in 2013 [25].

Risk of bias within studies

The included studies were graded as having a low (n=4; 57.1%) or moderate (n=3; 42.8%) risk of bias. About 58% (n=4) of the studies did not clearly exposure measured in a valid and reliable away and about 43% (n=3) did not clearly define the study subjects and the setting described in detail. The assessment of RoB in cross-sectional studies is summarized in **Figure 2** and the assessment of RoB in cohort study and in cross-sectional studies are described in detail in Supplementary material (**Appendix 3**).

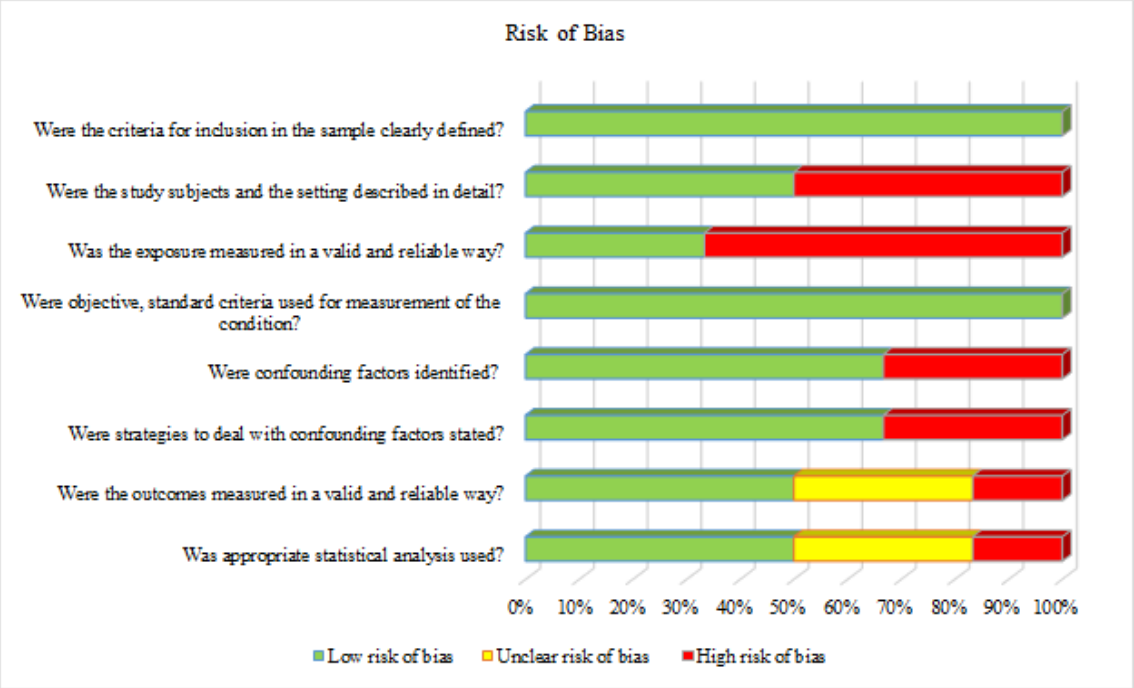

Figure 2. Risk of bias summary: Reviewers' judgments about each checklist item are presented as percentages across cross-sectional studies.

Results of individual studies

All included studies reported an increase in excise taxes of cigarette (ad valorem and/or specific tax) that increased the retail prices and values on cigarette per stick or per pack during a followed-up period [4,6,10,17,23-25]. Most of included studies (n=4) [4,6,23,25] reported a decreased on the prevalence of tobacco smoking after increase in cigarette taxes and prices. The synthesis of results were represented in **Figure 3** with the average cigarette prices in dollars (US$) and the average tobacco smoking prevalence in percentages before and after implementation taxes.

Figure 3. The synthesis of results: (a) The means of cigarette prices in dollars (US$) before (0.56 SDs) and after (0.86 SDs) taxes; and (b) The means in percentages of the prevalence on tobacco smoking before (34.39% SDs) and after (29.54% SDs) taxes. The averages were calculated based on the values provided from all included studies before and after-tax measure. When the price was not in dollars, the conversion was performed according to the value in November 2022.

Decreased on tobacco smoking prevalence

Four articles (57.1%) showed a decreased on tobacco smoking prevalence after an increased cigarette taxes and prices in Brazil (n=3; 75%) and Colombia (n=1; 25%) [4,6,23,25]. Gallego et al. (2021) [4] estimated the cigarette price smoking participation elasticities (PPEs) for Colombia, using household data from the National Psychoactive Substances Consumption Survey 2008 and 2013 (NPSCS). In 2008 the prevalence of tobacco consumption among the population was 17.3%; in 2013, 13.5%. The change in taxation implied an increase of the real inflation adjusted average price per cigarette of nearly 60%. Divino et al. (2021) [6] analyzed the tax increase in cigarettes for Brazil by using household survey data from the National Household Sample Survey (PNAD) of 2008 and the National Health Survey (PNS) of 2013. Smoking behavior by age group in share of smokers for 2008 to 2013 were: 15-29 (14.1% for 11.8%), 30-39 (18.4% for 13.1%), 40-49 (22.8% for 17.4%), 50-59 (24% for 20.5%), and 60 or more (14.5% for 12.4%). The data confirm that there is an overall tendency to reduce smoking (95% CI) and cigarette prices in the different population groups increased by 50% and more, while the general price level increased by 28.5%. Szklo et al. (2012) [23] also compared two population-based household surveys conducted in Brazil, 1989 (the National Health and Nutrition Survey, PNSN) and 2008 (Global Adult Tobacco Survey, GATS-Brazil). The tax rate was 60% of the retail price in 2006. The cigarette smoking prevalence decreased from 32.4%

(1989) to 17% (2008) (adjusted absolute difference -12.4%; CI-95% -9.5;-15.3). The estimated annual average decline in current smoking prevalence between 1989 and 2008 in Brazil was approximately 0.8%. Similarly, Iglesias et al. (2017) [25] compared the size of illicit tobacco consumption in Brazil between 2008 and 2013 using the GATS-Brazil, in order to assess the relationship between the tax rate increases after 2008. The average price for legal cigarettes grew 101.5%. Daily manufactured cigarette smoking prevalence rates decreased between 2008 (13.3%) and 2013 (10.8%) (95% CI).

Tobacco smoking prevalence stayed stable over time

Two of the seven articles (28.5%) showed that the tobacco smoking prevalence stayed stable over time after an increase in cigarette taxes and prices in Colombia and Mexico [10,24]. Maldonado et al. (2020) [24] estimated Colombia's patterns of smoking behavior after the tax increase in 2016. The study was based on primary data from two waves (2016 and 2017) of the Demand for Illicit Cigarettes Survey for Colombia (DEICS-COL). The average price of a cigarette from a pack increased 32.2%. The real increase in price for packs was 28.2%. Smoking frequency remained stable over time. The proportion of daily smokers went down from 85.1% in 2016 to 79.5% in 2017, although the difference was not statistically significant. Guerrero-López et al. (2013) [10] analyzed the tobacco use in Mexico from the National Health Survey (ENSA) 2000 and the National Health and Nutrition Surveys (ENSANUT) 2006 and 2012. Since 2011, cigarettes are subject to an excise tax of 160% on the retail price and 35 cents per cigarette. The two components represented about 55% of the retail price for the most consumed brand. Between 2000 and 2012, there was no change in smoking prevalence among adolescents (9.7% in 2000, 7.6% in 2006 and 9.2% in 2012), just a reduction in adults (from 22.3% in 2000, 19% in 2006 and 19.9% in 2012) (95% IC).

No association on tobacco smoking prevalence

Just one of the seven articles (14.2%) [17] reported a no statistically significant difference with the tobacco smoking prevalence after an increase in cigarette taxes and prices in Mexico, where cigarette was subject to two ad valorem taxes: the Special Production and Services Tax (SPST) and Value added tax (VAT). At the beginning of 2007, the SPST was increased from 110% of the price to the retailer to 140%, with subsequent annual increases to 150% in 2008 and 160% in 2009. The VAT remained at 15% of the price to the consumer in those years. Expressed as a percentage of the final price, the joint incidence of the SPST and the VAT was 54.2% in 2006 and 58.9% in 2007. Saenz-de-Miera et al. (2010) [17] made a study to assess the potential impact of this cigarette tax increase. The data were taken from the Mexican administration of the International Tobacco Control Policy Evaluation Survey (ITC-

Mexico). No statistically significant differences were found between the entire baseline sample and the sample that was followed-up. A total of 98 baseline smokers (13.3%, 95% CI 9.7%, 16.5%) reported being quit for at least 30 days at follow-up.

DISCUSSION

The increase in cigarette taxes and prices impacts positively on the prevalence of tobacco smoking and it is a rationale governmental effective measure. However, it is important to keep in mind that this strategy cannot be considered as an isolated measure because there are many others, such as monitoring tobacco use and prevention policies, smoke-free laws, cessation services, warning about the dangers of tobacco, enforcing bans on tobacco advertising, promotion and sponsorship, that could also influence in the tobacco smoking prevalence rate [4-11]. A systematic review conducted by Nazar et al. (2021) [27] evaluated this topic in South East Asia, in which the majority of included studies supported the use of tobacco tax and price measures as effective tools to address the tobacco epidemic in reducing the affordability and consumption of tobacco products. Since the regions around the world have its socioeconomical and cultural peculiarities, this systematic review aimed to investigate this measure in Latin America to provide scientifical support to policy makers and stakeholders in decision making process.

Most included studies showed a favorable association between the increase of cigarette taxes and prices and decrease of tobacco smoking prevalence in Colombia, Brazil and Mexico [4,6,23,25]. In other hand, two included Papers [17,24] concluded that tobacco smoking prevalence remained stable after the tax reform intervention and the difference was not statistically significant. However, it is important to emphasize that the follow-up period of these studies was approximately one year, in contrast with the other four papers which showed a decrease in tobacco smoking prevalence after the tax reform over a longer period of time (5 to 19 years). Indeed, it is well described that smokers took more than 1 year to quit the habit and a longer follow-up could be required to confirm this association [28,29].

Tobacco excise taxes in almost all countries account for less than 70% of retail prices, with taxes in most accounting for less than half of retail prices [8,12]. Despite a wide range of tobacco control policies as the MPOWER, taxes and prices are not at the recommended rates [4,12]. The findings of this systematic review identified that as none included article had excise taxes more than 70% of retail price, being the largest increase of the real average price per pack nearly 60% (n=5; 71.42%) [4,6,10,17,23]. In a study performed in Chile, a reduction on smoking prevalence was observed between 2010 (40.6%) and 2017 (33.3%). In 2016 taxes

accounted for more than 75% of the final price of the most sold cigarette pack, reaching up to 82.5% in 2019. However, the final price of a cigarette packet (around US$ 4 dollars) remains affordable for most Chileans [30]. Saenz-de-Miera et al. (2010) [17] showed that among smokers who had quit by follow-up (n=98), 40.1% reported that the price of cigarettes was either a very important (12.7%) or a somewhat important (27.4%) reason for quitting. Nevertheless, other self-reported reasons for quitting appeared more relevant than price, such as one's family being concerned about their health (75.8%) and health reasons (60%).

There are other barriers that must be discussed, including pressure from tobacco companies to avoid further tobacco tax increases and concern about job losses or other adverse economic effects, despite abundant evidence of positive labor and economic scenarios [14,31]. The tobacco industry use compensating pricing strategies, such as the development of lower price branded generics and the introduction of multipack discounts to offset increases in taxes [17]. Furthermore, some smokers offset increases in taxes by making special efforts to buy cheaper cigarettes, also adopting the illicit cigarette trade [3,17,25]. Iglesias et al. (2017) [25] showed that the tax cigarette increase, illicit daily consumption increased from 16.6% to 31.1% in Brazil between 2008 to 2013.

It is clear that the price affects all aspects of tobacco consumption, with higher prices preventing initiation among potential users, inducing cessation among current users, and reducing the frequency of consumption and amount consumed by continuing users, while changes in the relative prices of tobacco products will lead to some substitution among products [12]. However, it is important to highlight that some taxes are more difficult to control, such as ad valorem tobacco excises, because increase opportunities for tax avoidance and evasion, and create greater gaps in prices between high- and low-priced brands. As a result, tobacco tax increases will increase tax revenues over the short to medium term [11,12,25]. Over time, inflation will erode the value of tobacco tax revenues, unless these taxes are increased often enough to keep pace with inflation [10-12]. Thus, success of tobacco control policies in the long run requires a continual and comprehensive monitoring system. This system should centralize information, using the most reliable data and then minimize asymmetries of information among policy-makers and stakeholders of these policies [24].

Despite clear evidence of the benefits of raising taxes on tobacco products, many countries in Latin America still have not done so or taken sufficient action in this regard, mainly due to the lack of evidence at the local level that could reduce decision makers' uncertainty about the potential impact of the measure [14].

Furthermore, it is important to highlight some limitations that were found in this systematic review. Latin America comprise 20 countries with a range of cultures and socioeconomical status. However, only three countries in Latin America (Colombia, Brazil and Mexico) have been researching the impact of cigarette taxes and prices on the prevalence of tobacco smoking. Consequently, this systematic review was not be able to characterize the Latin America as overall due to the scarcity of available data, because, from a methodological point of view, we searched all available studies in all Latin America countries.

CONCLUSION

The present systematic review found that higher taxes and prices of cigarettes can be an adjunct tool in decreasing the prevalence of tobacco smoking in Latin America. However, it is vital the development of further research on this topic in other countries of Latin America since the included studies were performed only in Brazil, Colombia and Mexico.

OTHER INFORMATIONS

Protocol and registration

A systematic review protocol based on PRISMA-P [32] was registered in the Prospective Register of Systematic Reviews (PROSPERO), under the registration number CRD42022319407 [33].

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Data sharing

There are data available associated with this manuscript, as this is a systematic review.

Author contributions

Ana Letícia Mores: Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Validation; Visualization; Writing - Original Draft. **Maria Eduarda Pérez-de-Oliveira:** Conceptualization; Data curation; Investigation; Methodology; Validation; Writing – Review & editing. **Ana Gabriela Costa Normando:** Conceptualization; Formal analysis; Validation; Writing – Review & editing. **Leticia Rodrigues-Oliveira:** Writing – Review & editing. **Gustavo Nader Marta:** Writing – Review & editing. **Renata Ferrarotto:** Writing –

Review & editing. **Thaís Bianca Brandão:** Writing – Review & editing. **Alan Roger Santos-Silva:** Conceptualization; Supervision; Writing – Review & editing. **Ana Carolina Prado-Ribeiro:** Conceptualization; Supervision; Writing – Review & editing.

Declarations of interest

None.

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SUPPLEMENTAL MATERIAL

Appendix 1. Search strategies with appropriated key words and number of references retrieved from each database.

Database	Search strategy (Search date: April 23th, 2022)	Results
PubMed	("Latin America"[MeSH Terms] OR "Latin America" OR Mexico OR "Central America" OR Guatemala OR Honduras OR "El Salvador" OR Nicaragua OR "Costa Rica" OR Panama OR "South America" OR Colombia OR Venezuela OR Ecuador OR Peru OR Bolivia OR Brazil OR Paraguay OR Chile OR Argentina OR Uruguay OR Caribbean OR Cuba OR Haiti OR "Dominican Republic" OR "Puerto Rico") AND ("Tobacco Products"[MeSH Terms] OR "tobacco products" OR "tobacco product" OR cigarillo OR cigarillos OR cigar OR cigars OR kretek OR kretek OR bidi OR bidis OR cigarette OR cigarettes OR tobacco[MeSH Terms] OR tobacco OR tobaccos OR nicotiana OR nicotianas OR nicotine[MeSH Terms] OR nicotine OR smoking[MeSH Terms] OR smoking) AND (price OR prices OR taxes[MeSH Terms] OR taxes OR tax OR taxation OR taxing OR excise OR excises OR duties OR impost OR imposts OR cost OR costs)	1,052
Scopus	TITLE-ABS-KEY("Latin America" OR Mexico OR "Central America" OR Guatemala OR Honduras OR "El Salvador" OR Nicaragua OR "Costa Rica" OR Panama OR "South America" OR Colombia OR Venezuela OR Ecuador OR Peru OR Bolivia OR Brazil OR Paraguay OR Chile OR Argentina OR Uruguay OR Caribbean OR Cuba OR Haiti OR "Dominican Republic" OR "Puerto Rico") AND TITLE-ABS-KEY("tobacco products" OR "tobacco product" OR cigarillo OR cigarillos OR cigar OR cigars OR kretek OR kretek OR bidi OR bidis OR cigarette OR cigarettes OR tobacco OR tobaccos OR nicotiana OR nicotianas OR nicotine OR smoking) AND TITLE-ABS-KEY(price OR prices OR taxes OR tax OR taxation OR taxing OR excise OR excises OR duties OR impost OR imposts OR cost OR costs)	727
Embase	('latin america'/de OR 'central america'/de OR 'south america'/de OR 'caribbean'/de OR 'argentina'/de OR 'bolivia'/de OR 'brazil'/de OR 'chile'/de OR 'colombia'/de OR 'costa rica'/de OR 'cuba'/de OR 'ecuador'/de OR 'el salvador'/de OR 'guatemala'/de OR 'haiti'/de OR 'honduras'/de OR 'mexico'/de OR 'nicaragua'/de OR 'panama'/de OR 'paraguay'/de OR 'peru'/de OR 'dominican republic'/de OR 'uruguay'/de OR 'venezuela'/de) AND ('tobacco products'/de OR 'tobacco product'/de OR 'cigarillo'/de OR cigarillos OR 'cigar'/de OR cigars OR kretek OR bidi OR bidis OR 'cigarette'/de OR cigarettes OR 'tobacco'/de OR tobaccos OR 'nicotiana'/de OR nicotianas OR 'nicotine'/de OR 'smoking'/de) AND ('price'/de OR 'prices'/de OR 'taxes'/de OR 'tax'/de OR 'taxation'/de OR taxing OR excise OR excises OR duties OR impost OR imposts OR 'cost'/de OR costs)	212
Web of Science	TS=("Latin America" OR Mexico OR "Central America" OR Guatemala OR Honduras OR "El Salvador" OR Nicaragua OR "Costa Rica" OR Panama OR "South America" OR Colombia OR Venezuela OR Ecuador OR Peru OR Bolivia OR Brazil OR Paraguay OR Chile OR Argentina OR Uruguay OR Caribbean OR Cuba OR Haiti OR "Dominican Republic" OR "Puerto Rico") AND TS=("tobacco products" OR "tobacco product" OR cigarillo OR cigarillos OR cigar OR cigars OR kretek OR kretek OR bidi	468

	OR bidis OR cigarette OR cigarettes OR tobacco OR tobaccos OR nicotiana OR nicotianas OR nicotine OR smoking) AND TS=(price OR prices OR taxes OR tax OR taxation OR taxing OR excise OR excises OR duties OR impost OR imposts OR cost OR costs)	
LILACS	(“Latin America” OR “América Latina” OR “Central America” OR “América Central” OR “South America” OR “América do Sul” OR Caribbean OR Caribe) AND (cigarette OR cigarro OR tobacco OR tabaco OR smoking OR fumar OR nicotine OR nicotina) AND (taxes OR tax OR imposto OR impostos OR impuestos OR price OR preço OR preços)	7
TOTAL		2,466
	Grey Literature	
Google Scholar	First 100 more relevant hits. No patents and no citations. (tobacco OR smoking) AND (price OR tax)	100
ProQuest	TI,AB("Latin America") AND TI,AB(cigarillo OR cigarillos OR cigar OR cigars OR cigarette OR cigarettes OR tobacco OR tobaccos OR nicotiana OR nicotiana OR nicotine OR smoking) AND TI,AB(price OR prices OR taxes OR tax OR taxation OR taxing OR excise OR excises OR duties OR impost OR imposts OR cost OR costs)	234
TOTAL		334

Appendix 2. Excluded articles and reasons for exclusion (n=67)

	References	Reasons for exclusion*
1	Valdés-Salgado R, Lazcano-Ponce EC, Hernández-Avila M. Current panorama of tobacco consumption and control measures in Mexico. Prevention and Control. 2005;1:319–27. doi:10.1016/j.precon.2005.12.004	1
2	Mejia R, Pérez-Stable EJ. Tobacco epidemic in Argentina: The cutting edge of Latin America. Prevention and Control. 2006;2:49–55. doi:10.1016/j.precon.2006.04.003	1
3	Jiménez-Ruiz JA, Sáenz-de-Miera B, Reynales-Shigematsu LM, et al. The impact of taxation on tobacco consumption in Mexico. Tob Control. 2008;17:105–110. doi:10.1136/tc.2007.021030	3
4	Storr CL, Cheng H, Posada-Villa J, et al. Adult smokers in Colombia: Who isn't giving it up? Addictive Behaviors. 2008;33:412–21. doi:10.1016/j.addbeh.2007.10.003	3
5	Franco-Marina F, Lazcano-Ponce E. Adult smoking trends in Mexico between 1988 and 2008. Salud Publica Mex. 2010;52(2):108–19.	6
6	Levy D, Maria-de-Almeida L, Szklo A. The Brazil SimSmoke Policy Simulation Model: The Effect of Strong Tobacco Control Policies on Smoking Prevalence and Smoking-Attributable Deaths in a Middle Income Nation. Plos Med. 2012;9(11):e1001336. doi:10.1371/journal.pmed.1001336	4
7	Lugo NS. The price of cigarettes and the reduction of smoking in Cuba. Revista Cubana de Salud Pública. 2012;38(1):4–19.	6
8	Siahpush M, Thrasher JF, Yong HH, et al. Cigarette prices, cigarette expenditure and smoking-induced deprivation: findings from the International Tobacco Control Mexico survey. Tob Control. 2013;22:223–26. doi:10.1136/tobaccocontrol-2012-050613	1
9	Kostova D, Chaloupka FJ, Yurekli A, et al. A cross-country study of cigarette prices and affordability: evidence from the Global Adult Tobacco Survey. Tob Control. 2014;23:e3. doi:10.1136/tobaccocontrol-2011-050413	3
10	Juárez B, Thrasher JF, Shigematsu LM, et al. Tax, price and cigarette brand preferences: a longitudinal study of adult smokers from the ITC Mexico Survey. Tob Control. 2014;23:i80–i85. doi:10.1136/tobaccocontrol-2012-050939	3
11	Chaloupka FJ, Kostova D, Shang C. Cigarette excise tax structure and Cigarette Prices: evidence From the global adult tobacco survey and the U.S. national adult tobacco survey. Nicotine Tob Res. 2014;16(1):3–9. doi:10.1093/ntr/ntt121	4
12	Garcés A, Garcés M, Barnoya J, et al. Conference Report on Tobacco Taxes in Central America: Current Situation and opportunities to Reduce prevalence and Increase fiscal Revenues. Nicotine Tob Res. 2014;16(1):65–70. doi:10.1093/ntr/ntt048	1
13	Gigliotti A, Figueiredo VC, Madruga CS, et al. How smokers may react to cigarette taxes and price increases in Brazil: data from a national survey. BMC Public Health. 2014;14:327. doi:10.1186/1471-2458-14-327	3
14	Kostova D, Tesche J, Perucic AM, et al on behalf of the GATS Collaborative Group. Exploring the relationship Between Cigarette Prices and smoking among adults: a Cross-Country study of low- and Middle-income nations. Nicotine Tob Res. 2014;16(1):10–15. doi:10.1093/ntr/ntt170	4
15	Nikaj S, Chaloupka FJ. The effect of Prices on Cigarette Use among Youths in the global Youth tobacco survey. Nicotine Tob Res. 2014;16(1):16–23. doi:10.1093/ntr/ntt019	3
16	Reynales-Shigematsu LM, Fleischer NL, Thrasher JF, et al. Effects of tobacco control policies on smoking prevalence and tobacco-attributable deaths in Mexico: the SimSmoke model. Rev Panam Salud Publica. 2015;38(4):316–25.	4

17	Martinez E, Mejia R, Pérez-Stable EJ. An empirical analysis of cigarette demand in Argentina. Tob Control. 2015;24:89–93. doi:10.1136/tobaccocontrol-2012-050711	3
18	Curti D, Shang C, Ridgeway W, et al. The Use of Legal, Illegal, and Roll you-own Cigarettes to Increasing Tobacco Excise Taxes and Comprehensive Tobacco Control Policies-Findings from the ITC Uruguay Survey. Tob Control. 2015;24(3):17–24. doi:10.1136/tobaccocontrol-2014-051890	3
19	Garcia LP, Sant'Anna AC, Santana-de-Freitas LR, et al. Tobacco control policy and variation in Brazilian family spending on cigarettes: results of the Brazilian Household Budget Surveys in 2002/2003 and 2008/2009. Cad. Saúde Pública. 2015;31(9):1894–1906. doi:10.1590/0102-311X00087814	3
20	Rodríguez-Iglesias G, González-Rozada M, Champagne BM, et al. Real price and affordability as challenges for effective tobacco control policies: an analysis for Argentina. Rev Panam Salud Publica. 2015;37(2):98–103.	3
21	Chávez R. Price elasticity of demand for cigarettes and alcohol in Ecuador, based on household data. Rev Panam Salud Publica. 2016;40(4):1–6.	3
22	Gonzalez-Rozada M, Ramos-Carbajales A. Implications of raising cigarette excise taxes in Peru. Rev Panam Salud Publica. 2016;40(4):250–55.	3
23	Ramos-Carbajales A, González-Rozada M, Vallarino H. La demanda de cigarrillos y el aumento de impuestos en El Salvador. Rev Panam de Salud Publica. 2016;40(4):237–42.	3
24	Iglesias RM. Increasing excise taxes in the presence of an illegal cigarette market: the 2011 Brazil tobacco tax reform. Rev Panam Salud Publica. 2016;40(4):243–9.	1
25	Maldonado N, Llorente B, Deaza J. Cigarette taxes and demand in Colombia. Rev Panam Salud Publica. 2016;40(4):229–36.	3
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27	Triunfo P, Harris J, Balsa A. Evaluation of Uruguay's antismoking campaign: progress and challenges after ten years. Rev Panam Salud Publica. 2016;40(4):256–62.	1
28	Crosbie E, Sosa P, Glantz SA. The importance of continued engagement during the implementation phase of tobacco control policies in a middle-income country: the case of Costa Rica. Tob Control. 2017;26:60–68. doi:10.1136/tobaccocontrol-2015-052701	1
29	Goodchild M, Sandoval RC, Belausteguigoitia I. Generating revenue by raising tobacco taxes in Latin America and the Caribbean. Rev Panam Salud Publica. 2017;41:e151. doi:10.26633/RPSP.2017.151	3
30	Szklo AS, Yuan Z, Levy D. Update and extension of the Brazil SimSmoke model to estimate the health impact of cigarette smoking by pregnant women in Brazil. Cad Saúde Pública. 2017;33(12):e00207416. doi:10.1590/0102-311X00207416	3
31	Pizarro ME, Rodríguez-Iglesias G, Gutkowski P, et al. Avances en impuestos del tabaco: el caso de Argentina. Rev Panam Salud Publica. 2018;42:e46. doi:10.26633/RPSP.2018.46	1
32	Curti D, Shang C, Chaloupka FJ, et al. Tobacco taxation, illegal cigarette supply and geography: findings from the ITC Uruguay Surveys. Tob Control. 2019;28:53–60. doi:10.1136/tobaccocontrol-2017-054218	3
33	Gonzalez-Rozada M, Montamat G. How Raising Tobacco Prices Affects the Decision to Start and Quit Smoking: Evidence from Argentina. Int J Environ Res Public Health. 2019;16:3622. doi:10.3390/ijerph16193622	6
34	Gallego JM, Llorente B, Maldonado N, et al. Tobacco taxes and illicit cigarette trade in Colombia. Econ Hum Biol. 2020;39:100902. doi:10.1016/j.ehb.2020.100902	3

35	González-Rozada M. Impact of a recent tobacco tax reform in Argentina. Tob Control. 2020;29:300–303. doi:10.1136/tobaccocontrol-2019-055238	3
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37	Szklo AS, Iglesias RM. Interference by the tobacco industry in data on cigarette consumption in Brazil. Cad Saúde Pública. 2020;36(12):e00175420. doi:10.1590/0102-311X00175420	3
38	GBD 2019 Tobacco Collaborators. Spatial, temporal, and demographic patterns in prevalence of smoking tobacco use and attributable disease burden in 204 countries and territories, 1990–2019: a systematic analysis from the Global Burden of Disease Study 2019. Lancet. 2021;397:2337–60. doi:10.1016/S0140-6736(21)01169-7	1
39	Huesca L, Araar A, Llamas L, et al. The impact of tobacco tax reforms on poverty in Mexico. SN Bus Econ. 2021;1:142. doi:10.1007/s43546-021-00141-x	3
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43	Divino JA, Ehrl P, Candido O, et al. Effects of the Brazilian tax reform plans on the tobacco Market. Tob Control. 2021;0:1–9. doi:10.1136/tobaccocontrol-2021-056822	3
44	Salazar JI, Pérez DP, Martínez MF. La incidencia del Impuesto Especial sobre Producción y Servicios al tabaco en México. Contaduría y Administración. 2021;66(1):1–30. doi:10.22201/fca.24488410e.2021.2385	3
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46	Alcaraz A, Caporale J, Bardach A, et al. Burden of disease in Argentina attributable to tobacco use and potential impact of price increases through taxation. Rev Panam Salud Publica. 2016;40(4)204–12.	3
47	Hernandez-Vasquez A. Burden of smoking-related disease and potential impact of cigarette price increase in Peru. MPRA. 2017;75677.	3
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49	Castillo-Riquelme M, Bardach A, Palacios A, et al. Health burden and economic costs of smoking in Chile: The potential impact of increasing cigarettes prices. Plos One. 2020;15(8):e0237967. doi:10.1371/journal.pone.0237967	3
50	Divino JA, Ehrl P, Candido O, et al. Assessing the Effects of a Tobacco Tax Reform on the Industry Price-Setting Strategy. Int J Environ Res Public Health. 2021;18:10376. doi:10.3390/ijerph181910376	3
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52	Cruces G, Falcone G, Puig J. Differential price responses for tobacco consumption: implications for tax incidence. Tob Control. 2022;0:1–6. doi:10.1136/tobaccocontrol-2021-056846	3
53	Ferrante D, Levy D, Peruga A, et al. The role of public policies in reducing smoking prevalence and deaths: the Argentina Tobacco Policy Simulation Model. Rev Panam Salud Pública. 2007;21(1):37–49.	7
54	Fleischer NL, Thrasher JF, Reynales-Shigematsu LM, et al. Mexico SimSmoke: how changes in tobacco control policies would impact smoking prevalence and smoking attributable deaths in Mexico. Glob Public Health. 2017;12(7):830–845. doi:10.1080/17441692.2015.1123749	7
55	Paraje G, Araya D, De Paz A, et al. Price and expenditure elasticity of cigarette demand in El Salvador: a household-level analysis and simulation of a tax increase. Tob Control. 2020;0:1–6. doi:10.1136/tobaccocontrol-2019-055568	7
56	Saenz-de-Miera B, Wu DC, Essue BM, et al. The distributional effects of tobacco tax increases across regions in Mexico: an extended cost-effectiveness analysis. Int J Equity Health. 2022;21:8. doi:10.1186/s12939-021-01603-2	7
57	Maldonado N, Llorente B, Reynales-Shigematsu LM, et al. Tobacco Taxes as the Unsung Hero: Impact of a Tax Increase on Advancing Sustainable Development in Colombia. Int J Public Health. 2022;67:1604353. doi:10.3389/ijph.2022.1604353	7
58	Lugo NS. Consumptions, price and cigarettes market segmentation Cuba, 2017. Revista Cubana de Salud Publica. 2018;44(4):125–139.	5
59	Lugo NS. Market for and consumption of cigarettes in Cuba and the choice between tobacco and health. Revista Cubana de Salud Publica. 2014;40(3):331–344.	5
60	Sesma-Vázquez S, Campuzano-Rincón JC, Carreón-Rodríguez VG, et al. Trends of tobacco demand in Mexico: 1992-1998. Salud Publica Mex. 2002;44(1):82–92.	5
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65	Miguel P, Teixeira AP. Public policy of tobacco control in Brazil and Portugal: taxes and product accessibility. Lex Humana. 2017;9(2):68–95.	5
66	Pizarro ME, Rodríguez-Iglesias G, Gutkowski P, et al. New strides in tobacco taxation: The case of Argentina. Pan American Journal of Public Health. 2018;42:e46.	5
67	Monteiro CA, Cavalcante TM, Moura EC, et al. Population-based evidence of a strong decline in the prevalence of smokers in Brazil (1989–2003). Bull World Health Organ. 2007;85:527–534. doi:10.2471/BLT.06.039073	6

***(1) Reviews, letters, posters, conference abstracts, study protocols, book, personal opinions, laboratory research; (2) Studies in other language than English, Spanish or Portuguese; (3) Studies that did not analyze the impact of cigarette taxes and prices on the prevalence of tobacco smoking in American Latin countries; (4) Studies that analyzed the impact of cigarette taxes and prices on tobacco smoking prevalence but not in Latin America countries; (5) Studies whose full texts were not available; (6) Studies that did not clearly report or could not be calculated the association of cigarette taxes and prices on prevalence of tobacco smoking/Poor**

delimitation; (7) Studies 'predicting' the impact of cigarette taxes and prices changes with prevalence simulation (economic studies).

Appendix 3 – Risk of Bias assessed by the Joanna Briggs Institute Critical Appraisal Tools for use in JBI Systematic Reviews. Risk of bias was categorized as High when the study reaches up to 49% score "yes", Moderate when the study reached 50% to 69% score "yes", and Low when the study reached at least 70% score "yes".

A. Quality assessment tool JBI Critical Appraisal Checklist for Analytical Cross-Sectional Studies

Authors	Q.1	Q.2	Q.3	Q.4	Q.5	Q.6	Q.7	Q.8	% yes / risk
Gallego et al., 2021	Y	N	N	Y	Y	Y	N	N	50% / M
Divino et al., 2021	Y	N	Y	Y	Y	N	U	U	66.6% / M
Maldonado et al., 2020	Y	Y	Y	Y	N	Y	U	U	83.3% / L
Iglesias et al., 2017	Y	N	N	Y	Y	Y	Y	Y	75% / L
Guerrero-López et al., 2013	Y	Y	N	Y	N	N	Y	Y	62.5% / M
Szklo et al., 2012	Y	Y	N	Y	Y	Y	Y	Y	87.5% / L
% Yes	100%	66.67%	33.34%	100%	66.67%	66.67%	100%	83.34%	

Q1. Were the criteria for inclusion in the sample clearly defined? Q2. Were the study subjects and the setting described in detail? Q3. Was the exposure measured in a valid and reliable way? Q4. Were objective, standard criteria used for measurement of the condition? Q5. Were confounding factors identified? Q6. Were strategies to deal with confounding factors stated? Q7. Were the outcomes measured in a valid and reliable way? Q8. Was appropriate statistical analysis used? Y - Yes; N- No; U – Unclear; H – High, M – Moderate; L – Low.

B. Quality assessment tool JBI Critical Appraisal Checklist for Cohort Studies

Authors	Q.1	Q.2	Q.3	Q.4	Q.5	Q.6	Q.7	Q.8	Q.9	Q.10	Q.11	% yes/ risk
Saenz-de-Miera et al., 2010	Y	Y	Y	Y	Y	Y	Y	Y	N	N	Y	81.82%/ L
% Yes	100%	100%	100%	100%	100%	100%	100%	100%	0%	0%	100%	

Q1. Were the two groups similar and recruited from the same population? Q2. Were the exposures measured similarly to assign people to both exposed and unexposed groups? Q3. Was the exposure measured in a valid and reliable way? Q4. Were confounding factors identified? Q5. Were strategies to deal with

confounding factors stated? Q6. Were the groups/participants free of the outcome at the start of the study (or at the moment of exposure)? Q7. Were the outcomes measured in a valid and reliable way? Q8. Was the follow up time reported and sufficient to be long enough for outcomes to occur? Q9. Was follow up complete, and if not, were the reasons to loss to follow up described and explored? Q10. Were strategies to address incomplete follow up utilized? Q11. Was appropriate statistical analysis used?

Y- Yes; N- No; U- Unclear; H– High, M- Moderate, L- Low.

3 DISCUSSÃO

O primeiro artigo apresentado foi um estudo prognóstico realizado através de uma coorte retrospectiva de dez anos no Instituto do Câncer do Estado de São Paulo (ICESP), na cidade de São Paulo, Brasil, onde 3275 pacientes tiveram carcinoma espinocelular primário na região de cabeça e pescoço e foram atendidos pelo Serviço de Odontologia Oncológica. A maioria deles eram fumantes e etilistas atuais no momento do diagnóstico, com uma porcentagem de 66,4% e 44,9%, respectivamente. Apenas 24,1% abandonaram o tabagismo e 34,3% o etilismo previamente ao diagnóstico, mostrando que a cessação do tabagismo e etilismo permanecem um grande desafio para os pacientes e também para o governo, pois é um forte problema de saúde pública no mundo. Além disso, o consumo de tabaco foi caracterizado por um longo período de tempo, sendo superior a 20 anos em 82,4% dos casos. Como o tabagismo e o etilismo são os principais fatores de risco para o CCP (Hashibe et al. 2007, 2009; Boras et al. 2019; Di Credico et al. 2019, 2020), medidas de prevenção são extremamente necessárias, a curto e longo prazo (Hashim et al. 2019).

Em nosso segundo estudo realizado através de uma Revisão Sistemática avaliando o impacto dos impostos e preços dos cigarros industrializados sobre a prevalência do tabagismo na América Latina, tivemos como resultado que, todos os estudos incluídos (n=7) constataram que um aumento nos impostos levou a um aumento no preço de varejo, e quatro deles (57,1%) relataram que o aumento desses impostos foram uma medida governamental altamente eficaz e econômica para diminuir a prevalência do tabagismo na América Latina. No entanto, é fundamental o desenvolvimento de mais pesquisas sobre esse tópico em outros países da América Latina, pois os estudos incluídos foram realizados apenas no Brasil, na Colômbia e no México.

O preço mais alto do cigarro impacta na iniciação do tabagismo, induz sua cessação e reduz sua frequência e consumo diário. Monitorar o uso de tabaco e políticas de prevenção é essencial pois os impostos devem acompanhar a inflação ao longo dos anos. Além disso, é importante ter em mente que essa estratégia não pode ser considerada uma medida isolada, pois há muitas outras, como: proteger a população contra a fumaça do tabaco, oferecer ajuda para cessação do fumo, advertir sobre os perigos do tabaco e fazer cumprir as proibições sobre publicidade, promoção e patrocínio, que também influenciaram a diminuição da taxa de prevalência do tabagismo no período estudado (Chaloupka et al. 2012; Jethwa and Khariwala 2017; Gallego et al. 2021).

O primeiro estudo revelou que a sobrevida global do câncer de cabeça e pescoço continua baixa no Brasil, onde em 5 anos foi 33,7% para todos os sítios, 40,1% para laringe,

38,5% para orofaringe, 28% para cavidade oral e apenas 15,5% para hipofaringe. A idade, o estágio e o consumo de álcool no momento do diagnóstico foram fatores prognósticos independentes. Comparados a outros estudos, no Brasil o prognóstico dos pacientes é desfavorecido (de França et al. 2022; Louredo et al. 2022b) porque a maioria dos pacientes são diagnosticados em estágios tardios da doença (III/IV = 86,9%), decorrentes do tabagismo, de um atraso no diagnóstico, somado à presença de comorbidades (53,4%) e a idade avançada (≥60 anos = 51,3%) onde o plano de tratamento se torna prejudicado devido a baixa capacidade do paciente suportar a terapia estabelecida (Stordeur et al. 2020; Zavarez et al. 2020; de França et al. 2022). Isso foi melhor evidenciado nos pacientes com câncer de orofaringe HPV-positivos, onde mostraram uma sobrevida global em 10 anos superior (47,3%) comparado aos HPV-negativos (0%). Pacientes com câncer de orofaringe HPV-positivo apresentam redução significativa no riso de morte comparados aos HPV negativos (Du et al. 2019; Abrahão et al. 2020; de França et al. 2022; Louredo et al. 2022a). Essa redução se deve ao fato dos pacientes serem mais jovens (≤ 59 anos = 62,8%) e com melhor capacidade de responder e suportar as terapias estabelecidas.

A idade e o estágio já são fatores prognóstico estabelecidos independentes e desfavoráveis na sobrevida dos pacientes com CCP (Leoncini et al. 2015; Giraldi et al. 2017; Abrahão et al. 2018, 2020; Du et al. 2019; Lee et al. 2019; de França et al. 2022), onde nosso estudo agregou com essas evidências e a idade mais velha (≥60 anos), o estágio avançado da doença (III/IV) no momento do diagnóstico para os sítios da cavidade oral, orofaringe e laringe aumentaram o risco de morte entre os pacientes.

O consumo atual ou prévio de álcool no momento do diagnóstico de CCP evidenciou um maior risco de morte para os sítios de orofaringe e laringe, semelhante ao estudo realizado por Lee et al. (2019) onde encontraram tal risco para os sítios de orofaringe, laringe e hipofaringe analisados conjuntamente (Lee et al., 2019). Abrahão et al. (2020) e Giraldi et al. (2017) também tiveram uma mortalidade maior para os sítios de laringe ou hipofaringe comparados aos que nunca beberam (Giraldi et al. 2017; Abrahão et al. 2020). O gênero masculino foi um fator prognóstico desfavorável apenas para o sítio da cavidade oral.

O tabagismo é muito associado como um fator prognóstico desfavorável na sobrevida do CCP (Adeoye et al.; Giraldi et al. 2017; Abrahão et al. 2018; Du et al. 2019). O nosso estudo encontrou que o tabagismo aumentou o risco de morte apenas no sítio de orofaringe na análise univariada, porém após os ajustes entre as variáveis significativas (gênero, idade, estágio, status de tabagismo e etilismo no momento do diagnóstico) acabou perdendo significância.

Em 2018 foi implementada a oitava edição do Manual de Estadiamento do Câncer da AJCC, incluindo fatores relevantes não anatômicos, como os moleculares (para detecção do HPV) durante o processo de estadiamento do CCP (Amin et al. 2017; Louredo et al. 2022a). Decorrente disso, como nossa coleta englobou os anos de 2011 a 2021, a maioria dos pacientes com câncer de orofaringe não reportaram seu status p16 (71,76%) e uma análise de Cox separada foi realizada. A análise univariada mostrou que o gênero masculino, o estágio avançado e o consumo de álcool no momento do diagnóstico podem ser fatores prognóstico independentes para o câncer de orofaringe HPV-positivo, porém uma análise múltipla seria necessária para confirmar isso, a qual não foi possível de ser realizada devido baixo número de variáveis significativas.

De acordo com a nossa investigação da literatura, apenas um estudo de coorte prospectivo realizado no Reino Unido investigou a interação do tabagismo, etilismo e infeção pelo HPV nos diferentes sítios do CCP, onde constatou que o tabagismo foi um fator prognóstico independente desfavorável para o sítio de laringe e o consumo moderado a nocivo de álcool no momento do diagnóstico foi para pacientes com câncer de orofaringe HPV-negativos (Beynon et al., 2018).

Além disso, a correlação do nosso estudo em trazer que o etilismo apresentou maior risco de morte entre os pacientes HPV-positivos pode ser pelo fato da maioria dos nossos pacientes diagnosticados com câncer de orofaringe HPV-positivo possuírem comorbidades (59,7%) e histórico atual ou prévio de tabagismo (68,9%) e etilismo (51,9%) no momento do diagnóstico, contrariando o perfil clínico patológico padrão evidenciado na maioria dos estudos (Louredo et al. 2022a).

Esta pesquisa encontrou diversas limitações. A generalização não pode ser considerada pois, a pesquisa foi realizada em apenas um centro de saúde do Brasil. Além disso, as avaliações de tabagismo e consumo de álcool foram baseadas nos autorrelatos dos participantes, sem verificação bioquímica. Por fim, não dispúnhamos de dados sobre o tabagismo e etilismo dos pacientes após o diagnóstico, o que pode ter afetado a sobrevida geral.

Dado o número limitado de estudos que investigam as interações pré-diagnóstico entre tabagismo, álcool e infecção do HPV na determinação do risco de mortalidade na sobrevida do CCP por sítios, incluindo o câncer orofaríngeo HPV positivo e negativo, são necessárias mais investigações.

4 CONCLUSÃO

A partir dos dois capítulos apresentados, concluímos, que:

- A idade mais avançada (acima de 60 anos) e o estágio avançado do tumor (III e IV) no momento do diagnóstico foram fatores prognósticos independentes desfavoráveis na sobrevida global de pacientes brasileiros com carcinoma espinocelular na região de cabeça e pescoço, nos sítios de cavidade oral, orofaringe e laringe;
- O consumo prévio ou atual de álcool no momento do diagnóstico foi um fator prognóstico independente desfavorável na sobrevida dos sítios de orofaringe e laringe;
- O gênero masculino foi um fator prognóstico independente desfavorável na sobrevida do sítio de cavidade oral;
- As análises múltiplas dos pacientes com câncer orofaríngeo de acordo com o status p16 foram inconsistentes, exigindo mais estudos nessa área;
- Todo profissional de saúde deve incentivar o abandono do tabagismo e consumo de álcool no momento do diagnóstico afim de melhorar as taxas de sobrevivência entre os pacientes oncológicos.
- O aumento dos impostos e dos preços dos cigarros é uma ferramenta auxiliar na redução da prevalência do tabagismo na América Latina.

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*De acordo com as normas da UNICAMP/FOP, baseadas na padronização do International Committee of Medical Journal Editors - Vancouver Group. Abreviatura dos periódicos em conformidade com o PubMed.

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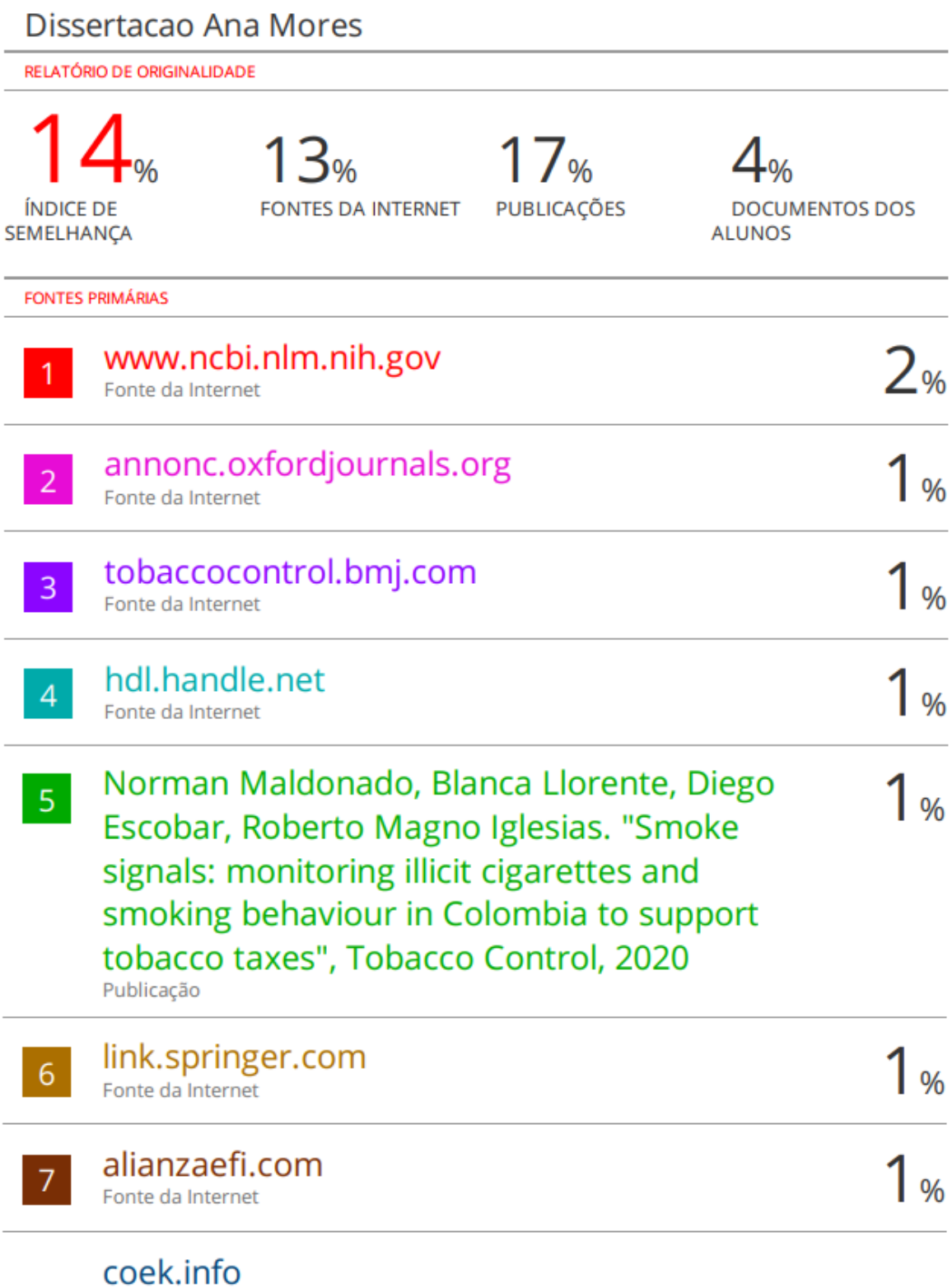
ANEXOS

Anexo 1 - Relatório de verificação de originalidade e prevenção de plágio.



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Título da Pesquisa: RELAÇÃO ENTRE A CARGA TABÁGICA, CARGA ETÍLICA E TEMPO DE DESENVOLVIMENTO DO CÂNCER DE CABEÇA E PESCOÇO EM PACIENTES TRATADOS NO INSTITUTO DO CÂNCER DO ESTADO DE SÃO PAULO.

Pesquisador: ANA LETICIA MORES

Área Temática:

Versão: 3

CAAE: 54779521.0.0000.5418

Instituição Proponente: Faculdade de Odontologia de Piracicaba - Unicamp

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A **Ana Carolina Prado Ribeiro**
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