UNIVERSIDADE DE SÃO PAULO

FACULDADE DE SAÚDE PÚBLICA

FABRÍCIO DOS SANTOS MENEZES

Sobrevida e incidência do câncer de cabeça e pescoço segundo sítios anatômicos relacionados ao HPV

São Paulo

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Versão Original

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Orientadora: Profa. Dra. Tatiana Natasha Toporcov

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Aprovado em:

Banca Examinadora

Prof. Dr.	José Leopoldo Ferreira Antunes
Instituição:	Faculdade de Saúde Pública, Universidade de São Paulo.
Julgamento:	Aprovado

Profa. Dra.	Luisa Lina Villa
Instituição:	Faculdade de Medicina, Universidade de São Paulo.
Julgamento:	Aprovado

Profa. Dra.	Stela Verzinhasse Peres
Instituição:	Fundação Oncocentro de São Paulo (FOSP).
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especialmente Ana, Benício e Beatriz, que ainda
nascerá, amo vocês!

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“The true measure of any society can be found in how it treats its most vulnerable members.”

Mahatma Gandhi

RESUMO

Menezes FS. Sobrevida e incidência do câncer de cabeça e pescoço segundo sítios anatômicos relacionados ao HPV [tese]. São Paulo: Universidade de São Paulo, Faculdade de Saúde Pública; 2020.

Introdução: Estudos laboratoriais e epidemiológicos demonstraram uma epidemia viral no câncer de cabeça e pescoço (CCP) relacionada ao papilomavírus humano (HPV). Entretanto, não está claro se esse aumento na incidência afeta igualmente as populações e seus subgrupos ou se essa epidemia viral se limita a países específicos. Por tais motivos, investigou-se a epidemiologia do câncer de boca, orofaringe e laringe segundo a relação com o HPV. **Métodos:** A tese compreende três manuscritos: (i) uma revisão sistemática sobre as tendências de incidência globais do CCP segundo sítios anatômicos associados ao HPV; (ii) um estudo de base populacional prévio à implementação da vacina para o HPV no município de São Paulo (1997-2013), analisando as tendências de incidência e o efeito idade-período-coorte do CCP estratificado por localizações anatômicas HPV-relacionadas; e (iii) um estudo de base hospitalar sobre a influência do HPV e das iniquidades sociais na sobrevida por CCP dos pacientes do estado de São Paulo (2000-2018). **Resultados:** No primeiro artigo, confirmou-se a hipótese de que há uma mudança significativa nas tendências de incidência globais de CCPs devido à carga emergente nos sítios anatômicos HPV-relacionados. Em geral, as tendências de incidência padronizadas por idade, ou *age-standardized rate* (ASRs), aumentaram em localizações anatômicas HPV-relacionadas. Porém, as ASRs diminuíram para os CCPs relacionados ao consumo de álcool e tabaco. No segundo artigo, analisou-se 15.391 cânceres de boca e orofaringe (CBO). Para tanto, observou-se um aumento nas ASRs em localizações anatômicas HPV-relacionadas em mulheres (8,6%/ano) e homens (3,8%/ano) com idade ≤39 anos. Ademais, houve um risco crescente nas coortes de nascimento em ambos os sexos no CBO HPV-relacionado, enquanto o risco reduziu no CBO HPV-não relacionado. No terceiro artigo, investigou-se a sobrevida em sítios anatômicos HPV-relacionados (n= 12.238), no câncer de boca (n= 12.858) e laringe (n = 12.095), sendo a *net survival* ajustada por idade em cinco anos de 24,4%, 34,1% e 44,9%, respectivamente. Independentemente da relação do sítio anatômico com o HPV, o maior risco de morte ocorreu nos estratos sociais mais vulneráveis (i.e., analfabetos ou pacientes com assistência pública de saúde), ajustando-se por faixa etária, sexo, estadiamento clínico e tratamentos (cirurgia, quimioterapia e radioterapia). As disparidades na sobrevida aumentaram em 34,9% em sítios anatômicos HPV-relacionados, enquanto houve uma redução de 10,2% e 29,6% no câncer de boca e laringe. **Considerações finais:** Existe um aumento na carga dos CCPs HPV-relacionados no Brasil e no mundo. Portanto, tem-se a recomendação do uso profilático da vacina para o HPV em ambos os sexos e o desenvolvimento de políticas públicas para proporcionar justiça social no acesso universal à saúde.

Palavras-chave: HPV. Papillomaviridae. Neoplasias de Cabeça e Pescoço. Sobrevida. Orofaringe. Neoplasias Laríngeas. Neoplasias Bucais.

ABSTRACT

Menezes FS. Survival and incidence in head and neck cancers according to HPV-related subsites [thesis]. São Paulo: University of São Paulo, School of Public Health; 2020.

Introduction: Molecular and epidemiological findings have demonstrated a "virus-related cancer epidemic" in head and neck cancer (HNC) caused by the human papillomavirus (HPV) infection. However, it is unclear whether this increasing incidence affects populations and their subgroups likewise, or whether it is restricted to certain countries. This investigation assessed the epidemiology of oral cavity cancers (OCC), oropharyngeal cancers (OPC), and larynx cancers (LC) according to HPV-related subsites. **Methods:** This thesis includes three manuscripts: (i) The systematic review focusing on global incidence trends in HNCs according to HPV-related subsites; (ii) The population-based study previous to prophylactic HPV vaccinations introduction in the city of São Paulo (1997-2013), which assessed incidence trends and age-period-cohort effect; and (iii) The hospital-based cohort study on the impact of HPV and inequalities on the survival of patients diagnosed with HNC in the state of São Paulo (2000-2018). **Results:** In the first study, we confirmed the hypothesis on the significative change in global incidence trends in HNCs due to the emerging burden of cancers in HPV-related subsites. Overall, age-standardized incidence rates (ASR) increased in HPV-related subsites. Conversely, ASRs decreased in HNCs associated with alcohol and tobacco use. In the second study, we analyzed 15,391 cases of OCC and OPC. Hence, we found an upward incidence trend in HPV-related subsites in females and males aged ≤39 years of 8.6% and 3.8% per year, respectively. Furthermore, there was an emerging risk in recent birth cohorts in both sexes in HPV-related OCC/OPC, whereas the risk reduced in HPV-unrelated OCC/OPC. In the third study, we assessed the survival in HPV-related subsites (n= 12,238), OCC (n= 12,858), and LC (n= 12,095). These subsites had an age-standardized 5-year relative survival (RS) of 24.4%, 34.1%, and 44.9%, respectively. For all subsites, we found the highest hazard of death in the most vulnerable social strata – i.e., illiterates or public funded healthcare patients, adjusted for age group, sex, clinical staging, and treatments (chemotherapy, radiotherapy, and surgery). Survival inequalities rose 34.9% in HPV-related subsites, whereas it diminished in OCC and LC by 10.2% and 29.6%, respectively. **Conclusions:** There is an increasing burden in HPV-related HNCs in Brazil and the world. Therefore, we recommend prophylactic HPV vaccination use in both sexes, as well as public policies to ensure social justice in universal healthcare access.

Keywords: HPV. Papillomaviridae. Head and Neck Neoplasms. Survival. Oropharynx. Laryngeal Neoplasms. Mouth Neoplasms.

LISTA DE ILUSTRAÇÕES

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LISTA DE SIGLAS

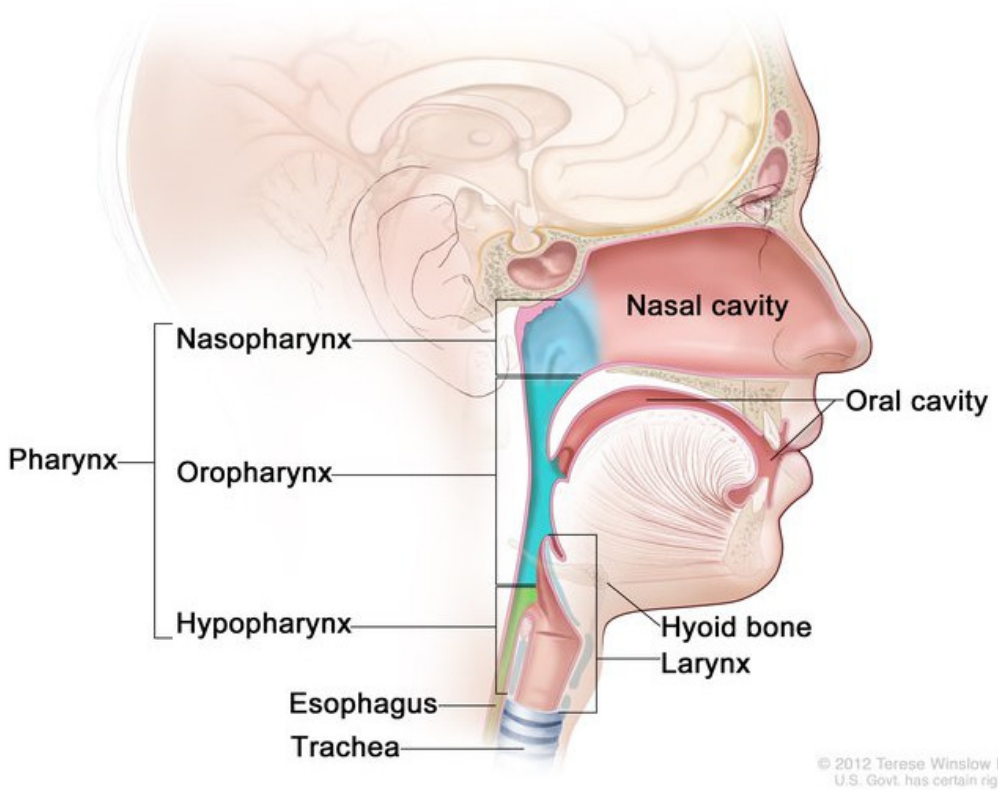
APC	Annual percentage change
ASR	Age-standardized incidence rate
CBI	Coeficientes brutos de incidência
CBO	Câncer de boca e de orofaringe
CCP	Cânceres de cabeça e pescoço
CEC	Carcinomas de células escamosas
CEP	Comitê de Ética em Pesquisa
CID-O	Classificação Internacional de Doenças para Oncologia
CO	Câncer de orofaringe
FOSP	Fundação Oncocentro de São Paulo
Fundação SEADE	Fundação Sistema Estadual de Análise de Dados
HPV	Papiloma vírus humano
HR	*Hazard ratio*
IARC	Agência Internacional de Pesquisa sobre o Câncer
IBGE	Instituto Brasileiro de Geografia e Estatistica
IC95%	Intervalo de confiança de 95%
ICSS	International Cancer Survival Standard
IDHM	Índice de Desenvolvimento Humano Municipal
INCA	Instituto Nacional de Câncer José Alencar Gomes da Silva
MAR	Missing at random
MICE	Multiple imputations by chained equations
OMS	Organização Mundial de Saúde
PIB	Produto interno bruto
PRO-AIM	Programa de Aprimoramento das Informações de Mortalidade
RR	Risco relativo
RS	*Relative survival*
SES	Status socioeconômico
SIM-MS	Sistema de Mortalidade do Ministério da Saúde
SISRHC	Sistema de Registro Hospitalar de Câncer
VPA	Variação percentual anual

SUMÁRIO

1 INTRODUÇÃO

O câncer de cabeça e pescoço (CCP) compreende neoplasias malignas que se originam de células escamosas localizadas no epitélio,[1] envolvendo o sistema digestório e as vias aéreas superiores. Embora não exista um consenso sobre quais sítios anatômicos envolvem o termo "CCP",[2] esse grupo heterogêneo de neoplasias malignas compreende o lábio, cavidade bucal, faringe (incluindo base de língua, palato mole e úvula), laringe, cavidade nasal e seios paranasais, bem como as glândulas salivares (Figura 1).[3] Geralmente, os estudos epidemiológicos avaliam a tireóide a parte das demais localizações anatômicas,[2] visto que, ela apresenta fatores etiológicos que diferem dos demais sítios anatômicos, isto é, associam-se mais à exposição à radiação ionizante e à deficiência de iodo.[4]

Figura 1 – Anatomia da faringe.

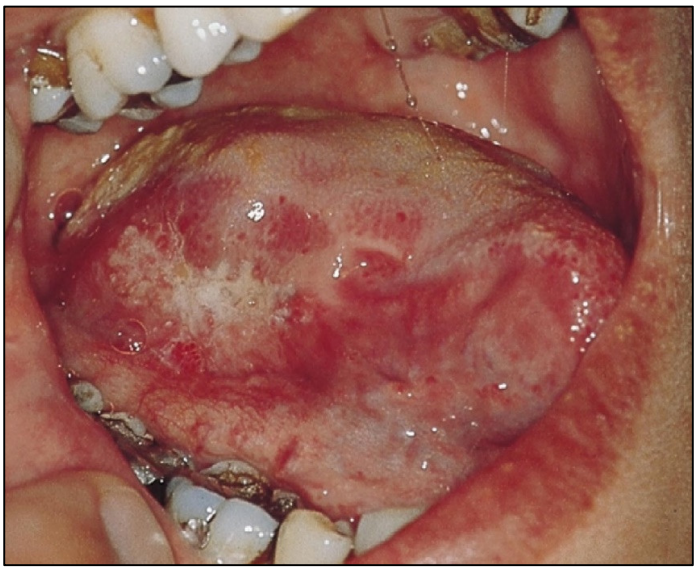


Credits: For the National Cancer Institute © (2012) Terese Winslow LLC, U.S. Govt. has certain rights.[5,6]

Morfologicamente, aproximadamente 91% dos CCPs são carcinomas de células escamosas (CEC), 2% são sarcomas, e os outros 7% são adenocarcinomas,

melanomas e tumores não especificados.[7] Clinicamente, o CCP é indolor em seu estágio inicial, evidenciando, por vezes, uma área leucoeritroplásica. Contudo, em estágios avançados podem existir úlceras e nódulos com rigidez ao toque e margens irregulares (Figura 2).[8] Embora os aspectos epidemiológicos tenham se alterado em alguns sítios anatômicos devido à infecção pelo HPV, essa neoplasia maligna se desenvolve com maior frequência no sexo masculino e na faixa etária superior aos 40 anos.[9]

Figura 2 – Câncer de boca.



Fonte: Scully & Bedi (2000).[10] Uso autorizado pela Elsevier (The Lancet Oncology).

Apesar dos significativos progressos no tratamento e diagnóstico do CCP,[11] as iniquidades aumentaram dentro das populações e entre os países.[12,13] A maioria dos pacientes europeus ainda são diagnosticados com câncer metastático ou com acometimento de linfonodos regionais.[11] E em países em desenvolvimento, pressupõe-se que a falta de recursos para o diagnóstico e tratamento precoces resulta em piores taxas de sobrevida, especialmente nos gradientes socioeconômicos mais vulneráveis. Adicionalmente, os tumores HPV-positivos em cabeça e pescoço ocorrem mais em pessoas com melhores condições socioeconômicas,[13] e a melhor resposta desses cânceres ao tratamento radioterápico[14] tem aumentado, por vezes artificialmente, as taxas de sobrevida e, consequentemente, as diferenças nas sobrevidas entre os estratos sociais ricos e pobres.

Considerando o enfoque da tese, nessa abordagem inicial serão explorados os seguintes aspectos envolvendo o câncer de boca, orofaringe e laringe: a epidemiologia, os fatores de risco associados, a classificação do CCP segundo sítios anatômicos relacionados ao papiloma vírus humano (HPV), bem como o impacto do status socioeconômico (SES) nas taxas de sobrevida.

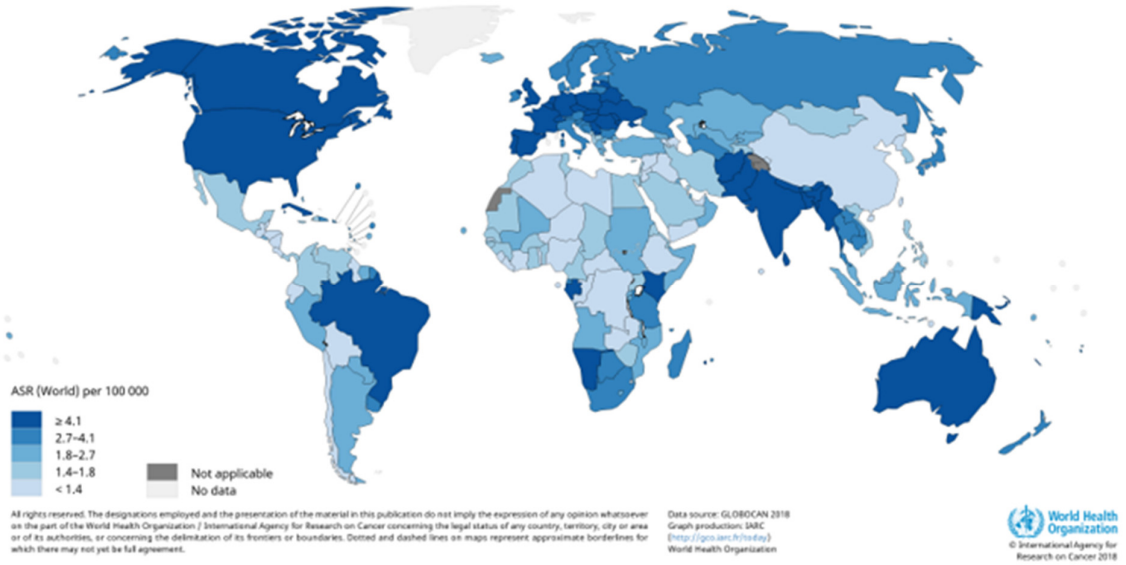
1.1 Epidemiologia do câncer de boca, orofaringe e laringe

Em 2018, houve uma estimativa de 453.000 mortes por CCP em todo o mundo com uma razão de incidência de homem:mulher de 3:1, e aproximadamente 75% dessas mortes ocorreram em países de baixa e média renda.[1] Dentre esses tumores, têm-se o câncer de boca, orofaringe e laringe, que tiveram mais casos estimados em 2018 na Índia (166.616), China (61.944), Estados Unidos (51.794), Paquistão (24.480) e Brasil (23.033).[15]

Em uma análise estratificada, em 2018 o câncer de boca teve uma estimativa mundial de 177.384 óbitos e 354.864 novos casos, e, no mesmo período, houve 51.005 mortes e 92.887 casos incidentes no câncer de orofaringe.[15] De forma combinada, o câncer de boca e orofaringe (CBO) é o sexto tipo de câncer mais frequente no mundo,[15–17] ressaltando-se que dois terços dos tumores ocorreram em países em desenvolvimento.[17]

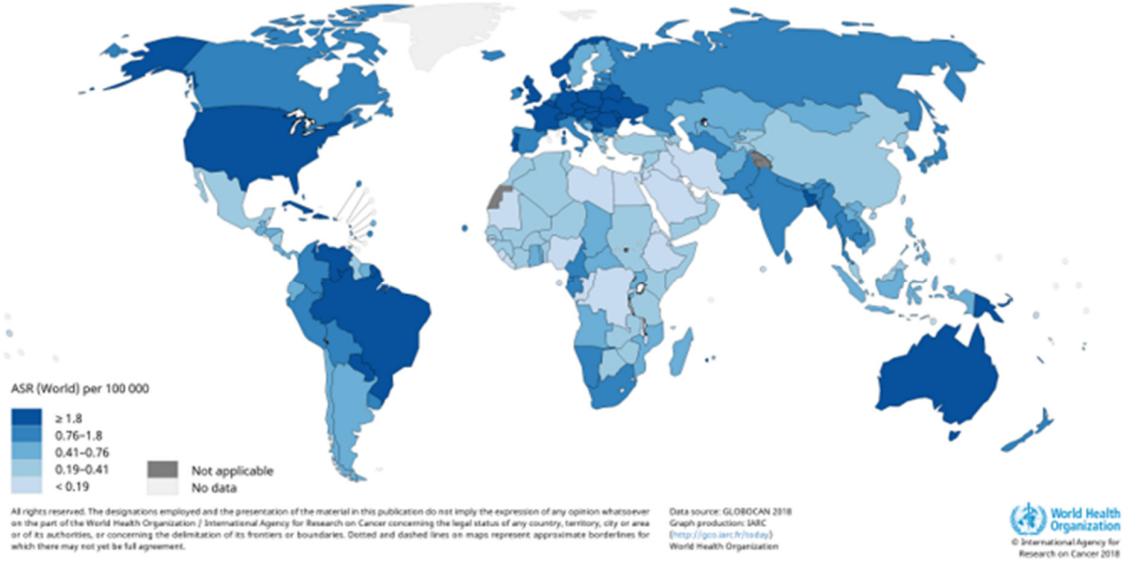
Em relação à distribuição entre os sexos, o CBO tem uma razão de incidência de homem:mulher de 2,5, representando de forma isolada para o câncer de orofaringe e boca 4,0 e 2,3, respectivamente.[15] Para os dois sexos combinados, o câncer de boca tem a maior taxa de incidência padronizada por idade, ou *age-standardized incidence rate* (ASR), do mundo dentre os CCPs: 4/100 mil.[1] Assim, as maiores ASRs são observadas na Papua Nova Guiné (20,4/100 mil), Paquistão (12,2/100 mil), Bangladesh (9,5/100 mil) e Índia (9,1/100 mil) (Figura 3).[1] Na orofaringe, os países com as mais altas ASRs (por 100 mil) são Romênia (Homem (H): 7,8; Mulher (M): 0,8), Bielorrússia (H: 7,3; M: 0,3), Hungria (H: 7,3; M: 2,4) e Dinamarca (H: 7,0; M: 2,0) (Figura 4).[15]

Figura 3 – Estimativa das taxas de incidência e mortalidade padronizadas pela idade em 2018 para lábio e cavidade oral (C00-06) em todos os sexos e grupos etários.



Fonte: Global Cancer Observatory: Cancer Today.[18]

Figura 4 – Estimativa das taxas de incidência padronizadas pela idade em 2018 para orofaringe (C09-10) em todos os sexos e grupos etários.

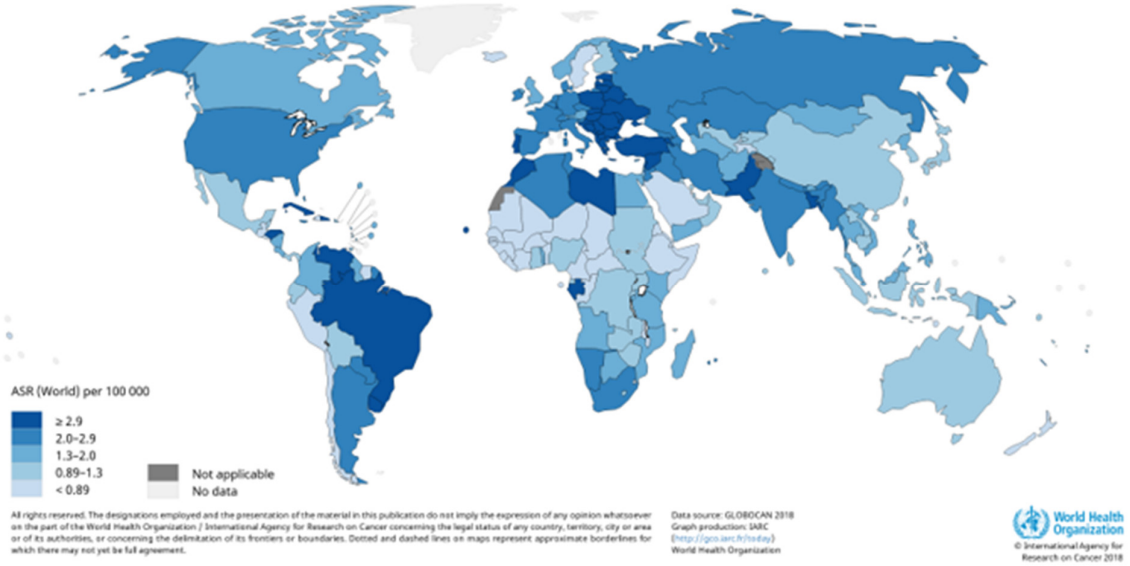


Fonte: Global Cancer Observatory: Cancer Today.[18]

No câncer de laringe, tem-se uma estimativa anual de 177.422 casos incidentes e 94.771 óbitos no mundo,[19] representando um terço de todos os CCPs.[20] A razão de incidência de homem:mulher é de 6,9:1, e os países com as maiores ASRs

(por 100 mil) são Cuba (H: 16,2; M: 1,9), República da Moldávia (H: 15,9; M: 0,4), Montenegro (H: 13,0; M: 3,4) e Hungria (H: 12,0; M: 2,0) (Figura 5).[15]

Figura 5 – Estimativa das taxas de incidência padronizadas pela idade em 2018 para laringe (C32) em todos os sexos e grupos etários.



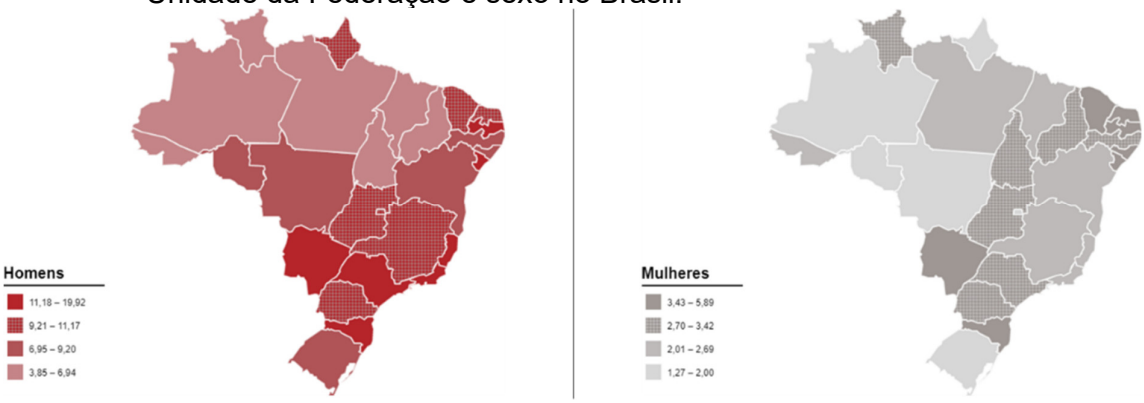
Fonte: Global Cancer Observatory: Cancer Today.[18]

No Brasil, o Instituto Nacional de Câncer José Alencar Gomes da Silva (INCA) estima para a cavidade oral (inclui-se boca e orofaringe) 11.200 novos casos em homens e 4.010 em mulheres, para cada ano entre 2020-2022. Tais valores representam um risco estimado de 10,69 casos novos a cada 100 mil homens, e 3,71 para cada 100 mil mulheres (Figura 6).[21] Na laringe, estimam-se 6.470 casos incidentes em homens (risco estimado: 6,20 casos/100 mil) e de 1.180 em mulheres (risco estimado: 1,06 casos/100 mil).

Excluindo-se os tumores de pele não melanoma, os cânceres na cavidade oral em homens é o quinto mais frequente nas Regiões Sudeste (13,58/100 mil), Centro-Oeste (8,94/100 mil) e Nordeste (7,65/100 mil), ocupando a sexta posição nas Regiões Sul (13,32/100 mil) e Norte (3,80/100mil). Em mulheres, trata-se do décimo primeiro câncer mais frequente na Região Nordeste (3,75/100 mil), e se encontra na décima segunda posição na Região Norte (1,69/100 mil). Nas Regiões Centro-Oeste (2,90/100 mil) e Sudeste (4,12/100 mil), representa a décima terceira posição, ocupando a décima quarta posição na Região Sul (4,08/100 mil). Na laringe, esses

carcinomas é o oitavo mais frequente nas Regiões Centro-Oeste (5,47/100 mil) e Nordeste (5,02/100 mil).[21]

Figura 6 – Taxas de incidência ajustadas por idade por 100 mil habitantes estimadas para o ano de 2020 em neoplasias malignas da cavidade oral, segundo Unidade da Federação e sexo no Brasil.



Fonte: Adaptado do INCA.[22]

Embora o câncer de boca e laringe esteja reduzindo as ASRs devido à diminuição do tabagismo,[20,23] o câncer de orofaringe está aumentando a incidência em proporções epidêmicas.[24] Por tais motivos, tem-se a necessidade de melhor compreender os fatores de risco na etiologia desses tumores.

1.2 Fatores de risco

Os principais fatores de risco envolvidos na gênese do câncer de boca, orofaringe e laringe são o consumo de álcool e tabaco.[25,26] Em região de cabeça e pescoço, o uso de álcool ou tabaco é responsável por 72% das neoplasias malignas, em que 4% se deve ao uso de álcool, 33% ao tabaco e 35% pelo uso combinado de ambas as substâncias.[25]

Adicionalmente, estima-se que a proporção do SES (educação e ocupação) explicada pelo tabagismo e o uso de álcool no CCP seja de 54% em pacientes com menos de quatro anos de estudo e de 45% para as ocupações manuais.[27]

Em alguns países como a Índia, o câncer de boca é causado principalmente pela mastigação de *betel quid* (gutka),[1] isto é, uma mistura de tabaco, noz de areca triturada, especiarias e outros ingredientes. Geralmente, essa goma de tabaco é

mastigada na boca entre a gengiva e a mucosa jugal. Além disso, ela contém nicotina e substâncias cancerígenas que podem levar à dependência química (Figuras 7 e 8).[28]

Figura 7 – Produtos transculturais de tabaco. a) Bidis tradicionais (tipo de cigarro sem filtro enrolado à mão); b) *Gutkha* (tabaco de mascar adocicado).

Fonte: Scully & Bedi (2000).[10] Uso autorizado pela Elsevier (The Lancet Oncology).

Figura 8 – Componentes do *betel quid*.

Fonte: Scully & Bedi (2000).[10] Uso autorizado pela Elsevier (The Lancet Oncology).

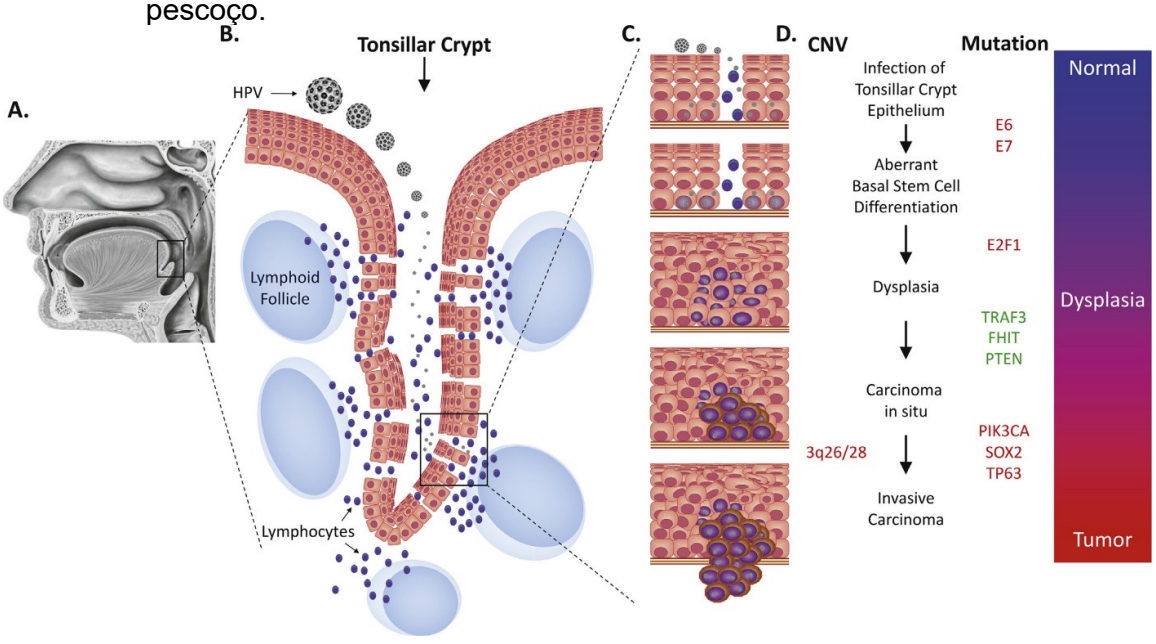
Além desses fatores de risco, tem-se também o consumo reduzido de frutas e vegetais,[29,30] a situação socioeconômica desfavorável,[27,31,32] névoa ácida e asbestos para a laringe[1] e o HPV, que tem sido considerado o principal fator de risco para o aumento na incidência de câncer de orofaringe.[1,24,33]

1.3 A classificação do CCP segundo sítios anatômicos relacionados ao HPV

O HPV consiste em um vírus oncogênico transmitido sexualmente, sendo responsável por aproximadamente 4,5% dos cânceres no mundo.[34] Em 1983, houve o primeiro relato associando o HPV ao câncer de boca.[35] Posteriormente, no ano 2000, um estudo laboratorial identificou que o HPV era um importante fator de risco para desenvolvimento do câncer de orofaringe (CO), uma vez que os tumores HPV-positivos apresentavam características epidemiológicas, clínicas e moleculares únicas.[36] Em 2006, observaram-se diferenças moleculares entre as neoplasias HPV-positivas e HPV-negativas, que sinalizavam vias carcinogênicas únicas. Ou seja, uma decorrente de agentes carcinogênicos ambientais (como álcool e tabaco) e outra induzida pelo HPV.[37] Desde então, a crescente evidência científica subsidiou a Agência Internacional de Pesquisa sobre o Câncer (IARC) para apontar o papel carcinogênico do HPV 16 na etiologia do CBO em 2007.[38]

A plausibilidade biológica que relaciona o HPV ao câncer de orofaringe se justifica pela diferença morfológica no tropismo tecidual e a presença de criptas nesse sítio anatômico. Assim, tais características anatômicas podem contribuir para o processo infeccioso, que desencadeia alterações somáticas e o desenvolvimento dos carcinomas HPV-positivos (Figura 9).[39,40]

Figura 9 – Modelo de carcinogênese associado ao HPV em região de cabeça e pescoço.



Fonte: Faraji et al (2017).[41] Uso autorizado pela Elsevier (Microbes and Infection).

No entanto, o reconhecimento do HPV como um fator de risco para o desenvolvimento dos tumores de cabeça e pescoço ainda é heterogêneo.[42] Embora o HPV seja um fator de risco associado ao desenvolvimento do CO[36,43,44] e esteja presente em 4-60% das lesões (a prevalência varia conforme o local do estudo),[45] o seu papel etiológico no câncer de boca ainda gera controvérsias. [36,46]

Para a melhor compreensão das alterações epidemiológicas nos cânceres de cabeça e pescoço, os termos “HPV-relacionado” e “HPV-não relacionado” têm sido utilizados na literatura científica para investigar as tendências dos tumores de acordo com as localizações anatômicas,[2,24,47–56] visto que, os registros de câncer geralmente não dispõem da informação referente ao status molecular e sorológico dos cânceres em relação à detecção do HPV.[50,57]

Essa classificação tem demonstrado consistência para lidar com as informações extraídas dos registros de câncer,[58] uma vez que essa proposta teve resultados semelhantes aos dados laboratoriais, que evidenciaram um crescimento de 40,5% para 72,2% na prevalência do HPV em cânceres de orofaringe.[49] Por esse motivo, ela tem sido muito empregada na literatura.[2,47,50–53,57,59–61]

Embora os estudos utilizem códigos similares, não existe um consenso em relação aos termos utilizados (Quadro 1). Inicialmente, classificaram-se os tumores em cânceres potencialmente HPV-associados e sítios anatômicos de comparação.[50] Posteriormente, houve uma proposta especificando como “HPV-associado”, “potencialmente HPV-associado” e “potencialmente não relacionado ao HPV”.[2] Com a evolução do conhecimento sobre a etiologia do CCP, os códigos foram alterados e se denominou “HPV-relacionado” e “HPV-não relacionado”.[47,57,58]

O nome “HPV-relacionado” ou “HPV-associado” está amplamente associado ao câncer de orofaringe.[47,51,53,56,61,62] Porém, a denominação para os demais cânceres “HPV-não relacionados” emprega diferentes terminologias, tais como: “câncer de cabeça e pescoço HPV-não relacionado”,[47] “câncer da cavidade oral HPV-não relacionado”[52] e “carcinomas de células escamosas da cavidade oral HPV-não relacionado”,[57] por exemplo.

Nessa pesquisa, adotou-se o conceito de CO em localizações anatômicas HPV-relacionadas quando envolver a orofaringe, as tonsilas, a base de língua, o palato mole, a úvula e o anel de Waldeyer. Por outro lado, empregou-se o câncer de boca em localizações anatômicas HPV-não relacionadas quando englobar partes da

língua, boca, gengiva e palato duro, visto que, esses sítios estão mais relacionados à exposição ao tabaco.[47]

Quadro 1 – Nomenclaturas dos sítios anatômicos segundo a relação com o HPV.

AUTORES (ANO)	NOMENCLATURAS	CÓDIGOS
Auluck et al. (2011)	"Oropharyngeal cancers"; "Oral cavity cancer".	"Oropharyngeal cancers": C01.9, C02.4, C09.0, C09.1, C09.8, C09.9, C10.2, C10.3, C10.8 e C10.9. "Oral cavity cancer": C02.0-2.3, C02.8, C02.9, C03.0-3.1, C03.9, C06.0-6.2, C04.0-4.1, C04.8-4.9, C00.3-5, C05.0, C06.8-6.9, C05.1-5.2 e C05.8-5.9.
Blomberg et al. (2011)	"HPV-associated"; "Potentially HPV-associated"; "Potentially unrelated to HPV".	"HPV-associated": C01.9, C02.4, C09, C14.2, C02.8, C10.2, C10.8, C10.9, C14.0, C14.8. "Potentially HPV-associated": C02.0-C02.3, C02.9, C03, C04, C05.0, C06, C3.2, C05.1, C05.2, C05.8, C05.9, C10.0, C10.1 e C10.3. "Potentially unrelated to HPV": C00, C07, CO8, C10.4, C11-13, C14.1, C30 e C31.
Brouwer, Eisenberg e Meza (2016)	"HPV-Related and HPV-Unrelated Oral Cancer"	"HPV-related": C01.9, C02.4, C09.0, C09.1, C09.8, C09.9, C10.0, C10.1, C10.2, C10.3, C10.4, C10.8, C10.9 e C14.2. "HPV-unrelated": C02.0, C02.1, C02.2, C02.3, C02.8, C02.9, C03.0, C03.1, C03.9, C04.0, C04.1, C04.8, C04.9, C05.0, C05.1, C05.2, C05.8, C05.9, C06.0, C06.1, C06.2, C06.8, C06.9, C12.9, C13.0, C13.1, C13.2, C13.8, C13.9, C14.0, C14.8.
Cole, Polfus e Peters (2012)[63]	"HPV-associated sites"; "non HPV-associated sites".	"HPV-associated sites": C01.9, C02.4, C09.0–C09.9, C10.2–C10.9 e C14.2. "Non HPV-associated sites": C02.0–C02.9 (exceto 2.4), C03.0–C03.9, C04.0–C04.9, C05.0–C05.9, C06.0–C06.9, C10.0–C10.1, C12.9,C13.0–C13.9, C14.0, C14.3–C14.8, C32.0–C32.9.
Forte et al. (2012)	"HPV-associated oropharyngeal cancer"; "head and neck cancer overall".	"HPV-associated oropharyngeal cancer": C01.9, C02.4, C09.0–C09.9, C10.0–C10.9 e C14.2. "Head and neck cancer overall": C00.0–C14.8.

AUTORES (ANO)	NOMENCLATURAS	CÓDIGOS
Hocking et al. (2011)	“Potentially HPV-associated”; “comparison site cancers”.	Adotou a proposta de Ryerson et al. (2008).[50]
Hwang et al. (2015)	“HPV-related head and neck cancer (HNC)”; “HPV-unrelated HNC”.	“HPV-related sites”: C01, C02.4, C02.8, C09.0, C09.1, C09.8, C09.9, C10.2, C10.8, C10.9, C14.0, C14.2 e C14.8. “HPV-unrelated sites”: C02.0, C02.1, C02.2, C02.3, C02.9, C03.0, C03.1, C03.9, C04.0, C04.1, C04.8, C04.9, C05.0, C05.1, C05.2, C05.8, C05.9, C06.0, C06.1, C06.2, C06.8, C06.9, C10.0, C10.1, C10.3, C12, C13.0, C13.1, C13.2, C13.8, C13.9, C32.0, C32.1, C32.2, C32.3, C32.8 e C32.9.
Lam et al. (2015)	“Oropharyngeal squamous cell carcinoma (OPSCC) HPV-related”; “Non-oropharyngeal head and neck squamous cell carcinoma”.	“Oropharyngeal squamous cell carcinoma (OPSCC) HPV-related”: C01.9, C02.4, C05.1-C05.2, C09.0-C09.1, C09.8-C09.9, C10.0-C10.4, C10.8-C10.9 e C14.2. “Non-oropharyngeal head and neck squamous cell carcinoma”: C02.0-C02.3, C02.8-C02.9, C03.0-C03.1, C03.9, C04.0-C04.1, C04.8-C04.9, C05.0, C05.8-C05.9, C06.0-C06.2 e C06.8-C06.9.
Jéhannin-Ligier et al. (2017)	“Potentially HPV-related”; “HPV-unrelated”.	“Potentially HPV-related”: C01.9, C02.4, C09, C10 e C14.2. “HPV-unrelated”: C00, C02 (exceto C02.4), C03, C04, C05, C06, C12, C1), C14 (exceto C14.2), C32.
Ryerson et al. (2008)	“Sites of Potentially HPV-Associated Cancers”; “Comparison Sites”.	“Sites of Potentially HPV-Associated Cancers”: C01.9, C02.4, C02.8, C09.0, C09.1, C09.8, C09.9, C10.2, C10.8, C10.9, C14.0, C14.2 e C14.8. “Comparison Sites”: C02.0, C02.1, C02.2, C02.3, C02.9, C03.0, C03.1, C03.9, C04.0, C04.1, C04.8, C04.9, C05.0, C05.1, C05.2, C05.8, C05.9, C06.0, C06.1, C06.2, C06.8, C06.9, C10.0, C10.1, C10.3, C32.0, C32.1, C32.2, C32.3, C32.8 e C32.9.
Shin et al. (2013)	“HPV-related sites (oropharynx including tonsil)”; “HPV-unrelated sites”.	“HPV-related sites (oropharynx including tonsil)”: C09–C10 e C14. “HPV-unrelated sites”: C00–C06, C01–C02, C12–C13 e C32.
Souza et al. (2012)	“Oral cavity and oropharyngeal cancers”.	"Oral cavity": C00.3–C00.9, C02.0–C2.3, C02.8–9, C03.0–1, C03.9, C04.0–1, C04.8–9,

AUTORES (ANO)	NOMENCLATURAS	CÓDIGOS
		C05.0, C05.8–9, C06.0, C06.1, C06.2, C06.8 e C06.9. “Oropharyngeal cancers”: C01.9, C02.4, C05.1, C05.2, C09.0–1, C09.8–9, C10.0–C10.4 e C10.8–9.

Deste modo, estudos apontaram uma epidemia viral relacionada ao HPV, [24,64,65] visto que, o crescimento do CO em localizações anatômicas HPV-relacionadas não é explicado por mudanças no tratamento, registro dos dados ou rastreamento das lesões.[60] E paralelamente, as variações temporais demonstraram um aumento na tendência de CO em localizações anatômicas HPV-relacionadas na América do Norte,[51,53,57,63,66,67] América do Sul,[68] Ásia[55,56,69] e Europa,[70,71] mesmo com a redução dos cânceres relacionados ao consumo de tabaco.[42] Vale ressaltar, que as tendências de incidência não foram estabelecidas para a África.[72]

Nos Estados Unidos, observou-se um aumento na tendência de incidência em tumores em localizações anatômicas HPV-relacionadas variando de 2,1% a 3,2%,[51,57,63,66] enquanto que dados laboratoriais reportaram um crescimento concomitante na prevalência de HPV de 16,3% para 71,7%.[49] No Canadá, encontrou-se um aumento significativo na taxa de incidência padronizada por idade de 1,6/100.000 habitantes em 1992 para 2,6/100.000 habitantes em 2009 (Variação percentual anual (VPA)= 2,7%; p= 0,001). Por outro lado, os tumores em sítios anatômicos HPV-não relacionados diminuíram 3% ao ano entre 1992 a 1998.[53]

Na Inglaterra, a incidência de cânceres em localizações HPV-relacionadas cresceu 45,5% de 1,8/100.000 habitantes em 2002 para 3,3/100.000 habitantes em 2011 (p<0,0001).[70] Em uma análise agregada envolvendo países europeus, tais como Áustria, Alemanha, Itália, Holanda, Polônia, Escócia, Eslovênia, Suécia, Suíça e País de Gales, identificou-se um aumento de 3,4% na VPA entre 1988 e 2002.[71] Contudo, na Eslovênia entre 1983 e 2009 as tendências de incidência decresceram em sítios anatômicos HPV-relacionados (VPA= -0,6%) e HPV-não relacionados (VPA= -0,9%).[73]

Na Ásia, observou-se um crescimento na incidência dos tumores em sítios anatômicos HPV-relacionados em Hong Kong entre 1994 e 2014 com um incremento de 2,7%/ano,[69] e de 2,4%/ano na Coréia do Sul entre 1999 e 2009.[56] De maneira análoga, em Taiwan as neoplasias em localizações anatômicas HPV-relacionadas

cresceram expressivamente de 1,3/100.000 habitantes em 1995 para 3,3/100.000 habitantes em 2009 com uma VPA de 6,9% ao ano (p< 0.0001).[55]

Em relação aos sexos, entre 1987 a 2008 houve um aumento nas tendências de incidência em homens (VPA= 5,4) e mulheres (VPA= 3,8) no Peru.[68] Em Singapura, também se observou um crescimento em sítios anatômicos HPV-relacionados no período de 1993–2012 para homens (VPA= 1,9%; p<0,001) e de 1968–2012 para mulheres (VPA= 2,0%; p= 0,01).[47]

Dessa forma, os acréscimos nas tendências foram mais observados no sexo masculino,[47,53,55,56] observando-se uma VPA de até 7,5% (p< 0,0001).[55] Embora existam evidências científicas relacionando o HPV aos comportamentos sexuais de risco,[24,74,75] ainda não está claro por que os homens têm uma maior susceptibilidade em relação às mulheres para a infecção oral pelo HPV.[55]

Dentre as possíveis hipóteses, têm-se que: (i) os homens têm mais parceiros de sexo oral e vaginal ao longo da vida e uma maior prevalência do HPV-16 do que as mulheres (p<0,001);[76] (ii) a transmissão do HPV por meio do sexo oral da mulher para o homem é mais eficiente do que a transmissão do homem para a mulher devido às características anátomo-histológicas das genitálias;[77] e (iii) as mulheres com alto índice de anticorpos HPV16 decorrente da infecção cervical reduzem o risco de um novo processo infeccioso relacionado ao HPV.[78]

De uma forma geral, os carcinomas em sítios anatômicos HPV-relacionados ocorreram mais na faixa etária de 30-59 anos,[2,53,55,56] notando-se uma maior incidência para o grupo etário de 45-54 anos quando se compara às outras faixas etárias (VPA= 4,42%; p< 0,05).[63] Além disso, as taxas de incidência em tumores em localizações anatômicas HPV-relacionadas foram maiores nas minorias étnicas do que na população em geral,[52] como se evidenciou em negros nos Estados Unidos com taxas de incidência mais altas do que outros grupos raciais ou cor da pele.[50,58]

Contudo, existem controvérsias em relação à raça/cor, visto que, autores evidenciaram um maior crescimento em homens brancos,[79] e Cole et al. (2012) apontaram uma maior incidência em brancos não-hispânicos (VPA= 4,09%; p<0,05) e hispânicos (VPA= 1,08%; p<0,05).[63]

Adicionalmente, as taxas de incidência podem ser influenciadas pela variação na idade dos participantes,[17] por fatores relacionados a um período específico (efeito do período) e pelas diferentes exposições do passado nas sucessivas gerações (efeito coorte).[80] Nos Estados Unidos, identificou-se que a

incidência em sítios anatômicos HPV-relacionados se elevou significativamente para as coortes de nascimento entre 1940 e 1970, bem como ocorreu uma tendência crescente após o início da década de 90.[58] Assim, a mudança nos comportamentos sexuais, por exemplo o aumento do sexo oral e de parceiros sexuais, tem sido apontada como a principal justificativa para o aumento da incidência de câncer de orofaringe nos Estados Unidos e em alguns países do norte da Europa[64] – sobretudo – nas gerações mais jovens.[2]

A infecção pelo HPV necessita de um período superior a dez anos para desenvolver uma neoplasia maligna, e uma mudança no comportamento sexual justificaria o aumento dessa incidência.[48] E paralelamente, as coortes de nascimento evidenciaram uma idade mais precoce para a primeira relação sexual,[81] um crescimento do número de parceiros sexuais[82] e uma maior prática de sexo oral,[75] bem como os dados laboratoriais comprovam uma maior soroprevalência do HPV em pessoas de menor idade.[78]

Dessa forma, os pacientes diagnosticados com câncer em sítios anatômicos HPV-relacionados têm características clínico-epidemiológicas diferentes dos demais casos com tumores não relacionados ao HPV, visto que, são mais jovens,[57,83] consomem menos de álcool e tabaco[24] e possuem um maior número de parceiros sexuais.[83,84] Além disso, eles também apresentam uma melhor sobrevida global e têm menor risco de morte quando comparados aos casos de sorologia negativa.[14]

Em comparação com os Estados Unidos (2 casos/100.000 habitantes) e a Europa (~1 caso/100.000 habitantes), o Brasil tem uma menor incidência de câncer de orofaringe HPV16-positivo de ~0,2 caso/100.000 habitantes,[45] e a população saudável tem uma taxa de infecção pelo HPV de apenas 6,2%.[85] Por outro lado, estimou-se em 2012 15.943 novos casos e 8.205 óbitos de câncer de boca e orofaringe (exclui a nasofaringe),[86] evidenciando-se entre 1983 e 2002 um aumento significativo na incidência de CO em homens,[42] assim como se identificou um risco elevado de morte por CO em mulheres.[87]

No município de São Paulo, observou-se uma tendência crescente de mortalidade para o CO de +4,51%/ano,[88] e houve um aumento da porcentagem de carcinomas de cabeça e pescoço HPV-positivos entre 1998 e 2008.[89] Entretanto, mesmo com a crescente evidência do envolvimento do HPV no desenvolvimento do CCP,[90] inexistem estudos considerando os sítios anatômicos relacionados ao HPV

para caracterizar a tendência temporal e o efeito idade-período-coorte dos casos no município.

1.4 Sobrevida e desigualdades no CCP

O status socioeconômico está associado aos piores desfechos na sobrevida de pacientes com CCP.[12,13,32,91,92] Assim, as desigualdades se tornaram uma preocupação global devido ao seu papel em mortes evitáveis, visto que, embora o prognóstico esteja melhorando em países desenvolvidos,[11] as disparidades na sobrevida têm aumentado entre os países e dentro das populações.[12,13]

As iniquidades são desigualdades injustas e evitáveis, que surgem devido às circunstâncias em que as pessoas crescem, vivem, trabalham e envelhecem, e são moldadas por questões políticas, sociais e econômicas.[93] Na sobrevida do CCP, elas representam um fenômeno social multifacetado que se relaciona à privação material ou de renda, escolaridade e fatores comportamentais, tais como uso de álcool e tabaco e hábitos alimentares.[32] Adicionalmente, têm-se o acesso aos serviços de saúde,[94,95] incluindo a sua probabilidade de procura,[96] que se relaciona ao diagnóstico tardio e às piores taxas de sobrevida nos pacientes (Quadro 2).

Os mecanismos pelos quais o SES impacta na sobrevida dos CCPs são difíceis de serem mensurados devido aos fatores de risco desconhecidos.[32,91] No entanto, estudos têm investigado as desigualdades na sobrevida a partir de informações sobre seguro ou plano de saúde [92,97,98], grau de escolaridade [99] e fatores contextuais.[12,13,91,100] Embora a escolha das variáveis na mensuração do SES tenham variado amplamente,[101] as pesquisas supracitadas foram consistentes em apontar as disparidades na sobrevida em seus resultados.

Em países europeus, a sobrevida relativa (RS) em cinco anos variou consideravelmente para cânceres em orofaringe e tonsila (16,2-57,1%), cavidade bucal (19,1-60,9%) e laringe (42,8-77,5%).[11] Do mesmo modo, desigualdades na sobrevida ocorreram entre pacientes ricos e desfavorecidos no Canadá[91] e em Singapura.[12]

Sendo assim, o enfrentamento do impacto das iniquidades nas taxas de sobrevida é essencial para promover condições iguais entre os pacientes independentemente de seu SES.

Quadro 2 – Estudos sobre a relação entre o SES e o câncer de boca, orofaringe e faringe.

AUTORES (ANO)	LOCAL	PERÍODO	PRINCIPAIS RESULTADOS
Adrien et al (2014)[94]	França	2010-2012	Não foi encontrada associação significativa entre os fatores socioeconômicos (principalmente privação ou consumo de álcool e tabaco) e o diagnóstico tardio do HNSCC.
Agarwal et al (2019)[97]	Estados Unidos	1973-2014	Os pacientes utilizando Medicaid com o câncer de boca em estágio avançado têm uma menor probabilidade de receber terapias definitivas e têm uma sobrevida global significativamente pior do que aqueles com outras formas de seguro.
Auluck et al (2016)[91]	Canadá	1981-2009	O SES continua sendo um significativo determinante independente na sobrevida para CO e CB ao usar um indicador composto para o SES. As taxas de sobrevida do CO entre os homens melhoraram, embora de maneira mais lenta nas comunidades carentes.
Belot et al (2018)[100]	França	1997-2010	O câncer em lábio, cavidade bucal e faringe em homens apresentou o maior "gap" de privação, com a sobrevida relativa padronizada por idade em 5 anos em 41% e 29% para os quintis de privação 1 e 5, respectivamente, e se encontrou uma associação não-linear entre o *European Deprivation Index* (EDI) e o *Excess Mortality Hazard* (EMH).
Boing et al (2011)[27]	Brasil	1998-2006	Indivíduos com menor escolaridade (OR 2,27; IC 95% 1,61 a 3,19) e aqueles que realizavam trabalho manual (OR 1,55; IC 95% 1,26 a 1,92) apresentaram maior risco de doença. No entanto, 54% da associação com baixa escolaridade e 45% da associação com trabalho manual foram explicados por exposições proximais ao estilo de vida, e o status socioeconômico permaneceu significativamente associado à doença quando ajustado para o consumo de tabaco e álcool.
Bosetti et al (2001)[102]	Itália	1984-1997	Os cânceres do trato digestivo superior relacionados aos aspectos socioeconômicos mudaram nos últimos anos na Itália, com o desaparecimento do gradiente social.

AUTORES (ANO)	LOCAL	PERÍODO	PRINCIPAIS RESULTADOS
Chu et al (2016)[101]	Canadá	2003-2010	O SES foi associado à sobrevida, mas esse efeito foi perdido após se considerar outros fatores (idade, sexo, estágio TNM, tabagismo/álcool). O menor SES foi associado ao maior tabagismo, consumo de álcool, comorbidades e estadiamento.
Conway et al (2008)[103]	Análise agrupada com diversos países	1922-2004	O baixo SES foi significativamente associado ao aumento do risco de câncer de boca em países de alta e baixa renda em todo o mundo, e permaneceu ao se ajustar para possíveis fatores de confusão comportamentais.
Conway et al (2010)[104]	Escócia	2002-2004	Pessoas que vivem em áreas mais carentes (OR= 4,66, IC 95% 1,79–12,18); e aqueles que estavam desempregados (OR= 2,27, IC 95% 1,21-4,26) apresentaram um risco significativamente maior de câncer do que aqueles com altos níveis de escolaridade (OR= 0,17, IC 95% 0,05-0,58). Contudo, todas as medidas de classe social perderam a significância estatística quando foram se ajustou pelo tabagismo e o consumo de álcool.
Conway et al (2015)[32]	Análise agrupada com diversos países	1981-2012	Os níveis mais baixos de renda e escolaridade foram associados a um risco duas vezes maior de câncer de cabeça e pescoço, o que não é totalmente explicado pelas diferenças nas distribuições de fatores de risco comportamentais para esses tipos de câncer e que variam entre os locais de câncer, sexos, países e níveis de desigualdade de renda nos países.
Dantas et al (2016)[99]	Brasil	2000-2009	O tipo histológico, estágio do tumor e baixo grau de escolaridade influenciaram significativamente a sobrevida do câncer de boca.
Ferreira et al (2012)[105]	Brasil	1997-2008	As menores taxas de mortalidade do CBO se concentraram na área mais rica e economicamente menos desigual do município de São Paulo.
Kwok et al (2010)[92]	Estados Unidos	1998-2007	Pacientes utilizando Medicaid/não segurados e Medicare tiveram um maior risco de morte após o diagnóstico quando comparados a pacientes com seguro privado, após ajuste por idade, sexo, raça, tabagismo, uso de álcool, sítio anatômico, status socioeconômico, tratamento e estadiamento.

AUTORES (ANO)	LOCAL	PERÍODO	PRINCIPAIS RESULTADOS
McDonald et al (2014)	Canadá	1992-2005	A magnitude da diferença na sobrevida entre os mais altos e mais baixos quintis de renda aumentou significativamente ao longo do período estudado para o câncer de orofaringe, mas não mudou de maneira significativa para o câncer de cavidade oral ou outros tipos de câncer de cabeça e pescoço.
Rylands et al (2016)[106]	Inglaterra	2008-2012	Após o ajuste para os fatores clínicos e do paciente, os pacientes residentes em áreas mais carentes apresentaram uma pior qualidade de vida em relação ao funcionamento socioemocional e à qualidade de vida geral, mas não em relação à função física oral.
Shin et al (2018)[98]	Estados Unidos	2004-2013	O tipo do seguro saúde está associado ao tratamento e aos resultados em pacientes com câncer de cavidade oral. Estar sem seguro ou no Medicaid foi associado a um maior risco de um prognóstico pior quando comparado ao seguro privado. Os dados sugerem a necessidade de expandir a cobertura médica abrangente e otimizar o acesso a cuidados médicos adequados em populações vulneráveis de pacientes.
Wang et al (2018)[107]	Taiwan	1990-1994; 1998-2007	A cobertura universal por si só pode não reduzir a desigualdade de saúde entre os diferentes grupos de renda do câncer de boca, a menos que medidas preventivas efetivas sejam implementadas para regiões economicamente desfavorecidas.
Wong et al (2017)[12]	Singapura	1992-2014	Pacientes com CCP do tipo CCE que moram em apartamentos menores e com mais subsídios governamentais de moradia têm uma menor taxa de sobrevida, apesar de não haver atrasos no diagnóstico.

2 JUSTIFICATIVA

As pesquisas indicam que o HPV é um problema global, pois se estima que esse vírus gere 630.000 novos cânceres/ano.[34] Ele também é considerado uma causa necessária para os cânceres cervicais,[108] sendo identificado em 60% dos carcinomas em orofaringe.[45] Nos CCPs, os cânceres relacionados ao consumo de álcool e tabaco têm reduzido os novos casos,[42] enquanto que os tumores em localizações anatômicas HPV-relacionadas está aumentando a incidência na América do Norte,[50–53,59] Europa[2,60,61] e Ásia.[47,55,56] Em 2020, estima-se que a incidência do CO será maior do que a incidência do câncer de colo de útero. E em 2030, metade de todos os CCPs serão associados ao HPV.[49]

Em contrapartida, existem muitas lacunas sobre o tema,[24] por exemplo: como está a situação epidemiológica em relação aos carcinomas em localizações anatômicas HPV-relacionadas no mundo? Em países com baixa prevalência para o HPV, como se encontra a situação epidemiológica em relação à epidemia viral? Existe influência do efeito idade-período-coorte na ocorrência dos tumores em sítios anatômicos associados ao HPV? Quais os impactos dessa epidemiologia em transformação na sobrevida dos pacientes?

Mundialmente, não se sabe se essa epidemia viral afeta as populações e seus subgrupos de forma similar ou se ela se restringe a países específicos. Adicionalmente, a América do Sul tem a maior prevalência global de HPV oral em indivíduos saudáveis.[109] E no Brasil, observou-se uma presença de HPV em 59,1% dos tumores de orofaringe em pacientes de um hospital privado,[110] apesar da introdução das vacinas profiláticas para o HPV em 2014. Em paralelo, o país tem a segunda maior concentração de renda do mundo[111] e a maior taxa de incidência em CCPs na América Central e Caribe.[112] E embora tenha ocorrido a expansão da atenção primária e de programas de saúde bucal para a população,[113] as iniquidades no uso dos serviços de saúde persistem, visto que, existe uma distribuição desigual das taxas de mortalidade do CBO nos territórios.[105]

Considerando tais iniquidades e a heterogeneidade na prevalência do HPV, tem-se a necessidade de se diferenciar os cânceres de cabeça e pescoço relacionados ao HPV dos carcinomas associados ao consumo de álcool e tabaco, a fim de compreender se existe uma epidemia viral no Brasil e no mundo.

3 OBJETIVOS

3.1 Objetivo geral

Investigar a epidemiologia do câncer de boca, orofaringe e laringe segundo a relação com o HPV.

3.2 Objetivos específicos

i. Estimar os efeitos globais do HPV nas tendências de incidência do CCP por meio de uma revisão sistemática de acordo com a região geográfica, faixa etária, sexo e raça/etnia.

ii. Analisar as tendências de incidência e o efeito idade-período-coorte do CBO segundo sítios anatômicos HPV-relacionados e HPV-não relacionados nos anos anteriores à imunização em grande escala do HPV na cidade de São Paulo (1997-2013).

iii. Investigar se o status socioeconômico influencia na sobrevida dos cânceres em localizações anatômicas HPV-relacionadas e HPV-não relacionadas em pacientes do estado de São Paulo (2000-2018).

4 MÉTODOS

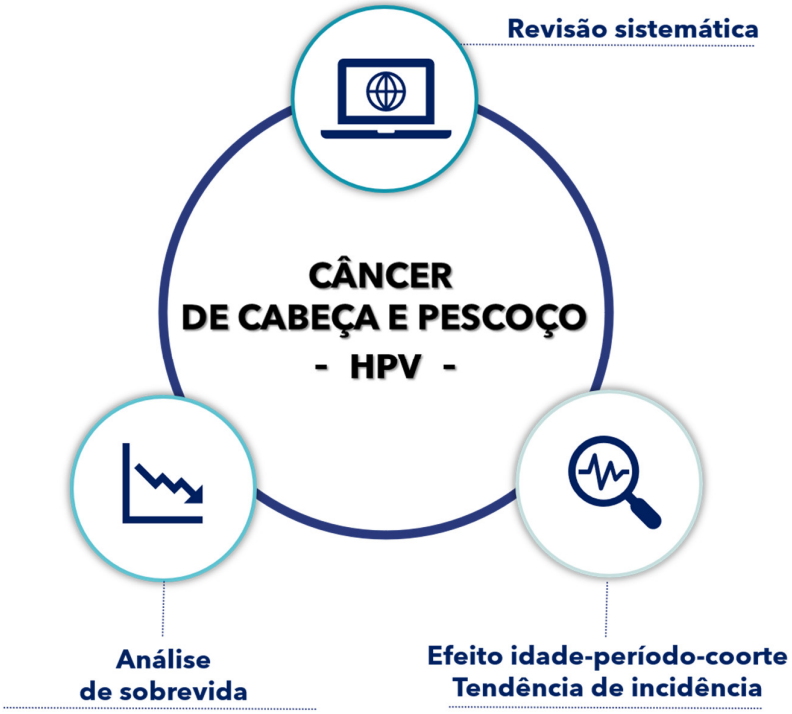
4.1 Delineamentos dos estudos

Para compreender as diferenças na epidemiologia do CCP segundo a relação do sítio anatômico com o HPV, essa tese empregou três tipos de delineamentos: (i) Revisão sistemática; (ii) Estudo ecológico de base populacional; e (iii) Estudo de coorte de base hospitalar (Figura 10).

A revisão sistemática consiste no estudo da evidência científica com a aplicação de estratégias para limitar vieses na seleção, análise crítica e síntese de todos os estudos relevantes sobre um tópico específico.[114]

O delineamento ecológico utiliza populações ou grupos de indivíduos como unidades de observação, que são geograficamente definidos em diferentes pontos do tempo. Por outro lado, o estudo de coorte se trata de uma abordagem prospectiva, que considera os indivíduos como unidades de observação, a fim de investigar se a incidência de um evento está relacionada a uma suspeita de exposição.[80] Maiores detalhes serão descritos nos próximos itens.

Figura 10 – Delineamento dos estudos realizados.

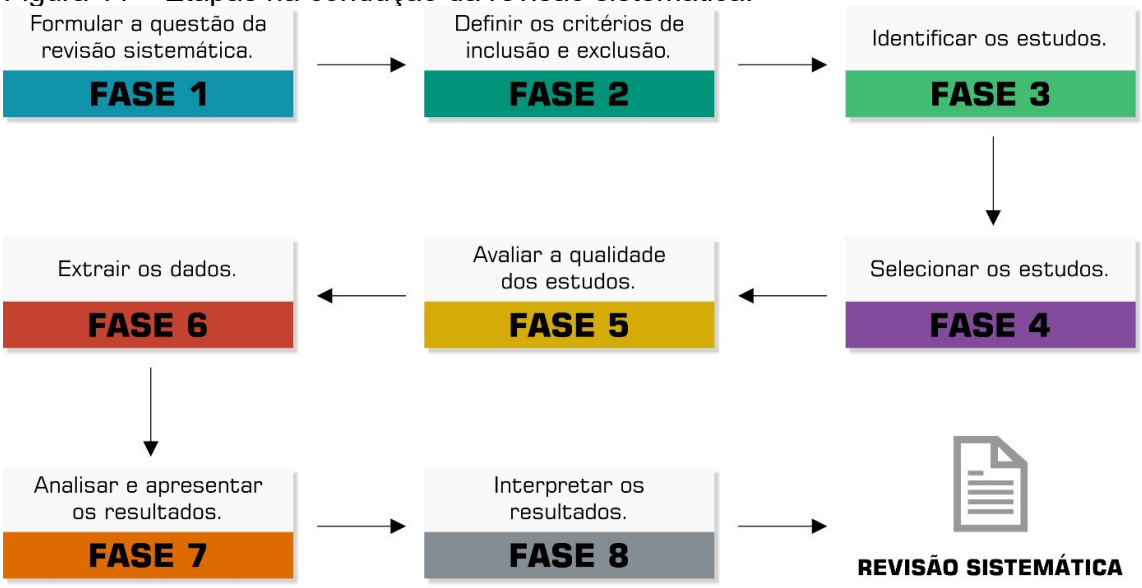


Fonte: produção do próprio autor.

4.2 Manuscrito 1: Revisão sistemática

O protocolo do estudo foi elaborado conforme o PRISMA e literaturas pertinentes (Figura 11).[115–117] A revisão sistemática foi registrada na "International prospective register of systematic reviews" (PROSPERO) com o número de registro CRD42019121589. Assim, desenvolveram-se buscas nas bases de dados eletrônicas envolvendo a PubMed, Embase e Scopus, compreendendo o período de 1964 a quatro de setembro de 2018 e sem o emprego de filtros (Quadro 3).

Figura 11 – Etapas na condução da revisão sistemática.



Fonte: produção do próprio autor a partir de Egger, Davey-Smith e Altman (2008).[117]

Quadro 3 – Descritores empregados nas estratégias de busca.

MeSH	Mouth neoplasms; oropharyngeal neoplasms; head and neck neoplasms; papillomaviridae; papillomavirus infections; epidemiology; registries; time factors; trends.
Emtree	Wart virus; Human papillomavirus type 16; Human papillomavirus type 18; head and neck cancer; mouth cancer; oropharynx cancer; Epidemiology; trends; register; time factor.

Fonte: produção do próprio autor.

A estratégia de busca envolveu o uso de operadores lógicos booleanos (AND, OR, and NOT) para conectar palavras-chaves obtidas por meio do Medical

Subject Headings (MeSH) e Embase subject headings (Emtree), adicionando-se os termos “oral cavity cancer” e “oropharyngeal cancer” para aumentar o número de registros. Paralelamente, pesquisas complementares foram realizadas na literatura cinzenta a partir do OpenGrey.

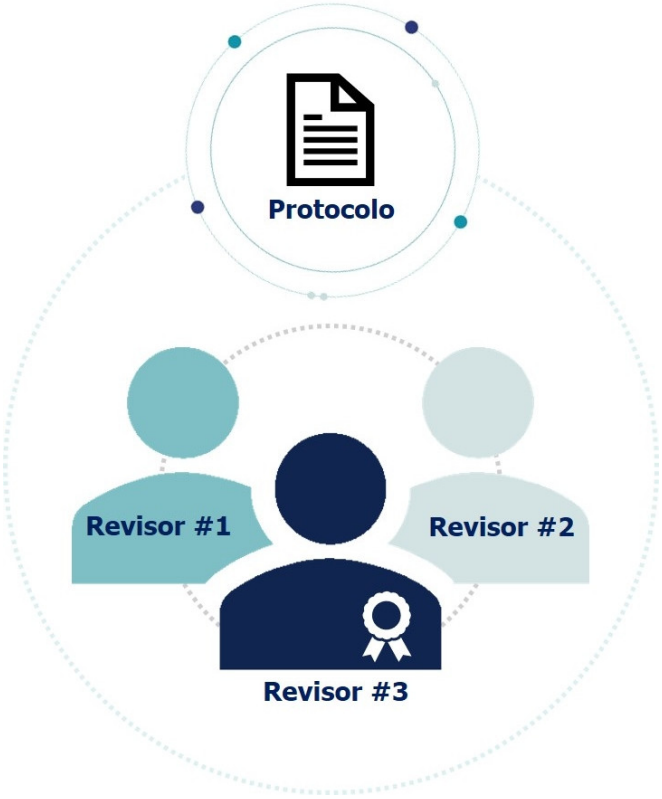
Além disso, estudos foram recuperados na revisão das referências dos artigos elegíveis (n= 1),[118] através do contato com outros autores (n= 2),[66,119] e pela busca manual de publicações relevantes (n= 2).[61,69] Por fim, os autores foram contatados por e-mail para se obter informações adicionais.[60,61,70]

Essa revisão sistemática incluiu apenas estudos de base populacional que classificaram os casos como um grupo (proxy) para a exposição ao HPV em sítios anatômicos de cabeça e pescoço, compreendendo pelo menos a tonsila (C09) com outra localização anatômica HPV-relacionada. É importante citar que os estudos elegíveis não identificaram a presença do HPV nos tumores, visto que, apenas a análise estratificada por localizações anatômicas foi desenvolvida.

Os dados foram extraídos das publicações selecionadas de acordo com as tendências de incidência gerais e específicas, ou seja, por faixa etária, raça/etnia e sexo, bem como o efeito idade-período-coorte. Estudos individuais e experimentais, relatos de caso, capítulos, protocolos clínicos, resumos, editoriais, prefácios, revisões e publicações sem revisão por pares foram excluídos. Adicionalmente, removeram-se três publicações classificadas como relatórios,[120–122] e um estudo que realizou análises para cada sítio anatômico individualmente.[50]

Após a identificação das publicações nas bases de dados eletrônicas, o *software* EndNote Web® foi utilizado para importar os estudos e excluir qualquer dado duplicado. Em consonância com o protocolo, dois revisores independentes filtraram os estudos por título, resumo e texto completo. Quando houve discordâncias, os examinadores discutiram os resultados até se obter um consenso. Caso a discordância persistisse, um terceiro examinador definiu se a publicação era relevante para o estudo (Figura 12).

Figura 12 – Seleção dos estudos elegíveis durante a revisão sistemática.



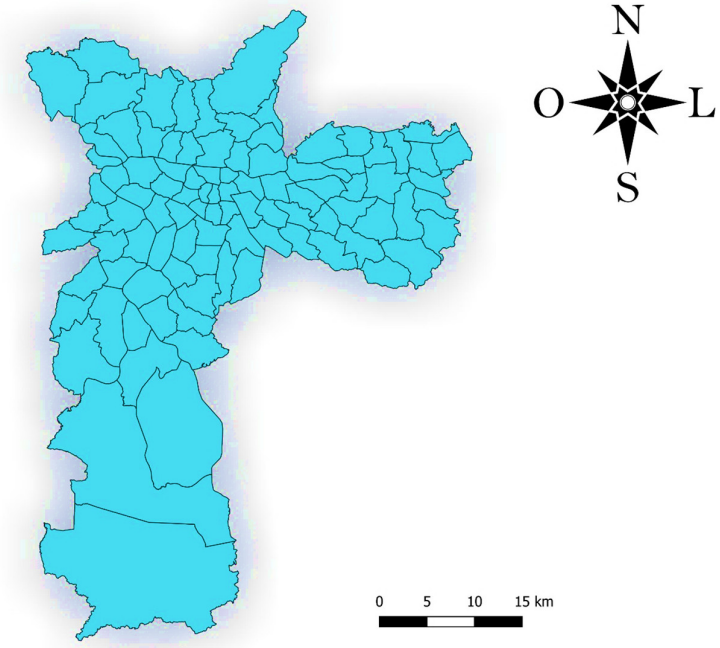
Fonte: produção do próprio autor.

Portanto, os dados foram extraídos e verificados em relação às seguintes variáveis: efeito idade-período-coorte, taxa de incidência padronizada pela idade ou incidência acumulada, códigos anatômicos, autoria, país de origem, fontes dos dados, códigos histológicos, tendência de incidência, número de casos, razão homem:mulher, população padrão, período e ano do estudo. Além disso, análises de sensibilidade foram executadas considerando os diferentes sítios anatômicos (C01 ou C01.9 e C09-10) e publicações que incluíram apenas casos diagnosticados com CCE.

4.3 Manuscrito 2: Análise das tendências de incidência segundo sítios anatômicos relacionados ao HPV

O município de São Paulo é a capital do estado e tem um território de 1.521,11 km² com uma população estimada de 12.038.175 habitantes,[123] organizando-se em 96 distritos administrativos (Figura 13).[124]

Figura 13 – Mapa do município de São Paulo segundo distritos administrativos.



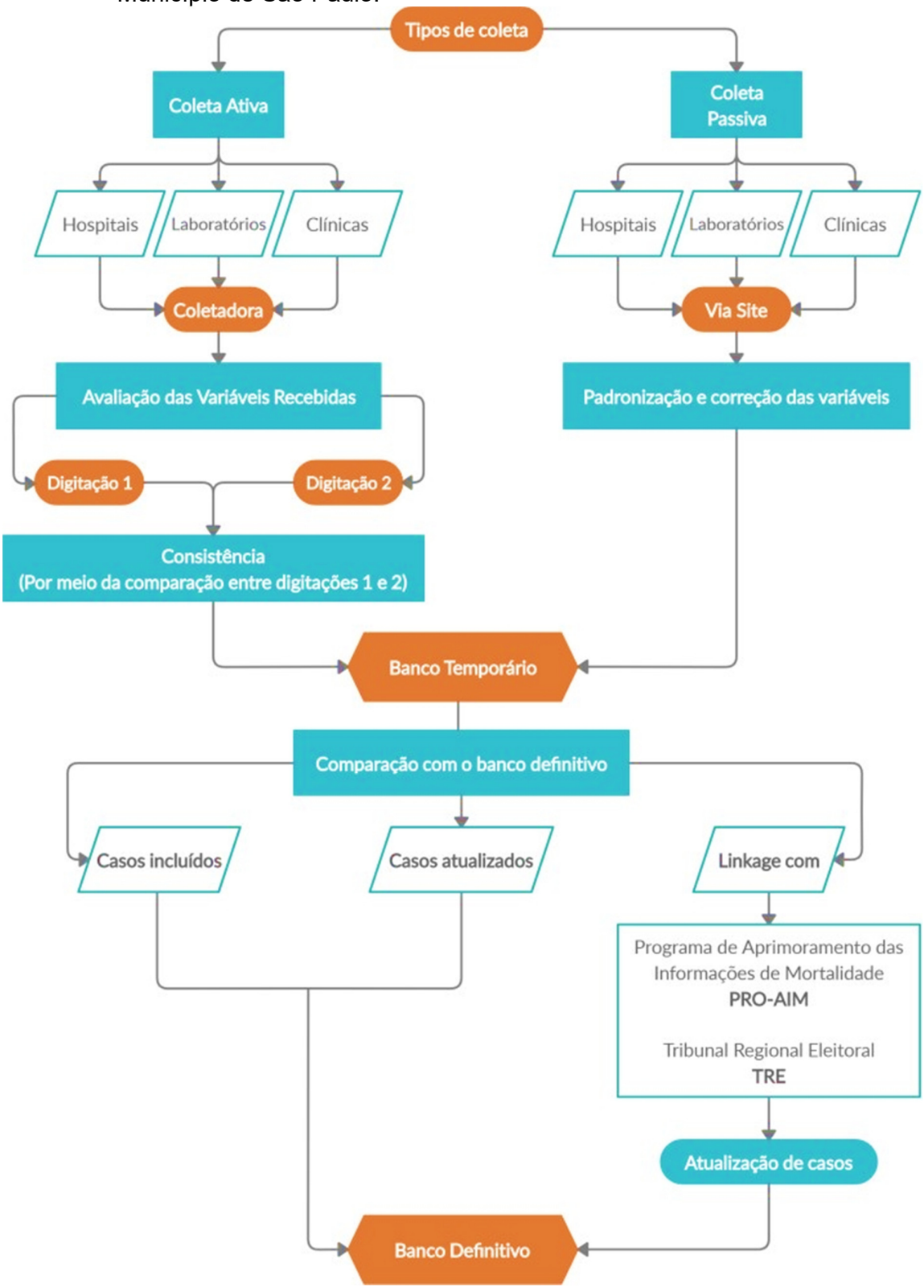
Fonte: produção do próprio autor.

Para a composição da amostra da pesquisa, utilizou-se os dados do Registro de Câncer de Base Populacional do Município de São Paulo (RCBP-SP). O RCBP-SP foi implantado oficialmente em 1969, e ele coleta e administra informações de novos casos de câncer de mais de 12 milhões de residentes do município de São Paulo de forma contínua e sistemática.[125] Trata-se de um dos maiores e mais antigos registros de câncer da América Latina.[126] Por esse motivo, é uma das principais fontes de informação em oncologia da cidade, sendo um órgão importante para subsidiar a construção de políticas de saúde sobre o câncer no Brasil. E devido à qualidade do banco de dados, diversos estudos já foram desenvolvidos.[125]

Dessa forma, os casos são registrados no RCBP-SP de forma ativa e passiva a partir de aproximadamente 300 fontes de dados, tais como: hospitais, laboratórios, clínicas, unidades básicas de saúde e o Sistema de Mortalidade do Ministério da Saúde (SIM-MS) pelo Programa de Aprimoramento das Informações de Mortalidade (PRO-AIM) (Anexo A).[126]

Para evitar a perda de seguimento da amostra, o RCBP-SP também desenvolve buscas ativas e realiza *linkage* a partir dos bancos de dados de hospitais, do PRO-AIM e do Tribunal Regional Eleitoral de São Paulo (Figura 14).

Figura 14 – Fluxograma de coleta do Registro de Câncer de Base Populacional do Município de São Paulo.



Fonte: Registro de Câncer de Base Populacional do Município de São Paulo.

Nesse estudo de base populacional, incluíram-se os casos novos de câncer de boca e orofaringe diagnosticados entre 1997 e 2013. Esse período foi definido, pois se trata do momento prévio à vacinação do HPV no município de São Paulo limitado à disponibilidade dos dados na base do registro. Ademais, de acordo com Chaturvedi et al. (2013), todos os códigos histológicos foram considerados, visto que, aproximadamente 95% dos CCP são carcinomas de células escamosas.[42]

Para investigar o potencial papel do HPV na carga de cânceres de boca e orofaringe, empregou-se uma classificação de códigos anatômicos como um *proxy* para a exposição ao HPV de acordo com a evidência científica,[33,47,50,59,71,127] visto que, os registros de câncer não dispõem da informação relativa à testagem da presença do HPV nos tumores.[50,128,129]

A classificação dos sítios anatômicos em "HPV relacionado" e "HPV não-relacionado" foi adotada de forma similar a estudos prévios.[2,47,50,52,55,56,59,118] Deste modo, as localizações anatômicas de CO HPV-relacionadas incluíram os seguintes códigos da Classificação Internacional de Doenças para Oncologia (CID-O): orofaringe (C10.0-C10.4, C10.8-C10.9), tonsilas (C02.4, C09.0-C09.1, C09.8-C09.9), base de língua (C01.9), palato mole e úvula (C05.1-C05.2) e anel de Waldeyer (C14.2). Para comparação, utilizou-se os sítios anatômicos mais relacionados à exposição ao tabaco, tais como: outras partes da língua (C02.0-C02.3, C02.8-C02.9), boca (C04.0-C04.1, C04.8-C04.9; C06.0-C06.2, C06.8-C06.9), gengiva (C03.0-C03.1, C03.9), e palato duro (C05.0, C05.8-C05.9) (Quadro 4).[47]

Quadro 4 – Classificação dos sítios anatômicos segundo a relação com o papiloma vírus humano.

HPV-RELACIONADOS (CÂNCER DE OROFARINGE)		**HPV-NÃO RELACIONADOS** (CÂNCER DE BOCA)	
C01.9	Base de língua	C02.0-C02.3	Outras partes da língua
C02.4	Tonsilas	C02.8-C02.9	Outras partes da língua
C05.1-C05.2	Palato mole e úvula	C03.0-C03.1	Gengiva
C09.0-C09.1	Tonsilas	C03.9	Gengiva
C09.8-C09.9	Tonsilas	C04.0-C04.1	Boca
C10.0-C10.4	Orofaringe	C04.8-C04.9	Boca
C10.8-C10.9	Orofaringe	C05.0	Palato duro
C14.2	Anel de Waldeyer	C05.8-C05.9	Palato duro
		C06.0-C06.2	Boca
		C06.8-C06.9	Boca

Fonte: produção do próprio autor.

4.3.1 Cálculo dos coeficientes de incidência e padronização da população

Os casos novos de câncer de cabeça e pescoço identificados entre 1997 a 2013 no município de São Paulo cadastrados no RCBP-SP foram investigados. Para cada ano, calcularam-se os coeficientes brutos de incidência (CBI), de acordo com a faixa etária e o sexo dos pacientes. Ademais, utilizou-se em todas as análises a população do município de São Paulo disponibilizada pela Fundação Sistema Estadual de Análise de Dados (Fundação SEADE).[130] Assim, dividiu-se o número de casos novos pela população total no meio do ano, sendo o quociente multiplicado por 100.000.

As diferenças nas estruturas etárias podem inviabilizar as comparações entre as populações. Por essa razão, padronizou-se os dados por uma população padrão no intuito de melhor caracterizar os coeficientes analisados, evitando-se análises errôneas.[131] De forma similar a outros estudos,[47,118] essa investigação adotou a população padrão da Organização Mundial de Saúde (OMS),[132] utilizando-se o método direto para o cálculo dos coeficientes de incidência padronizados por idade (Quadro 5).[80,131]

Quadro 5 – Ajuste direto para comparação da incidência em dois grupos de estudo.

Variável confundidora (1)	Grupo A			Grupo B			População padrão		
	No. (2)	Casos (3)	Incidência (4)= (3) / (2)	No. (5)	Casos (6)	Incidência (7)= (6) / (5)	No. (8)	Casos esperados (A) (9)= (4) x (8)	Casos esperados (B) (10)= (7) x (8)
Estrato 1	n_{A1}	x_{A1}	I_{A1}	n_{B1}	x_{B1}	I_{B1}	W_1	$I_{A1} \times W_1$	$I_{B1} \times W_1$
Estrato 2	n_{A2}	x_{A2}	I_{A2}	n_{B2}	x_{B2}	I_{B2}	W_2	$I_{A2} \times W_2$	$I_{B2} \times W_2$
Estrato 3	n_{A3}	x_{A3}	I_{A3}	n_{B3}	x_{B3}	I_{B3}	W_3	$I_{A3} \times W_3$	$I_{B3} \times W_3$
---	---	---	---	---	---	---	---	---	---
Estrato k	n_{Ak}	x_{Ak}	I_{Ak}	n_{Bk}	x_{Bk}	I_{Bk}	W_k	$I_{Ak} \times W_k$	$I_{Bk} \times W_k$
	N_A	X_A	I_A	N_B	X_B	I_B	$\sum_i W_i$	$\sum_i [I_{Ai} \times W_i]$	$\sum_i [I_{Bi} \times W_i]$

Taxa de incidência ajustada:	
$I_A^* = \frac{\sum_i [I_{Ai} \times W_i]}{\sum_i W_i}$	$I_B^* = \frac{\sum_i [I_{Bi} \times W_i]}{\sum_i W_i}$

Fonte: produção do próprio autor a partir de Szklo & Nieto (2014).[80]

4.3.2 Análise das tendências de incidência

Na análise de série temporal, modela-se o fenômeno estudado para, consequentemente, descrever o comportamento da série, realizar estimativas e, finalmente, analisar os fatores de importância para se identificar as potenciais relações de causa e efeito.[133] Em análise de séries temporais, os modelos estatísticos são vantajosos devido à facilidade de elaboração e interpretação, assim como eles têm maior poder estatístico.[134] Sendo assim, para executar a análise da tendência temporal, realizou-se os modelos a partir dos coeficientes de incidência no câncer de boca e de orofaringe, de acordo com as localizações anatômicas associadas ou não à infecção pelo HPV descritas anteriormente.

Inicialmente, os gráficos foram confeccionados, uma vez que consiste no "primeiro passo para compreender os processos subjacentes às medidas sequenciais ordenadas temporalmente" (p. 571).[135] Como os resultados se apresentaram instáveis e/ou com ruídos brancos e/ou oscilações expressivas, aplicou-se a técnica de alisamento por meio da média móvel de 5 termos.[136]

Para avaliar a tendência da incidência, foram ajustados modelos de regressão de Poisson para cada sexo, separadamente. A variável dependente em cada modelo foi o número anual de casos novos e as variáveis explicativas foram o tipo de câncer de boca e orofaringe segundo o sítio anatômico HPV-relacionado e HPV-não relacionado, a faixa etária (0 a 39, 40 a 59 e 60 anos ou mais) e o tempo (em anos). O tamanho da população segundo a faixa etária e o ano foi utilizado como *offset.* A partir dos modelos, estimaram-se as taxas de incidência e a variação percentual anual ou o *annual percentage change* (APC) em cada segmento (isto é, para cada o tipo de tumor e faixa etária), considerando um intervalo de confiança de 95% (IC95%). Para avaliar se a tendência e a incidência no meio do período eram semelhantes nos diferentes segmentos, foram construídos *contrasts under the general linear hypotheses*.[137]

Adicionalmente, aplicou-se o método joinpoint[138] em análises suplementares de forma similar a outros estudos.[47,118] Essa proposta testa se uma variação na tendência é estatisticamente significativa ao empregar o método de Monte Carlo, assumindo-se – por vezes – a distribuição de Poisson para ajustar um modelo de tendência a partir de um número mínimo de pontos, e analisa, por consequência, se a inserção de mais pontos é estatisticamente significativa para o modelo.[138]

Portanto, torna-se possível visualizar um gráfico para cada modelo, obtendo-se o respectivo IC95%.

4.3.3 Análise do efeito idade-período-coorte

A análise dos padrões temporais é um aspecto importante para a vigilância em saúde,[139] uma vez que as tendências temporais das taxas de uma determinada doença fornecem informações relevantes para a etiologia das doenças. Deste modo, existem fatores de tempo que devem ser considerados em uma investigação, tais como: (i) idade; (ii) data do diagnóstico ou "período"; e (iii) data de nascimento ou "coorte". Assim, as diversas combinações desses fatores podem evidenciar esclarecimentos de interesse para os estudos[140] e, por conseguinte, para a vigilância epidemiológica.

Durante a exposição aos fatores de risco para o câncer, tem-se a possibilidade de ocorrer os efeitos da idade, do período e da coorte de nascimento.[80,139,141] O efeito da idade modifica a taxa de um desfecho a partir da idade, independentemente da coorte de nascimento e da época, evidenciando as diferenças na suscetibilidade da doença entre as distintas faixas etárias.[80] O efeito da coorte altera uma taxa de um desfecho ou condição de acordo com o ano de nascimento, independentemente da idade e do período.[80] Por conseguinte, os fatores determinantes dos efeitos da coorte não se limitam a exposições relacionadas ao nascimento, mas incluem também as exposições que afetam principalmente a coorte e não a população como um todo.[139] Por fim, tem-se o efeito do período que afeta toda a população em um específico ponto do tempo, independentemente da idade e da coorte de nascimento.[80]

Os efeitos temporais da idade, período e coorte têm interpretações epidemiológicas úteis em relação aos tipos de variáveis que podem influenciar no acompanhamento de uma doença.[139] Por conseguinte, a interpretação das variações temporais nas taxas de câncer é relevante para a construção de evidências científicas.[141] Embora a observação visual das tendências do tempo seja importante, uma análise temporal a partir da modelagem estatística considerando os efeitos da idade, do período e da coorte também é necessária,[139] visto que, podem-se observar modificações nas taxas de mortalidade e incidência devido às distintas exposições, à

presença de cofatores relacionados e às intervenções preventivas ou terapêuticas, por exemplo.[80,142]

Entretanto, não é possível segregar por completo tais efeitos em decorrência da interdependência entre eles, que se denomina problema de identificação. Essa limitação é inerente aos modelos estatísticos usados para analisar os efeitos da idade, período e coorte.[139] Contudo, existem diversas possibilidades na literatura para lidar com essa dependência linear dos efeitos,[80,143,144] e nesse estudo se empregou a proposta de Cartensen (2007).[145]

Para a mensuração dos efeitos da idade, do período e da coorte de nascimento, realizaram-se análises separadas para cada sexo e tipo de câncer (HPV-relacionado e HPV-não relacionado), ajustando-se os modelos definidos pela seguinte equação:[145]

$$ln\,(d\_ap/y\_ap\,) = f(a) + g(p) + h(c)$$

Onde:

d_ap: é o número esperado de casos na idade *a* e no período *p;*

y_ap: representa a população sob risco de desenvolver o câncer na idade *a* e no período *p;*

$f, g\ e\ h$: funções da idade, do período e da coorte, respectivamente, que podem ser paramétricas ou não-paramétricas;

a, p e c: representam a média da idade, período e coorte para as unidades observacionais, *c=p-a*; e o número de casos segue uma distribuição Poisson.

Para esse modelo, assumiu-se que o número de casos teve uma distribuição de Poisson, isto é, pressupôs-se que eles resultaram de um processo de contagem. Além disso, consideraram-se diferentes formas para a relação entre o número de casos e as variáveis explicativas (idade, período e coorte), que usualmente são não-lineares. Dessa forma, ajustou-se os modelos para as funções *f, g* e *h* como *factor, natural splines, e β-splines*, selecionando-se a função que apresentou o melhor ajuste.[146]

Os modelos idade-período-coorte foram desenvolvidos de acordo com grupos etários organizados em 5/5 anos, ou seja, de 15 a 19 anos até 75 anos e mais. Do mesmo modo, o ano do diagnóstico foi agrupado em três períodos de cinco anos, tais como: 1999 a 2003, 2004 a 2008 e 2009 a 2013.

Para avaliar os efeitos da idade, período e coorte, foram utilizados testes de razão de verossimilhança (*likelihood-ratio test*) na comparação dos diferentes

submodelos, isto é, modelos contendo conjuntos diferentes das três variáveis explicativas (idade, período e coorte). Tais submodelos foram ajustados em uma sequência para fornecer os testes para os mencionados efeitos a partir da comparação entre eles, obtendo-se o modelo mais ajustado a partir da estatística *deviance* ($p<0,05$) (Quadro 6).[145]

Quadro 6 – Submodelos dos efeitos idade-período-coorte.

MODELO	**log[$\lambda(a, p)$]**
Idade	$f(a)$
Idade-*drift*	$f(a) + \delta c$
Idade-coorte	$f(a) + h(c)$
Idade-período-coorte	$f(a) + g(p) + h(c)$
Idade-período	$f(a) + g(p)$
Idade-*drift*	$f(a) + \delta p$

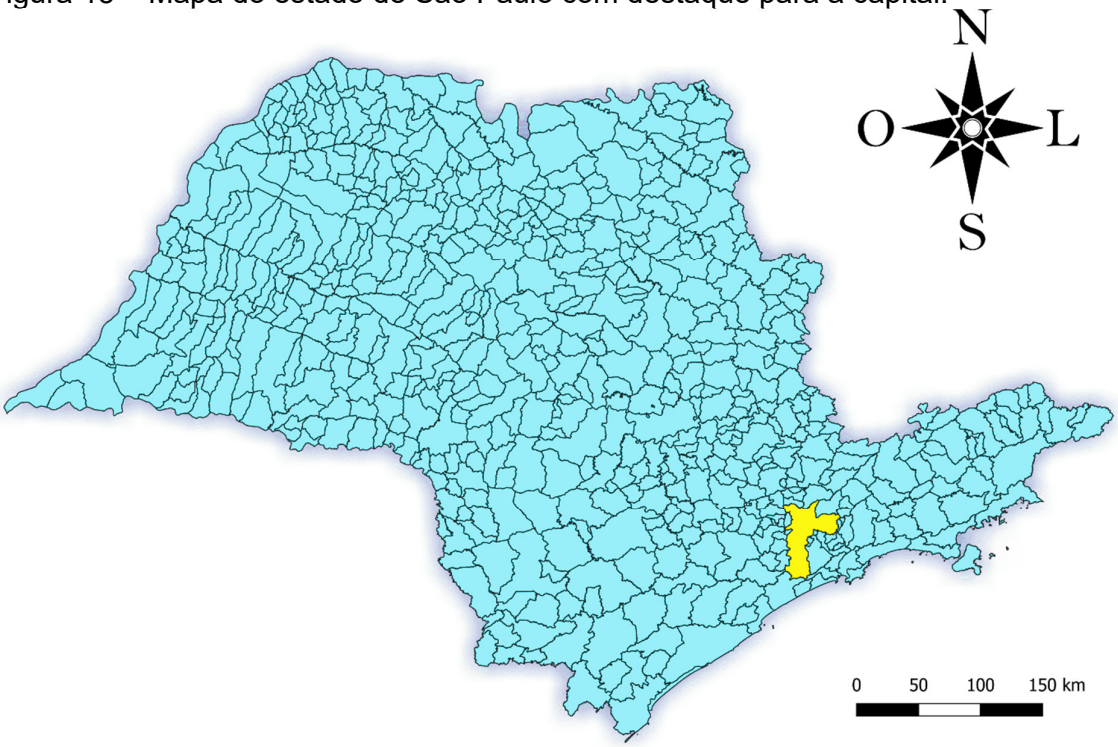
Fonte: Cartensen (2007).[145]

Considerando as estimativas do modelo final, o efeito da idade foi apresentado como taxas de incidência por 100 mil habitantes em função da idade, segundo a coorte ou o período de referência. Adicionalmente, os efeitos do período e da coorte foram representados graficamente como riscos relativos (RR), tendo em vista um período ou coorte de referência.[145]

4.4 Manuscrito 3: Análise de sobrevida segundo localizações anatômicas relacionadas ao HPV

O estado de São Paulo tem 44.749.699 habitantes, 645 municípios e 248.221,996 km²,[123] situando-se na região sudeste do Brasil (Figura 15).

Figura 15 – Mapa do estado de São Paulo com destaque para a capital.



Fonte: produção do próprio autor.

Para a composição da amostra desse estudo, utilizou-se os dados dos Registros Hospitalares de Câncer da Fundação Oncocentro de São Paulo (RHC/FOSP). O RHC/FOSP cadastra os casos novos diagnosticados a partir de 01/01/2000 no estado de São Paulo. No total, 77 Registros Hospitalares de Câncer enviam informações trimestralmente a base de dados, sendo 72 instituições habilitadas na Rede de Atenção Oncológica do SUS-SP e as demais são hospitais particulares ou filantrópicos.[147]

A logística da coleta dos dados envolve a notificação dos casos pelos RHCs durante o cadastro nos hospitais credenciados da rede Centro de Assistência de Alta Complexidade em Oncologia (CACON) e Unidade de Assistência de Alta

Complexidade em Oncologia (UNACON), ou nos hospitais voluntários (Anexo B). Esse registro foi realizado por registradores de câncer treinados a partir do Sistema de Registro Hospitalar de Câncer (SISRHC) (Anexo C).

A qualidade da informação é garantida pelo treinamento e acompanhamento dos recursos humanos pela FOSP, assim como o SISRHC dispõe de ferramentas para a validação de campos evitando erros de digitação. Adicionalmente, os prontuários foram reavaliados/revistos anualmente para as devidas atualizações (seguimento). Para a identificação do óbito, utilizou-se também as seguintes fontes de informações: Tribunal Superior Eleitoral, CADSUS, Receita Federal, Cadastro Nacional de Falecidos e mídias sociais (Google/Facebook).

Nesse estudo de base hospitalar, utilizou-se informações de pacientes diagnosticados entre 2000 a 2018 em 76 hospitais do estado de São Paulo. Todos os casos foram restritos às localizações anatômicas especificadas no Quadro 5, acrescentando-se a laringe (C32). Adicionalmente, consideraram-se apenas carcinomas de células escamosas de acordo com a Classificação Internacional de Doenças para Oncologia (CID-O) da 3ª edição.[148] Portanto, as análises foram restritas aos seguintes códigos CID-O-3: 8050 a 8076, 8078, 8083, 8084 e 8094.

Essa investigação incluiu apenas pacientes residentes no estado de São Paulo com idade ≥15 anos no momento do diagnóstico. Os casos sem acompanhamento e os carcinomas *in situ* foram excluídos das análises.

Considerando o propósito de investigar o impacto do SES na sobrevida dos cânceres de orofaringe, boca e laringe, analisaram-se fatores individuais e contextuais. O nível de escolaridade e o setor de assistência à saúde foram considerados como marcadores socioeconômicos individuais. No nível contextual, o Índice de Desenvolvimento Humano Municipal (IDHM) no ano de 2010 foi obtido a partir do Atlas do Desenvolvimento Humano no Brasil, disponibilizado pelo Programa das Nações Unidas para o Desenvolvimento.

O IDH-M é calculado a partir da média aritmética simples de três pilares: saúde, educação e renda. A saúde é medida pela expectativa de vida. A educação é avaliada por dois aspectos: i) média de anos de educação de adultos, ou seja, o número médio de anos de educação recebidos durante a vida por pessoas a partir de 25 anos; e ii) expectativa de anos de escolaridade de crianças com idade para começar a vida escolar, em que se descreve o número total de anos de escolaridade esperados durante a vida da criança de acordo as taxas de matrículas específicas por

idade. Por fim, mensura-se a renda *per capita*, ou seja, a renda média de cada residente. Deste modo, os três componentes descritos são agrupados por meio da média geométrica, resultando no cálculo do indicador.[149]

Adicionalmente, a Fundação Sistema Estadual de Análise de Dados (Fundação SEADE) em associação com agências governamentais e conselhos de classe (tais como: Medicina e Odontologia) disponibilizou informações para se estimar aspectos socioeconômicos e a qualidade da rede de assistência à saúde.[150] Nessa pesquisa, analisou-se a média do número de dentistas/2.000 habitantes e de médicos/100.000 habitantes de 2000 a 2018; a média do produto interno bruto (PIB) per capita de 2002 a 2017; e a quantidade média dos leitos de internação/mil habitantes de 2008 a 2018. É importante citar que toda a informação foi extraída dessa base de dados conforme o período do estudo, sendo todas as variáveis contextuais categorizadas em tercis para a análise de sobrevida.

A partir dos dados disponibilizados pela FOSP,[151] esse estudo considerou variáveis sociodemográficas (idade, faixa etária, grau de escolaridade, sexo, período de diagnóstico); variáveis de acesso aos serviços de saúde (setor de assistência à saúde, local da assistência oncológica); variáveis de características clínicas (estadiamento clínico e sistema TNM estratificado); variáveis relativas ao tratamento dos pacientes (cirurgia, radioterapia e quimioterapia); e a variável referente à organização dos departamentos regionais de saúde.

O estadiamento clínico foi classificado segundo a 5ª, 6ª e 7ª versões do sistema TNM. Consequentemente, os períodos de diagnóstico foram agrupados para considerar tais mudanças ao longo do tempo, ajustando-se os modelos para a faixa etária e o sexo. Assim, mensurou-se a magnitude da diferença na sobrevida global em 5 anos entre o mais alto e o mais baixo tercil para cada subsítio a fim de comparar os períodos inicial (2000-2005) e final (2014-2018).

4.4.1 Análise de sobrevida

A sobrevida é o tempo desde a entrada do indivíduo no estudo até a ocorrência do evento de interesse (óbito) ou até a censura (perda por tempo de observação incompleto) no acompanhamento.[152,153] Nesse estudo, considerou-se a sobrevida como o tempo decorrido a partir da data do diagnóstico até a data de óbito

ou a data da última informação (censura), estabelecendo-se cinco anos como o tempo de acompanhamento de acordo com a *American Joint Committee on Cancer*.[3]

Para se mensurar a função de sobrevivência, usou-se o estimador não paramétrico produto limite de Kaplan-Meier, representando-se graficamente as curvas de sobrevida acumulada que foram comparadas pelo teste log-rank.[153,154] Para cada subsítio anatômico, fatores contextuais e prognósticos foram investigados usando os modelos de riscos proporcionais de Cox para se mensurar a razão entre as funções de riscos, estimando-se o *hazard ratio* (HR).[153,155] Na análise múltipla utilizando os modelos de Cox, examinou-se o grau de escolaridade e o setor de assistência à saúde, ajustados pela faixa etária, sexo, estadiamento clínico e tratamentos (cirurgia, quimioterapia e radioterapia).

Para considerar a influência da idade e da probabilidade de morrer por outras causas, analisou-se a sobrevida relativa padronizada por idade, também denominada de *net survival*, por um período de acompanhamento de cinco anos. Para tanto, empregou-se o estimador Pohar Perme[156,157] e a população-padrão da *International Cancer Survival Standard* (ICSS) 1,[158] visto que, as neoplasias malignas do estudo aumentam a incidência concomitantemente com a idade.[158] Para se obter as estimativas populacionais, usou-se as tábuas de mortalidade disponibilizadas pelo Instituto Brasileiro de Geografia e Estatística (IBGE) estratificadas por sexo, idade e ano.[159]

A *net survival* leva em conta a probabilidade de sobrevida após o ajuste por outras causas de morte, isto é, que os riscos competitivos de morte são maiores em pacientes idosos do que os mais jovens. Deste modo, o estimador Pohar Perme considera pesos conforme a contribuição de cada indivíduo na amostra segundo o inverso da expectativa de probabilidade de sobrevida acumulada. Consequentemente, o efeito dos pesos é aumentar o número de mortes e de pessoas sob risco, contabilizando-se o tempo de acompanhamento e as mortes não observadas devido à mortalidade por causas concorrentes.[156]

4.4.2 Análise de sobrevida multinível

Em dados multiníveis, os indivíduos podem ser organizados em grupos. E se as características desses grupos podem afetar um desfecho, então, podem-se

modelar as variáveis para considerar os diferentes níveis de agrupamento a partir de modelos de efeitos mistos.[160]

Por esse motivo, realizaram-se análises de sensibilidade usando modelos de sobrevida multiníveis com efeitos mistos e paramétricos, assumindo-se uma distribuição Weibull, para se verificar o risco de morte relacionado ao IDH-M na sobrevida global. É importante citar que se analisou os casos completos, ou seja, sem a imputação dos dados, porque essa análise era inviável com dados imputados. Assim, ajustaram-se os modelos com três diferentes níveis envolvendo efeitos aleatórios e considerando o agrupamento dos casos por hospital, município e departamento regional de saúde. Todas as análises foram ajustadas por fatores socioeconômicos (grau de escolaridade e setor de assistência à saúde) e prognósticos (faixa etária, sexo, estadiamento clínico e tratamentos).

4.4.3 Imputação múltipla

As variáveis grau de escolaridade e setor de assistência à saúde apresentaram um preenchimento de 75,2% e 51,9%, respectivamente. Dessa forma, utilizou-se a técnica de imputação múltipla denominada *multiple imputations by chained equations* (MICE), pois os dados foram perdidos de forma aleatória ou *missing at random* (MAR).[161]

Nos modelos, incluíram-se a variável desfecho (status vital) e a idade com outras variáveis preditoras selecionadas por meio do teste de associação pelo qui-quadrado e modelos de regressão logística, tais como: estadiamento clínico, período de diagnóstico e tratamentos (cirurgia, quimioterapia e radioterapia). Tendo em vista a variável com a maior perda de dados, criou-se ao todo 50 bancos de dados.[162] Devido à alta completude nas variáveis da base de dados, obteve-se uma eficiência relativa maior do que 0,99 em todas as análises.

4.4.4 Outras análises e aspectos gerais

No estudo de base hospitalar, as frequências, os percentuais e as medianas foram calculados para descrever a amostra. Nas variáveis quantitativas

contínuas, analisou-se a normalidade e homocedasticidade a partir do teste de Shapiro-Wilks e Levene, respectivamente. Ademais, o teste de Kruskal-Wallis ou o teste de associação pelo qui-quadrado foi realizado para verificar diferenças entre os cânceres de boca, orofaringe e laringe.[163]

Todos os testes de hipóteses foram bicaudais e um p-valor< 0,05 indicou um resultado estatisticamente significativo.

4.5 *Softwares* utilizados na pesquisa

Para os cálculos dos coeficientes brutos e padronizados, elaboração de tabelas e confecção dos gráficos de tendência temporal e séries históricas, empregou-se o Microsoft Excel 2016.

Nas análises de série temporal, usou-se o aplicativo R na versão 3.5.3 para o Windows com o pacote Epi versão 2.3.5,[164] bem como o *Jointpoint Regression Program* na versão 4.6.0.0 (Surveillance Research Program, National Cancer Institute).

Para a análise de sobrevida, utilizou-se o STATA (Stata Corporation, College Station, Texas, USA) na versão 14. Além disso, os mapas foram confeccionados a partir do QGIS software versão 3.10.2, obtendo-se as malhas territoriais na base do IBGE.[165]

4.6 Cuidados éticos

Esse estudo foi autorizado pelo Conselho Técnico Administrativo do RCBP-SP em 25 de janeiro de 2018 (Anexos D e E). Posteriormente, ele foi submetido via Plataforma Brasil para a apreciação do Comitê de Ética em Pesquisa (CEP) da Faculdade de Saúde Pública da Universidade de São Paulo, sendo aprovado sob o número 83218318.8.0000.5421 (Anexo F). Adicionalmente, o estudo foi alterado para acrescentar os dados da FOSP, que teve as alterações aprovadas em uma nova análise ética (Anexo G).

Essa pesquisa não teve qualquer envolvimento direto com seres humanos, pois utilizou-se informações coletadas pelos registros de base populacional (RCBP-

SP) e hospitalar (FOSP). Em respeito à Resolução 466/2012 do Conselho Nacional de Saúde,[166] os dados foram analisados respeitando-se aos princípios éticos, assegurando-se o anonimato, a autonomia e a confidencialidade no uso das informações, ou seja, as informações foram acessadas sem a identificação dos pacientes.

5 RESULTADOS E DISCUSSÃO

5.1 Manuscrito 1

Esse artigo foi submetido para a apreciação da revista European Journal of Epidemiology em 13 de julho de 2020 (Anexo H).

Global incidence trends in head and neck cancer for HPV-related and -unrelated subsites: A systematic review of population-based studies

Fabrício dos Santos Menezes[1,ƶ,a,*], Gisele Aparecida Fernandes[ƶ], José Leopoldo Ferreira Antunes[ƶ], Luisa Lina Villa[3,4], and Tatiana Natasha Toporcov[ƶ].

[1]Department of Health Education, Federal University of Sergipe, Lagarto, Brazil;

[ƶ]Department of Epidemiology, School of Public Health, University of São Paulo, São Paulo, Brazil;

[3]Center for Translational Research in Oncology, Instituto do Câncer do Estado de São Paulo – ICESP, São Paulo, Brazil;

[4]Department of Radiology and Oncology, School of Medicine, University of São Paulo, São Paulo, Brazil.

[a]Current Address: Department of Health Education, Federal University of Sergipe, Lagarto, Sergipe, Brazil.

* Corresponding author

E-mail: fabriciomenezes@usp.br (FSM)

Panel

Evidence before this study: We searched PubMed for English-written articles with no filters on August 28, 2018, using terms “mouth neoplasms”, “oropharyngeal neoplasms”, “head and neck neoplasms”, “papillomaviridae”, and “papillomavirus infections”. In the literature, there is enough evidence supporting the causal association between high-risk human papillomavirus (HPV) and some subsites of head and neck cancers (HNCs), such as the oropharynx, tonsils, and base of the tongue. Also, genetic alterations in HNCs exhibit distinct carcinogenesis pathways associated with environmental carcinogens (e.g., alcohol and tobacco) and a pathway induced by HPV. Likewise, meta-analysis data shows a sharp increase in the prevalence of HPV in oropharyngeal cancers (OPC) from 40.5% to 72.2%, a finding consistent with population-based data confirming a rise in HPV-related HNCs. Despite several publications on this topic, to our knowledge, no previous systematic review has examined whether this growing incidence affects equally populations and their subgroups, or whether this virus-related cancer epidemic is limited to certain countries.

Added value of this study: Our results confirm the hypothesis that there is a dramatic shift in the global trends for HNCs due to the emerging burden in HPV-related HNC subsites over the last few years. Overall, incidence trends increased for subsites associated with HPV (excluding Slovenia), yet decreased or remained stable for most HPV-unrelated HNC subsites. For HPV-related HNC subsites, differences in worldwide trends between sexes were found. Also, the increase occurred in different age groups depending on country and period, revealing an increased risk in recent cohorts.

Implications of all the available evidence: This systematic review synthesized population-based data on the worldwide burden of HPV-related HNC subsites, supporting prevention through prophylactic HPV vaccination. Based on these findings, it is reasonable to hypothesize that exposures have shifted over time due to a change in sexual behaviors. This has led to an increase in the number of individuals at risk and to a marked change in epidemiology of HNCs. Future investigations employing standard methodologies to monitor these subsites separately should be conducted. Further, more high-quality data from cancer registries are required to elucidate the impact of HPV in HNCs for South America, the Caribbean, and African countries.

Abstract

Human papillomavirus (HPV) is a sexually transmitted virus with oncogenic properties. In head and neck cancer (HNC), some subsites are associated with HPV infection, whereas others are unrelated. Although HPV prevalence among countries is heterogeneous, the effects on incidence trends worldwide are unknown. Therefore, this systematic review examined the incidence trends for HPV-related HNC subsites, exploring patterns by geographic region, age group, sex, and race/ethnicity. In this systematic review, a search was conducted of English-language publications on PubMed, Embase, and Scopus for the period spanning from 1964 to September 4, 2018. Eligible articles included population-based studies that analyzed incidence trends for subsites classified as a proxy for HPV infection in the head and neck region (hereafter referred to as HPV-related subsites). The search retrieved 3,948 non-duplicate records, of which 31 were eligible articles, representing 18 countries on four continents (Asia, Europe, Oceania, and the Americas) covering a period of almost fifty years. Overall, the incidence of HPV-related HNC subsites rose (except for Slovenia), while most of the HPV-unrelated subsites declined or remained stable. For HPV-related HNC subsites, males outnumbered females, and incidence trends increased regardless of age group, highlighting a distinct global pattern between sexes. Also, an increased risk peaked similarly in recent cohorts from both Australia and the United States (U.S.). Regarding race/ethnicity, only the U.S. reported trends indicating a rising burden among white Americans. In conclusion, there is a dramatic shift in the global trends for HNCs due to the emerging burden of HPV-related HNC subsites. The results synthesized information on specific subgroups, supporting the hypothesis that prophylactic HPV vaccination may benefit both sexes. Future studies should use standard methodologies to monitor these subsites separately, given that this change in the epidemiologic profile poses a global challenge.

Keywords: epidemiology; trends; mouth neoplasms; oropharyngeal neoplasms; papillomavirus infections.

Introduction

Head and neck cancers (HNC) are the seventh most common tumors worldwide, with an estimated annual burden of 625,173 new cases and 323,160 deaths in 2018 (1). The first report linking human papillomavirus (HPV) to HNC was published in 1983 (2). The key role of HPV in the pathogenesis has since been demonstrated, with evidence suggesting that HPV-positive tumors have different epidemiologic, clinical, and molecular aspects than HPV-negative tumors (3). In 2007, the International Agency for Research on Cancer (IARC) recognized HPV as a carcinogen for head and neck anatomical subsites (4).

HPV is a sexually transmitted infection, responsible for almost 4.5% of all cancers diagnosed worldwide (5). There are over 200 types of HPV, and approximately 15 lead to malignancies (6). HPV16 is one of the most common (6) carcinogenic types of the virus (7). It was considered a necessary cause for confirming cervical cancers (8), and accounts for up to 60% of tumors involving the oropharynx (9). Although the natural history of HPV infection in head and neck tumors remains unclear (10,11), morphological characteristics, such as tissue tropism and crypts, were associated with HPV16 and with tonsillar carcinogenesis (12). Also, distinct molecular pathways are involved in head and neck squamous cell carcinomas (HNSCC) induced by environmental carcinogens (e.g. alcohol and tobacco) and those related to HPV (13).

Almost 90% of all HNC are squamous cell carcinomas (SCC) and 72% of these tumors are attributable to alcohol and tobacco consumption (14). However, there has been a sharp increase in the overall HPV prevalence in oropharyngeal cancers (OPC) over time (15). In the U.S., the estimated incidence of HPV-positive OPC will surpass that of cervical cancer in 2020 and, by 2030, the majority of all HNC will be HPV-associated (16). In general, cancer registries do not record data regarding the detection of HPV within tumors. HNCs were classified into anatomical subsites as a proxy for HPV infection (also referred to as HPV-related HNC subsites) or HPV-unrelated subsites in order to assess population discrepancies in trends according to the potential role of HPV in the carcinogenicity of these tumors (17,18). Previous studies from Canada (19), Hong Kong (20), Korea (21), and the U.S. have demonstrated a rising incidence in HPV-related HNC subsites and a decreasing trend in HPV-unrelated HNC subsites. However, these findings vary by country (22). Despite the robust evidence, it is not known whether this growing incidence affects the same

age group, sex, and race/ethnicity equally or whether the pattern is restricted to certain countries (23). Previously, reviews have addressed HPV's impact on populations through epidemiologic studies (11,24–27). However, these investigations did not systemically review publications exploring HPV trends for HNC stratified by subgroups, an essential approach to support HPV vaccination programs. Therefore, this systematic review aims to elucidate the global effects of HPV on specific populations and to investigate the worldwide trends for HNC at HPV-related and -unrelated anatomical sites in a bid to identify similarities and differences by geographic region, age group, sex, and race/ethnicity.

Methods

Search strategy and selection criteria

This review is registered in the International prospective register of systematic reviews (registration number: CRD42019121589). We conducted electronic searches on several databases, including PubMed, Embase, and Scopus, for the period from 1964 to September 4, 2018, without filters to identify English language publications. The search strategy used Boolean logical operators (AND, OR, and NOT) to connect keywords obtained from Medical Subject Headings (MeSH) and Embase subject headings (Emtree), including the terms "oral cavity cancer" and "oropharyngeal cancer" to increase the number of hits (Supplementary file table 1). In parallel, complementary searches in grey literature through OpenGrey were conducted. Further articles were retrieved by reviewing the references of the eligible articles (n= 1) (28), contacting the authors (n= 2) (29,30), and by hand-searching relevant publications (n= 2) (20,31) (Figure 1). Authors were also contacted by email to gather additional information (31–33).

This study included only original population-based studies that classified cases as a group (proxy) for HPV exposure at head and neck subsites, comprising at least the tonsil (C09) together with another HPV-related subsite. We highlight that the studies included did not check for HPV positivity, where only stratified analysis for HPV-related and unrelated subsites was performed. Data were extracted from eligible

publications by stratifying according to overall and specific trends (i.e. age groups, ethnicity/race, and sex), and the age-period-cohort effect. Experimental and individual studies, case reports, chapters, clinical guidelines, abstracts, editorials, prefaces, reviews, and non-peer-reviewed publications in general were excluded. Three publications classified as reports (10,34,35), and one study that performed analysis for each anatomical site individually (18). Further analysis was performed, and results proved consistent when stratified by more specific anatomical codes (C01 or C01.9 and C09-10) and SCC histology codes (Supplementary Figures 1-6).

Data extraction

After retrieval of the studies from electronic databases, the EndNote Web® software program was employed to import the studies and exclude any duplicates. Observing the protocol, two independent reviewers screened data by title, abstract, and full-text. In cases of disagreement, the examiners discussed the selection until a consensus was reached. In the event of ongoing discordance, a third examiner decided on the publication's relevance for the systematic review. Data were extracted and cross-checked based on the following variables: age-period-cohort effect, age-standardized incidence rate or cumulative incidence, anatomical codes, author, country, data source, histology codes, incidence trends, number of cases, male:female ratio, standard population, time period, and year.

Results

Anatomical classification of HNCs

The anatomical classification of HNCs varied among studies, especially for HPV-unrelated HNC subsites. The most frequent HPV-related subsite codes were C01.9, C02.4, C09.0, C09.1, C09.8, C09.9, C10.0, C10.2, C10.8, C10.9, and C14.2. The main codes for HPV-unrelated subsites were C02.0-C02.3, C02.9, C03.0-C03.1, C03.9, C04.0-C04.1, C04.8-C04.9, C05.0, C05.8-C05.9, C06.0-C06.2, and C06.8-

C06.9. Controversially, some anatomical codes were used for both HPV-related and -unrelated HNC subsites, such as C02.8, C05.1, C05.2, C10.1, C10.3, C14.0, and C14.8 (Supplementary Table 2).

General findings and overall incidence trends

Of the 3,948 non-duplicate records, a total of 31 eligible publications were retrieved from North America (n= 13), Europe (n= 11), Asia (n= 4), Oceania (n= 2) and South America (n= 1), representing 18 countries worldwide over a period spanning almost fifty years. For HPV-related HNC subsites, studies from the U.S. involved the largest samples (Table 1). Moreover, HPV-related HNC subsites affected more males than females in all publications, with the highest male:female ratios found in Spain (13.8), Taiwan (11.6) and Slovenia (9.0) (Table 1).

A total of 13 studies assessing overall trends for HPV-related and -unrelated HNC subsites were identified, while the other investigations performed only stratified trends analysis. In general, incidence trends rose over time for HPV-related HNC subsites and decreased or remained stable for most HPV-unrelated HNC subsites. An increase in HPV-related HNC subsites was observed in Canada (19), England (33), European countries (36), Hong Kong (20), Korea (21), Peru (37), Taiwan (38), and the U.S. (17,30,39–41). Notably, incidence trends increased for both HPV-related and -unrelated subsites in England, Taiwan, Peru, and European countries (Figure 2).

Incidence trends by age group, race/ethnicity, and sex

Incidence trends increased regardless of sex for HPV-related subsites in various geographic regions. For men, incidence trends rose for most of the HPV-related group yet declined for HPV-unrelated cancers in all countries, except Taiwan and England (Figure 3). In women, most of the studies showed a higher increase for HPV-related subsites than HPV-unrelated subsites. However, incidence trends rose for both groups in several geographic locations, especially Asian and European countries (Figure 4). These findings demonstrated a different global pattern between

sexes, with a more prominent increase in HPV-related HNC subsites among males than females.

For HPV-related subsites, the overall incidence trend increased for the youngest age groups in Australia (28), Canada (19), Taiwan (38), New Zealand (28), and the U.S. (1995-2005) (40), yet declined or remained stable in Hong Kong (20), European countries (36), and the U.S. in different periods (1973-2004 (17), 2002-2012 (39), 2000-2013 (30), and 2000-2012 (42)). In Canada (19), Taiwan (38), and the U.S. (40), upward trends were identified for all age groups. When stratified by sex, the incidence rose dramatically for the majority of age groups among both sexes in Denmark (43) and among men in Taiwan (38). In females, the incidence trends were stable among the youngest age groups (21,38,42,44) but showed an upward trends in middle-aged or older adults in Denmark (43), England (45), Italy (46), Taiwan (38), The Netherlands (44), and the U.S. (42). In males, a rising trend was identified in the youngest cases from Korea (30-59 years) (21) and Taiwan (30-39 years) (38), but incidence declined or remained stable in Italy (46), Slovenia (22), The Netherlands (44), and the U.S. (42). For the HPV-unrelated group, incidence trends increased among middle-aged or older women (21,37,43,44,46,47), but decreased or remained stable for all age groups in men (21,22,43,44,46). Additionally, a few studies reported a rise in young individuals among males (36–38) and females (Table 2) (36,37).

The trends analysis by race/ethnicity for HPV-related HNC subsites revealed only publications from the U.S. Regarding HPV-related HNC subsites, in the male population there were upward trends for white Americans (17,40,42,48–50) across all age groups (40). Although one study showed rising trends for black Americans (1973-1987) and other races (1973-2004) (17), the incidence trends decreased or remained stable for male American Asian/Pacific Islanders, blacks, and Hispanics (40,42,48–50). For American women, the incidence trends rose only among whites aged 45-54 (1995-2005) (40) and 45-64 (2000-2012) (42), declining or remaining stable for other races and ethnicities (17,40,42,48,50).

Age-period-cohort effect

Seven investigations performing age-period-cohort analysis were identified in Australia (51), Denmark (52), France (53), Hong Kong (20), and the U.S. (17,48,49).

The highest incidence for HPV-related HNC subsites occurred in recent birth cohorts, and peaked for cohorts born between 1945 and 1955 in Australia (51) and between 1943 and 1958 in the U.S. (17). Further, trends rose after the early 1990s in the U.S. (48). Analysis by sex evidenced a cohort effect among men in Hong Kong (20) and a rising cumulative risk among women in France (53). For race/ethnicity groups, the risk for HPV-related HNC subsites increased for white males born since the mid-1940s in the U.S. (49).

Discussion

Comparisons of incidence trends across different periods and geographic regions can provide significant insights into the burden of HPV-related HNC subsites worldwide (28). Based on this premise, the present systematic review of population-based data from 31 studies covering numerous countries and almost five decades was carried out. The results revealed a global emerging epidemic for HNCs at subsites associated with HPV, together with a decline or stable trend for most HPV-unrelated HNC subsites. For HPV-related HNC subsites, a male predilection was evident in all publications, besides an increased risk in recent birth cohorts, upward trends for different age groups and sexes depending on country and period, and a rising burden in white Americans.

The study findings corroborate differences in incidence trends for HNCs that suggest a distinct disease path for HPV-related tumors compared to HPV-unrelated tumors (40). The progress in tobacco control has reduced the global prevalence of daily smoking by 28.4% for men and 34.4% for women between 1990 and 2015 (54). These reductions affected the occurrence of HPV-unrelated HNCs due to the significant role played by tobacco in carcinogenesis (13,14). However, the smoking prevalence among women in Denmark, France, Italy, Netherlands, Norway, Slovenia, and the United Kingdom proved higher than the global average (54) and, in some cases, reduced at a lesser proportion than the decline seen worldwide, perhaps explaining results in the female HPV group. In parallel, growing OPC incidence among males was accompanied by decreasing lung cancer incidence, indicating that a factor other than smoking, such as HPV infection, might be responsible for these findings (23). In this work, trends for HPV-related HNC subsites rose regardless of sex or age

group. Incidence rates increased in Taiwan (1995-2009) from 1.3 to 3.3 per 100,000 (47), in Canada (1992-2009) from 1.6 to 2.6 per 100,000 (19), as well as in several countries, such as Hong Kong, Korea, England, Peru, and the U.S. This dramatic change in trends represents an emerging global concern of varying magnitude depending on the prevalence of high-risk HPV in the population.

In the present study, male cases outnumbered female at HPV-related HNC subsites for all available publications. This result is consistent with laboratory data showing that HPV-positive patients are more likely to be male (16). Moreover, this male predominance indicates distinct sexual behaviors and biological characteristics that lead men to acquire more HPV infections than women. There are several hypotheses to explain these findings. First, males have more lifetime oral and vaginal sexual partners and higher oral HPV16 prevalence than females (55). Second, women have lower risk of new infections due to HPV16 antibody in case of prior cervical infections (56). Third, HPV infection through oral sex affects more men than women because of histo-anatomical characteristics of the genitalia (57).

Many studies revealed upward trends for HPV-related HNC subsites in both sexes, irrespective of geographic location. However, differences in the global pattern between HPV-related and -unrelated subsites were evident. HPV occurrence has proven highly heterogeneous by cancer site, region, and sex (58). Pooled analysis has confirmed geographic disparities in HPV prevalence, with rates of 59.3%, 31.1%, and 4.1% in the U.S., Europe, and Brazil, respectively (9). It is unclear whether regional variations in the extent of HPV16 infection in HNC reflect etiologic differences (9), but these discrepancies likely impact HPV´s role in carcinogenesis and may also influence incidence trends by sex.

In Taiwan (1995-2009) (38) and the U.S. (1995-2005) (40), a dramatic increase was seen for all age groups. In parallel, high variability in incidence trends was observed across age groups among countries worldwide. For instance, incidence in HPV-related HNC subsites increased in young males from Korea (21), while Italy (46) and Slovenia (22) presented decline. By contrast, both the Netherlands (44) and the U.S. (42) had a higher incidence of cases in middle-aged or older men. This heterogeneity may reflect epidemics that took place at different times and during which HPV infection affected populations, producing a cohort effect.

In this regard, there is an increased risk for HPV-related HNC subsites which peaked for recent cohorts during similar periods in Australia (1945-1955) (51) and the

U.S. (1943-1958) (17). Moreover, changing sexual behaviors are consistent with rising rates of genital warts and genital herpes diagnoses (45). In addition, HPV DNA detection in HPV-associated HNCs has increased four-fold over time (16). Given these aspects, it is reasonable to hypothesize that exposures have shifted over time due to changes in patterns of sexual behavior, leading to a greater number at risk of developing the disease.

In Canada, ethnic minorities have a higher risk than the general population among males (59). Additionally, there is a marked increase in cases of HNC among American white males, while a decline can be observed in blacks and other races/ethnicities, likely due to differences in sexual behaviors among these groups (40). It is unclear whether distinct high-risk sexual behaviors contribute to disparities in oral HPV infection or whether environmental and genetic factors play a significant role for disease occurrence (40). Among American whites, this different pattern in trends in both sexes is partly explained by the higher initiation rates of cancer onset in men than women (48), and by other factors previously outlined. Patients engaging in high-risk sexual behaviors are more exposed to HPV, but little is known about these effects on different race/ethnicities, and there is a dearth of information on the natural history of oral HPV infection (10). In order to shed light on these differences, more studies are required that include social-cultural factors and involve countries besides the U.S.

In this systematic review, the U.S. presented the most significant data due to the coverage of registry cancer systems and population size. Conversely, only one study was found for South America (in Peru) and substantial gaps in data for the Caribbean and African countries were evident. No studies were found for these regions, highlighting an epidemiological silence and global disparity in the availability of high-quality cancer data. In parallel, information from eligible studies was conflicting and incomplete, precluding a clear transparent interpretation of reports. Although manuscripts described data quality indicators (20,29,38,40,46,49,60), some studies did not report or restricted tumor inclusion to squamous cell carcinomas diagnoses. Also, a wide variety of codes classifying HPV-unrelated subsites were used, and diverse terminologies for HNCs in anatomical sites associated with HPV infection were also adopted. Further, several publications used different standard-populations and cut-offs for age groups, and some authors did not calculate incidence trends by specific subgroups because of the small number of cases. These aspects hampered

interpretation of articles and precluded comparisons of incidence rates among different geographic regions.

The main study limitation was the use of the classification of HNCs according to subsites associated with HPV. This tumor classification was proposed due to the absence of information on testing positive for HPV DNA within the tumors in medical records (53) and cancer registries (18,53,61). Indeed, not all HPV-related HNC subsites are HPV-positive, where HPV prevalence ranges worldwide from 35.6% to 70% (53,62). Thus, HPV-related HNC subsite contamination by alcohol and tobacco cancers is plausible depending on the prevalence of these risk factors in populations (53). However, laboratory and population-level data proved that the incidence trend for OPC rose in line with HPV detection in specimens (16), and laboratory data from a systematic review (15) supported these results. Therefore, this classification serves as a useful and reliable tool for epidemiological surveillance, until testing for HPV in tumors becomes widely available.

We provided a summarized description of the burden of HPV-related HNC subsites worldwide and also reported information on specific subgroups, supporting prophylactic HPV vaccination for both sexes. Further, only population-based studies were included, allowing generalizability while minimizing selection bias. We confirmed a dramatic shift in the global patterns of incidence trends for HNC, reinforcing the importance of surveillance of HPV-related HNC subsites separately. Incidence trends rose over time for subsites associated with HPV, irrespective of sex or age group. Conversely, incidence rates decreased for most HNCs related to alcohol and tobacco consumption. These observations are consistent with the sharp increase in HPV prevalence in OPC from 40.5% to 72.2% (15), further supporting our data. In conclusion, this emerging epidemic poses a global challenge for clinicians, researchers, and policymakers due to its impact on the quality of life of patients and on health and social security systems.

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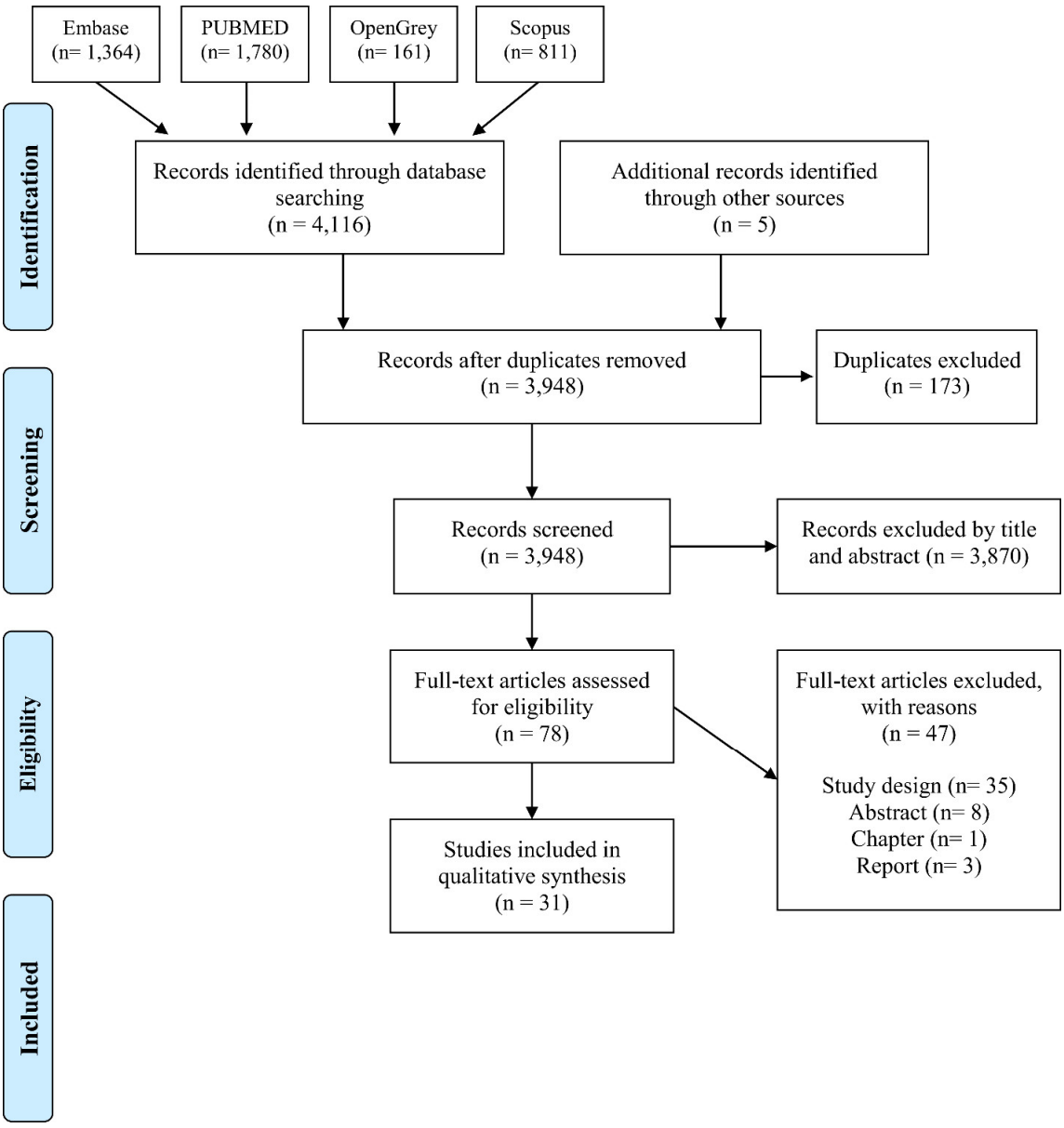


Figure 1. Flow diagram showing selection of eligible studies for inclusion in the systematic review.

Table 1. Global findings for HPV-related HNC subsites.

FIRST AUTHOR (YEAR)	COUNTRY	PERIOD	DATA SOURCE	STANDARD POPULATION	ANATOMICAL CODES	PATH	CASES†		ASR/CIR§		
							N	M:F	T	M	F
Auluck (2010)[59]	Canada	1980-2006	Cancer registry	"1991 British Columbia general population"	C01.9, C02.4, C09.0, C09.1, C09.8, C09.9, C10.2, C10.3, C10.8, and C10.9.	SCC	1,801	2.5	4.1	2.9	1.2
[a]Blomberg (2011)[43]	Denmark	1978-2007	Cancer registry	"2000 standard world population"	C01.9, C02.4, C02.8, C09, C10.2, C10.8, C10.9, C14.0, C14.2, and C14.8.	SCC	3,650	2.6	NA	NA	NA
Boscolo-Rizzo (2018)[46]	Italy	1988-2012	Cancer registry	"European age-standardized"	C01.9, C02.4, C09, C10, and C14.2.	Mixed	3,984	4.4	1.8	3.1	0.6
Brouwer (2016)[48]	United States	1973-2012	SEER	"U.S. population in the year 2000"	C01.9, C02.4, C09.0, C09.1, C09.8, C09.9, C10.0, C10.1, C10.2, C10.3, C10.4, C10.8, C10.9, and C14.2.	SCC	51,084	3.7	NA	NA	NA
Brown (2011)[49]	United States	1977-2007	SEER	"2000 US Standard Population"	C01.9, C02.4., C09.0-C10.9, and C14.2.	SCC	19,932	2.9	NA	NA	NA
Chan (2018)[20]	Hong Kong	1983-2014	Cancer registry	"World Health Organization's 2000 World Standard Population"	C01, C02.4, C05.1, C05.2, C09-C10, C14.0, C14.2, and C14.8.	Mixed	1,972	4.2	1.2	1.9	0.5
Chaturvedi (2008)[17]	United States	1973-2004	SEER	"US 2000 standard population"	C01.9, C02.4, C09.0-09.9, C10.0-10.9, and C14.2.	SCC	17,625	2.7	NA	NA	NA
Cole (2012)[40]	United States	1995-2005	Cancer registry	"US 2000 Standard Population"	C01.9, C02.4, C09.0-C09.9, C10.2-C10.9, and C14.2.	SCC	68,861	3.5	2.9	4.8	1.2
de Souza (2012)[31]	Spain	1991-2001	Cancer registry	"World standard population (Segi)"	C01.9, C02.4, C05.1, C05.2, C09.0- C09.1, C09.8- C09.9, C10.0-C10.4, and C10.8-C10.9.	Mixed	1,290	13.8	NA	NA	NA
Elwood (2014)[28]	New Zealand and Australia	1982-2010	Cancer registry	"2000 World Standard Population"	C01.9, C02.4, C09.0-C09.9, C10.0-C10.9, and C14.2.	SCC	±3,778	NA	1.4[b] 2.4[c]	NA	NA
Forte (2012)[19]	Canada	1992-2009	Cancer registry	"1991 Canadian population"	C01.9, C02.4, C09.0-C09.9, C10.0-C10.9, and C14.2.	SCC	10,929	3.1	2.6	4.1	1.1

FIRST AUTHOR (YEAR)	COUNTRY	PERIOD	DATA SOURCE	STANDARD POPULATION	ANATOMICAL CODES	PATH	CASES†		ASR/CIR§		
							N	M:F	T	M	F
Hocking (2011)[51]	Australia	1982-2005	Cancer registry	"Australian 2001 standard population"	C01.9, C02.4, C02.8, C09.0, C09.1, C09.8, C09.9, C10.2, C10.8, C10.9, C14.0, C14.2, and C14.8.	SCC	8,844	3.3	NA	NA	NA
Hwang (2015)[38]	Taiwan	1995-2009	Cancer registry	"2000 U.S. Standard Population"	C01, C02.4, C02.8, C09.0, C09.1, C09.8, C09.9, C10.2, C10.8, C10.9, C14.0, C14.2, and C14.8.	SCC	7,452	11.6	3.3	6.2	0.5
Jéhannin-Ligier (2017)[53]	France	1980-2012	Cancer registry	"World standard population"	C01.9, C02.4, C09, C10, and C14.2.	SCC	3,876	3.7	NA	6.2	1.6
Kurdgelashvili (2013)[50]	United States	1978-2007	SEER	"2000 U.S. population"	C01.9, C02.4, C09.0-09.9, C10.0-10.9, and C14.2.	SCC	18,895	2.9	NA	43.6[e]	12.8[e]
Lam (2015)[60]	Singapore	1968-2012	Cancer registry	"WHO world standard population"	C01.9, C02.4, C05.1-C05.2, C09.0-C09.1, C09.8-C09.9, C10.0-C10.4, C10.8-C10.9, and C14.2.	SCC	998	4.9	1.4[d]	2.4[d]	0.4[d]
Licitra (2008)[36]	Austria, Germany, Italy, Netherlands, Poland, Scotland, Slovenia, Sweden, Switzerland, and Wales.	1988-2002	Cancer registry	"European standard population"	C01.9, C02.4, C09.0-C09.9, C10.0-C10.9, and C14.2.	SCC	11,183	3.5	2.5	NA	NA
Louie (2015)[45]	England	1995-2011	Cancer registry	"European standard population (1976)"	C01, C09, and C10.	NA	2011: 1,772 cases	2011 : 3.1	NA	5.1	1.6
McCarthy (2015)[33]	England	2002-2011	Cancer registry	"2013 European Standard Population"	C01, C09, and C10.	NA	12,849	3.0	3.3	5.1	1.6

FIRST AUTHOR (YEAR)	COUNTRY	PERIOD	DATA SOURCE	STANDARD POPULATION	ANATOMICAL CODES	PATH	CASES†		ASR/CIR§		
							N	M:F	T	M	F
Mourad (2017)[39]	United States	2002-2012	SEER	"2000 US standard population"	C09-C10.	NA	37,965	NA	NA	NA	NA
Nygard (2012)[32]	Norway	1981-2007	Cancer registry	"World standard" (Doll, Payne, and Waterhouse, 1966)	C01 and C09-C10	SCC	1,441	NA	NA	NA	NA
Oh (2014)[61]	United States	1987-2011	Cancer registry	"U.S. 2000 standard population"	C01.9, C02.4, C02.8, C09.0, C09.1, C09.8, C09.9, C10.2, C10.8, C10.9, C14.0, C14.2, and C148.	SCC	940	NA	NA	NA	NA
Owosho (2019)[30]	United States	2000-2013	Cancer registry	"2000 US Standard Population"	C01.9, C02.4, C09.0-C09.1, and C09.8-C09.9.	SCC	2,132	4.1	4.2	7.4	1.3
Shack (2014)[29]	Canada	1975-2009	Cancer registry	"1991 Canadian cancer population"	C01.9, C02.4, C02.8, C09.0-C09.9, C10.2, C10.8, C14.0, C14.2, and C14.8.	NA	1,454	3.1	NA	3.7	1.0
Shin (2013)[21]	Korea	1999-2009	Cancer registry	"Middle-year population from 2005"	C09-C10, and C14.	NA	2009: 347 cases	NA	NA	1.1	0.1
Strojan (2015)[22]	Slovenia	1983-2009	Cancer registry	"European standard population"	C01.9, C02.4, C05.1-C05.2, C09.0-C09.9, C10.0-C10.9, and C14.2.	SCC	2,862	9.0	NA	NA	NA
Svahn (2016)[52]	Denmark	1978-2011	Cancer registry	"World Standard Population"	C01.9, C02.4, C05.1, C05.2, C09, C10.0-C10.3, C10.8, C10.9, C14.0, and C14.2.	SCC	4,785	2.7	NA	NA	NA
van Monsjou (2015)[44]	The Netherlands	1989-2008	Cancer registry	"European standard population"	C01, C02.4, C05.1, C05.2, C09, and C10.	SCC	6,799	2.2	NA	3.4	1.3
Walter (2014)[37]	Peru	1987-2008	Cancer registry	"2000 global population provided by the World Health Organization"	C01.9, C02.4, C05.1-C05.2, C09.0-C09.9, C10.0-C10.9, and C14.2.	SCC	466	1.9	0.8	1.2	0.5
Zahnd (2018)[41]	United States	1995-2013	NAACCR	"2000 US standard population"	C01.9, C02.4, C02.8, C05.1, C05.2, C09.0, C09.1, C09.8, C09.9, C10.0, C10.1, C10.2, C10.3, C10.4, C10.8, C10.9, C14.0, C14.2, and C14.8.	SCC	79,416	4.1	4.9[f] 4.6[g]	8.0[f] 7.9[g]	1.9[f] 1.7[g]

FIRST AUTHOR (YEAR)	COUNTRY	PERIOD	DATA SOURCE	STANDARD POPULATION	ANATOMICAL CODES	PATH	CASES†		ASR/CIR§		
							N	M:F	T	M	F
Zumsteg (2016)[42]	United States	2000-2012	SEER	"US Census 2000 population"	C01.9, C02.4, C05.1, C05.2, C09.0-C09.1, C09.8-C09.9, C10.0, C10.2-C10.3, C10.8-C10.9, and C14.2.	SCC	40,264	4.1	NA	NA	NA

† Although some studies comprised other anatomical sites, this number represents only HPV-related HNC subsites.
§ The most recent ASR available in the studies was used, rounding data to one decimal place.
[a] Only "HPV-associated sites" were considered.
[b] Age-adjusted average annual incidence rates for New Zealand, 2001-2010.
[c] Age-adjusted average annual incidence rates for Australia (Queensland), 2001-2010.
[d] Age-standardized incidence rates per 100,000 person-years from 1968 to 2012.
[e] Only invasive cancers (1978-2007).
[f] Rural cases of oropharyngeal squamous cell carcinomas.
[g] Urban cases of oropharyngeal squamous cell carcinomas.

Abbreviations: ASR: Age-standardized incidence rate per 100,000; CIR: cumulative incidence rate; HPV: human papillomavirus; HNC: head and neck cancer; M:F: male-to-female ratio; N: number of cases at HPV-related HNC subsites; NA: not available; NAACCR: North American Association of Central Cancer Registries; PATH: Pathology; SEER: Surveillance, Epidemiology, and End Results; and SCC: Squamous cell carcinoma; T: overall cases; US/U.S.: United States; and WHO: World Health Organization.

Table 2. Incidence trends for HPV-related and -unrelated HNC subsites by age group and sex.

FIRST AUTHOR (YEAR)	PLACE	MALE[§]		FEMALE[§]	
		POTENTIALLY HPV-RELATED	HPV-UNRELATED	POTENTIALLY HPV-RELATED	HPV-UNRELATED
[a]Blomberg (2011)[43]	Denmark	↑ <60 years (1978-2007) (APC= +5.1*) ↑ ≥60 years (1978-2007) (APC= +3.7*)	↓ <60 years (1978-2007) (APC= -1.8*) ↓ ≥60 years (1978-2007) (APC= -2.1*)	↑ <60 years (1978-2007) (APC= +5.0*) ↑ ≥60 years (1978-2007) (APC= +3.5*)	(—) <60 years (1978-2007) (APC= -0.0) ↑ ≥60 years (1978-2007) (APC= +1.5*)
Boscolo-Rizzo (2018)[46]	Italy	↓ 40-49 years (1988-2012) (APC= -2.0*) (—) 50-59 years (1988-2012) (APC= +0.1) (—) ≥60 years (1988-2012) (APC= -0.1)	(—) 40-49 years (1988-2002) (APC= +0.0) ↓ 40-49 years (2002-2012) (APC= -9.2*) ↓ 50-59 years (1988-2012) (APC= -2.5*) ↓ ≥60 years (1988-2012) (APC= -1.1*)	(—) 40-59 years (1988-2012) (APC= +2.0) ↑ ≥60 years (1988-2012) (APC= +2.9*)	↓ 40-49 years (1988-2012) (APC= +0.5) ↑ 50-59 years (1988-2012) (APC= +3.5*) ↑ ≥60 years (1988-2006) (APC= +3.7*) (—) ≥60 years (2006-2012) (APC= -6.1)
Hwang (2015)[38]	Taiwan	↑ 30-39 years (1995-2009) (APC= +6.6*) ↑ 40-49 years (1995-2009) (APC= +8.6*) ↑ 50-59 years (1995-2009) (APC= +7.3*) ↑ 60-69 years (1995-2009) (APC= +7.6*) ↑ 70-79 years (1995-2009) (APC= +6.8*) ↑ 80+ years (1995-2009) (APC= +6.5*)	↑ 30-39 years (1995-2009) (APC= +6.9*) ↑ 40-49 years (1995-2009) (APC= +6.7*) ↑ 50-59 years (1995-2009) (APC= +4.8*) ↑ 60-69 years (1995-2009) (APC= +5.7*) ↑ 70-79 years (1995-2009) (APC= +4.2*) ↑ 80+ years (1995-2009) (APC= +3.8*)	(—) 30-39 years (1995-2009) (APC= -0.6) ↑ 40-49 years (1995-2009) (APC= +8.4*) ↑ 50-59 years (1995-2009) (APC= +10.1*) (—) 60-69 years (1995-2009) (APC= +2.2) (—) 70-79 years (1995-2009) (APC= -1.0) (—) 80+ years (1995-2009) (APC= -3.5)	(—) 30-39 years (1995-2009) (APC= +0.8) ↑ 40-49 years (1995-2009) (APC= +5.8*) ↑ 50-59 years (1995-2009) (APC= +5.3*) ↑ 60-69 years (1995-2009) (APC= +3.6*) ↑ 70-79 years (1995-2009) (APC= +3.1*) ↑ 80+ years (1995-2009) (APC= +3.7*)
Licitra (2008)[36]	Austria, Germany, Italy, Netherlands, Poland, Scotland, Slovenia, Sweden, Switzerland, and Wales.	NA	↑ 30-39 years (1988-2002) (APC= -1.8*) (—) 40-49 years (1988-2002) (APC= -0.2) (—) 50-59 years (1988-2002) (APC= +0.4) ↑ ≥60 years (1988-2002) (APC= +0.6*)	NA	↑ 30-39 years (1988-2002) (APC= +3.5*) (—) 40-49 years (1988-2002) (APC= +1.8) ↑ 50-59 years (1988-2002) (APC= +3.9*) ↑ ≥60 years (1988-2002) (APC= +2.4*)

FIRST AUTHOR (YEAR)	PLACE	MALE[§]		FEMALE[§]	
		POTENTIALLY HPV-RELATED	HPV-UNRELATED	POTENTIALLY HPV-RELATED	HPV-UNRELATED
Louie (2015)[45]	England	↑ 50-59 years (1995-2011) (APC= +8.0*) ↑ 60-69 years (1995-2011) (APC= +7.8*)	NA	↑ 50-59 years (1995-2011) (APC= +7.7*) ↑ 60-69 years (1995-2011) (APC= +7.6*)	NA
[b]Shack (2014)[29]	Canada	<35 years (1975-1989) (APC= +27.3) <35 years (1990-2009) (APC= -20.3) 35-44 years (1975-2009) (APC= +6.9) 45-54 years (1975-2009) (APC= +4.4) 55-64 years (1975-2009) (APC= +3.8) 65-74 years (1975-2009) (APC= +2.4) 75-84 years (1975-2009) (APC= +1.5)	NA	<45 years (1975-2009) (APC= -1.7) 45-54 years (1975-2009) (APC= +0.9) 55-64 years (1975-2009) (APC= +1.0) 65-74 years (1975-2009) (APC= +0.8) 75-84 years (1975-2009) (APC= +1.9)	NA
[c]Shin (2013)[21]	Korea	↑ 30-59 years (1999-2009) (APC= +2.7*) (—) 60+ years (1999-2009) (APC= +1.8)	(—) 30-59 years (1999-2009) (APC= +1.0) ↓ 60+ years (1999-2009) (APC= -2.0*)	(—) 30-59 years (1999-2009) (APC= +2.4) (—) 60+ years (1999-2009) (APC= -0.1)	(—) 30-59 years (1999-2009) (APC= +2.0) ↑ 60+ years (1999-2009) (APC= +2.5*)
Strojan (2015)[22]	Slovenia	↓ <50 years (1983-2009) (APC = -1.6*) ↓ 50-60 years (1983-2009) (APC = -1.8*) (—) >60 years (1983-2009) (APC = -0.9)	↓ <50 years (1983-2009) (APC = -2.5*) ↓ 50-60 years (1983-2009) (APC = -2.3*) ↓ >60 years (1983-2009) (APC = -0.9*)	NA	NA
van Monsjou (2015)[44]	The Netherlands	(—) <50 years (1989-2008) (EAPC= -1.0) ↑ 50-64 years (1989-2008) (EAPC= +3.2*) ↑ 65-74 years (1989-2008) (EAPC= +1.3*) (—) 75+ years (1989-2008) (EAPC= +1.4)	↓ <50 years (1989-2008) (EAPC= -2.7*) (—) 50-64 years (1989-2008) (EAPC= +0.6) (—) 65-74 years (1989-2008) (EAPC= -0.4) (—) 75+ years (1989-2008) (EAPC= -0.1)	(—) <50 years (1989-2008) (EAPC= -1.4) ↑ 50-64 years (1989-2008) (EAPC= +3.2*) ↑ 65-74 years (1989-2008) (EAPC= +3.8*) ↑ 75+ years (1989-2008) (EAPC= +5.2*)	↓ <50 years (1989-2008) (EAPC= -2.9*) ↑ 50-64 years (1989-2008) (EAPC= +2.4*) ↑ 65-74 years (1989-2008) (EAPC= +2.9*) ↑ 75+ years (1989-2008) (EAPC= +2.4*)

FIRST AUTHOR (YEAR)	PLACE	MALE[§]		FEMALE[§]	
		POTENTIALLY HPV-RELATED	HPV-UNRELATED	POTENTIALLY HPV-RELATED	HPV-UNRELATED
Walter (2014)[37]	Peru	(—) 15-29 years (1987-2008) (APC= NA) (—) 30-44 years (1987-2008) (APC= NA) ↑ 45-59 years (1987-2008) (APC= +8.7*) (—) 60-74 years (1987-2008) (APC= NA) (—) 75+ years (1987-2008) (APC= NA)	(—) 15-29 years (1987-2008) (APC= NA) ↑ 30-44 years (1987-2008) (APC= +2.1*) (—) 45-59 years (1987-2008) (APC= NA) (—) 60-74 years (1987-2008) (APC= NA) (—) 75+ years (1987-2008) (APC= NA)	(—) 15-29 years (1987-2008) (APC= NA) (—) 30-44 years (1987-2008) (APC= NA) (—) 45-59 years (1987-2008) (APC= NA) (—) 60-74 years (1987-2008) (APC= NA) (—) 75+ years (1987-2008) (APC= NA)	↑ 15-29 years (1987-2008) (APC= +4.4*) ↑ 30-44 years (1987-2008) (APC= +3.1*) (—) 45-59 years (1987-2008) (APC= NA) ↑ 60-74 years (1987-2008) (APC= +1.9*) (—) 75+ years (1987-2008) (APC= NA)
Zumsteg (2016)[42]	United States	(—) <45 years (2000-2012) (APC= +0.8) ↑ 45-64 years (2000-2012) (APC= +2.5*) ↑ ≥65 years (2000-2012) (APC= +3.6*)	NA	(—) <45 years (2000-2012) (APC= +0.8) ↑ 45-64 years (2000-2012) (APC= +1.3*) (—) ≥65 years (2000-2012) (APC= -0.0)	NA

* Statistically significant.
§ Data were rounded to one decimal place.
[a] Only HPV-associated cancers (Supplementary Table 2).
[b] The study failed to describe whether results were significant or not.
[c] Oral cavity cancers for HPV-unrelated subsites.

Trend: increasing: ↑; decreasing: ↓; and stable or not significant: (—).
Abbreviations: APC: annual percent change; EAPC= Estimated annual percentage change; HPV: human papillomavirus; NA: not available.

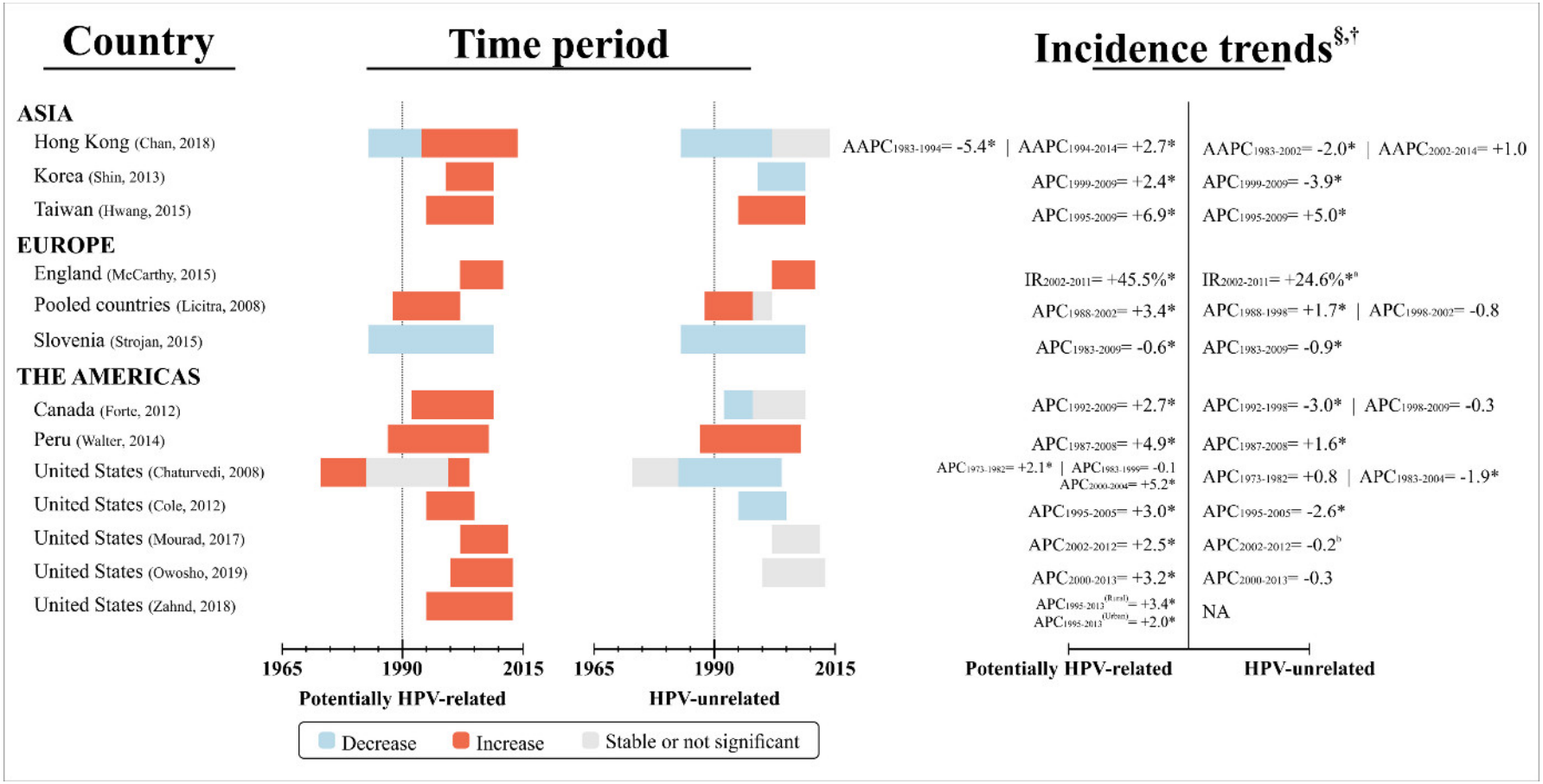


Figure 2. Overall incidence trends for HPV-related and -unrelated HNC subsites, 1965-2015.

§ Data were rounded to one decimal place.

† The studies had different standard populations (see Table 1).

* Statistically significant.

[a] Oral cavity subsites (Supplementary Table 2).

[b] Head and neck cancers (Supplementary Table 2).

Abbreviations: AAPC: average annual percent change; APC: annual percentage change; IR: incidence rate; and NA: Not available.

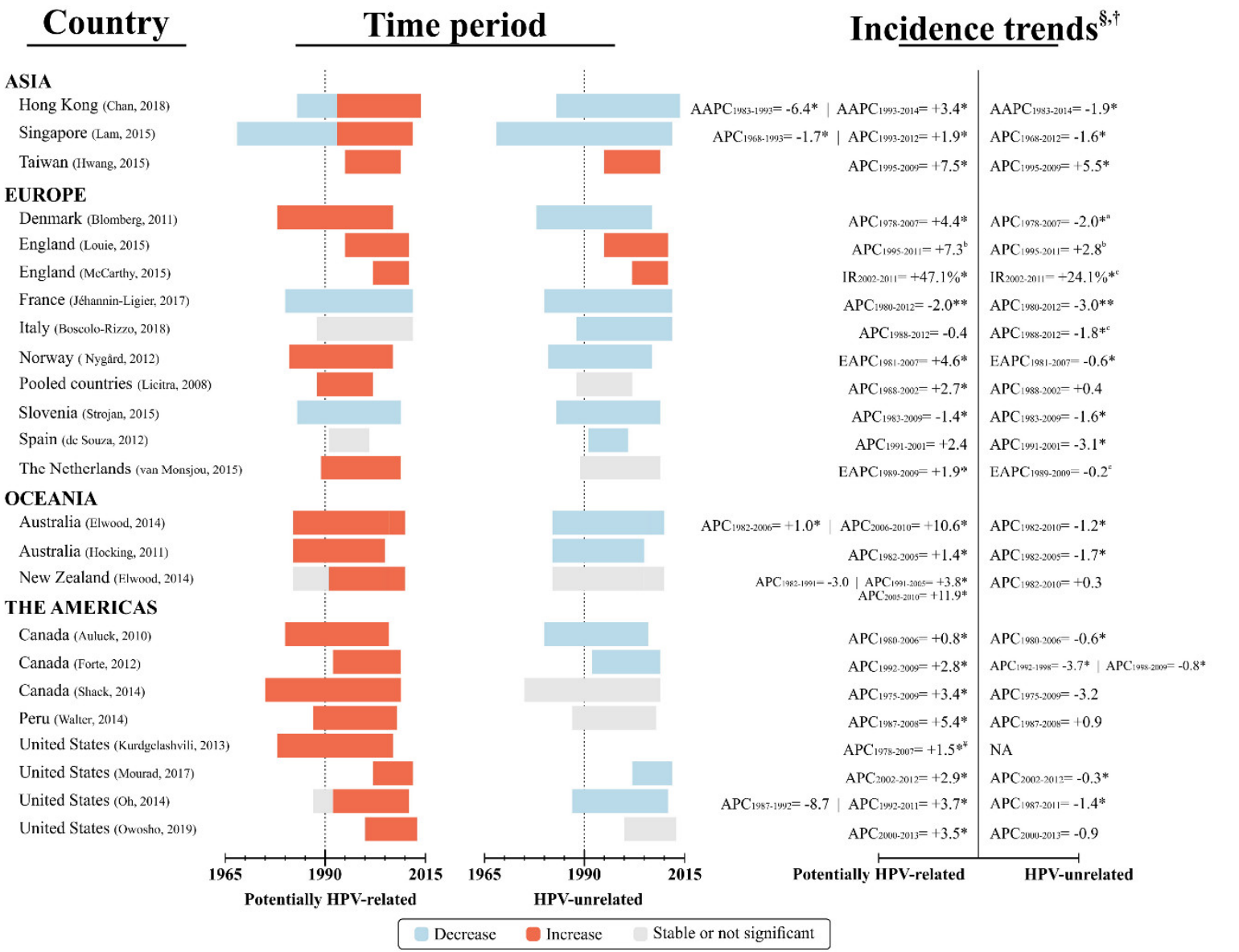


Figure 3. Global incidence trends for potentially HPV-related and -unrelated HNCs in males, 1965-2015.

§ Data were rounded to one decimal place.
† The studies had different standard populations (see Table 1).
¥ Only invasive cancers were considered.
* Statistically significant.
** Authors failed to report whether results were significant or not.
[a] Subsites potentially unrelated to HPV (Supplementary Table 2).
[b] Deemed oral cavity, excluding lip and hard palate (Supplementary Table 2). Also, authors failed to report whether results were significant or not.
[c] Oral cavity subsites (Supplementary Table 2).

Abbreviations: AAPC: average annual percent change; APC: annual percentage change; EAPC: estimated annual percentage change; IR: incidence rate; and NA: Not available.

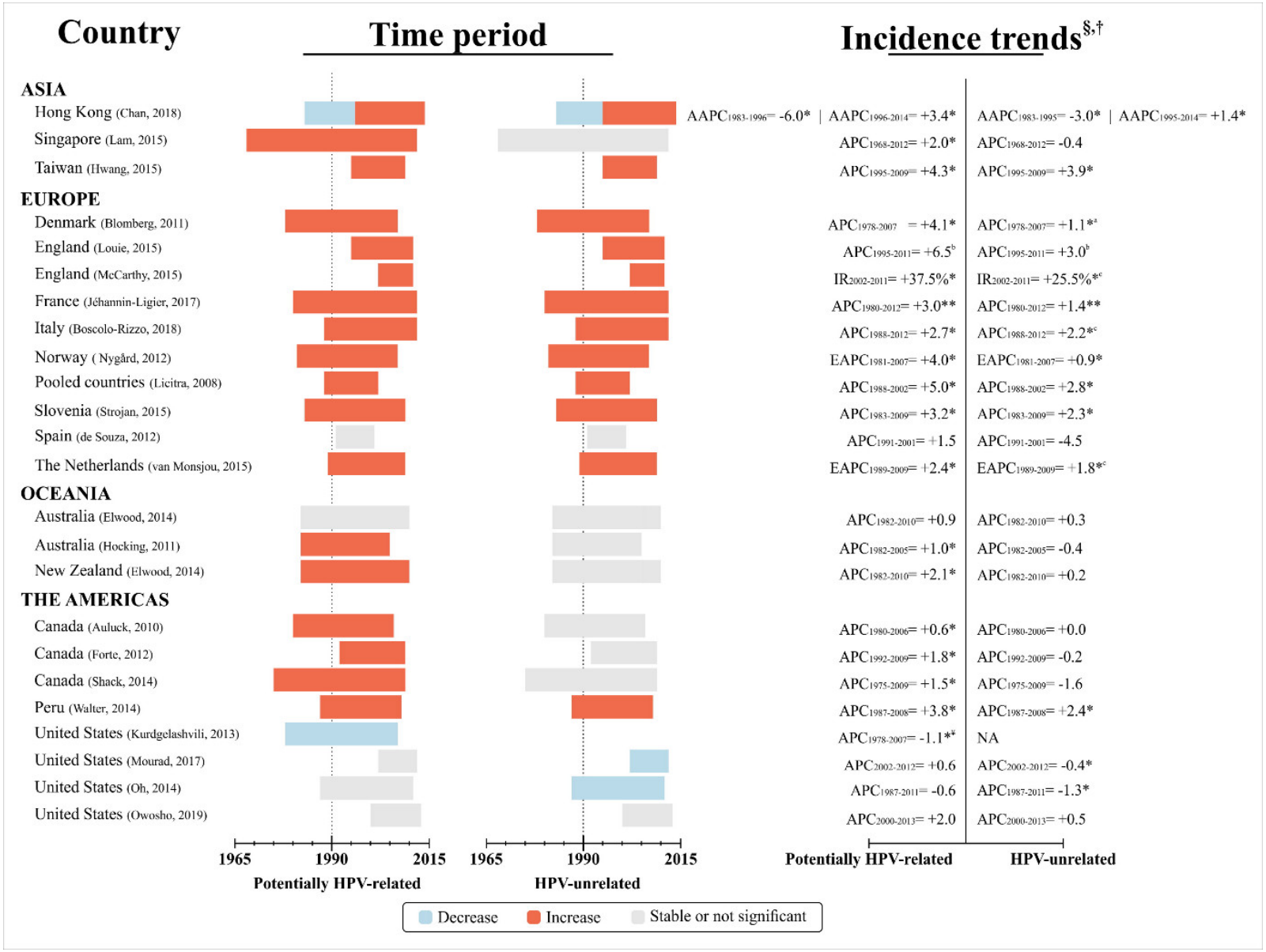


Figure 4. Global incidence trends for potentially HPV-related and -unrelated HNCs in females, 1965-2015.
§ Data were rounded to one decimal place.

† The studies had different standard populations (see Table 1).
¥ Only invasive cancers were considered.
* Statistically significant.
** Authors failed to report whether results were significant or not.
[a] Subsites potentially unrelated to HPV (Supplementary Table 2).
[b] Deemed oral cavity, excluding lip and hard palate (Supplementary Table 2). Also, the authors failed to report whether the results were significant or not.
[c] Oral cavity subsites (Supplementary Table 2).

Abbreviations: AAPC: average annual percent change; APC: annual percentage change; EAPC: estimated annual percentage change; IR: incidence rate; and NA: Not available.

Supplementary File Table 1. Electronic databases searched without filters plus search strategy.

DATABASE	WEBSITE	SEARCH STRATEGY
Medline/PUBMED via National Library of Medicine	http://www.ncbi.nlm.nih.gov/pubmed	(mouth neoplasms OR oropharyngeal neoplasms OR head and neck neoplasms OR "oral cavity cancer" OR "oropharyngeal cancer") AND (Papillomaviridae OR papillomavirus infections) AND (epidemiology OR registries OR time factors OR trends)
Embase	www.embase.com	(Wart virus OR Human papillomavirus type 16 OR Human papillomavirus type 18) AND (head and neck cancer OR mouth cancer OR oropharynx cancer OR Epidemiology) AND (trends OR register OR time factor)
Scopus	www.scopus.com	(mouth neoplasms OR oropharyngeal neoplasms OR head and neck neoplasms) AND (trends OR epidemiology)
OpenGrey	http://www.opengrey.eu	papillomavirus infections

Supplementary Table 2. Anatomical codes for studies included in the systematic review.

FIRST AUTHOR (YEAR)	ANATOMICAL CODES*
Auluck (2010)[52]	"Oropharyngeal cancers": C01.9, C02.4, C09.0, C09.1, C09.8, C09.9, C10.2, C10.3, C10.8, and C10.9. "Oral cavity cancers": C00.3-C00.5, C02.0-C02.3, C02.8, C02.9, C03.0-C03.1, C03.9, C04.0-C04.1, C04.8-C04.9, C05.0, C05.1-C05.2, C05.8-C05.9, C06.0-C06.2, and C06.8-C06.9.
Blomberg (2011)[2]	"HPV-associated": C01.9, C02.4, C02.8, C09, C10.2, C10.8, C10.9, C14.0, C14.2, and C14.8. "Potentially HPV-associated": C02.0-C02.3, C02.9, C03, C04, C05.0, C05.1, C05.2, C05.8, C05.9, C06, C10.0, C10.1, C10.3, and C32. "Potentially unrelated to HPV": C00, C07, C08, C10.4, C11-C13, C14.1, C30, and C31.
Boscolo-Rizzo (2018)[167]	"HPV-related": C01.9, C02.4, C09, C10, and C14.2. "Unrelated HPV": "Areas of the oral cavity": C02 (except C02.4), C03, C04, C05, and C06. "Larynx-hypopharynx": C12, C13, and C32.
Brouwer (2016)[58]	"HPV-related": C01.9, C02.4, C09.0, C09.1, C09.8, C09.9, C10.0, C10.1, C10.2, C10.3, C10.4, C10.8, C10.9, and C14.2. "Oral tongue sites to be HPV-unrelated": C02.0, C02.1, C02.2, C02.3, C02.8, and C02.9. "HPV-unrelated": C03.0, C03.1, C03.9, C04.0, C04.1, C04.8, C04.9, C05.0, C05.1, C05.2, C05.8, C05.9, C06.0, C06.1, C06.2, C06.8, C06.9, C12.9, C13.0, C13.1, C13.2, C13.8, C13.9, C14.0, and C14.8.
Brown (2011)[79]	"HPV-related": C01.9, C02.4, C09.0-C10.9, and C14.2. "HPV-unrelated": C02.0-C023, C02.5-C02.9, C03.0-C03.9, C04.0-C04.9, C05.0-C05.9, and C06.0-C06.9.
Chan (2018)[69]	"Oropharyngeal cancers": C01, C02.4, C05.1, C05.2, C09-C10, and C14. "Oral cavity cancers":

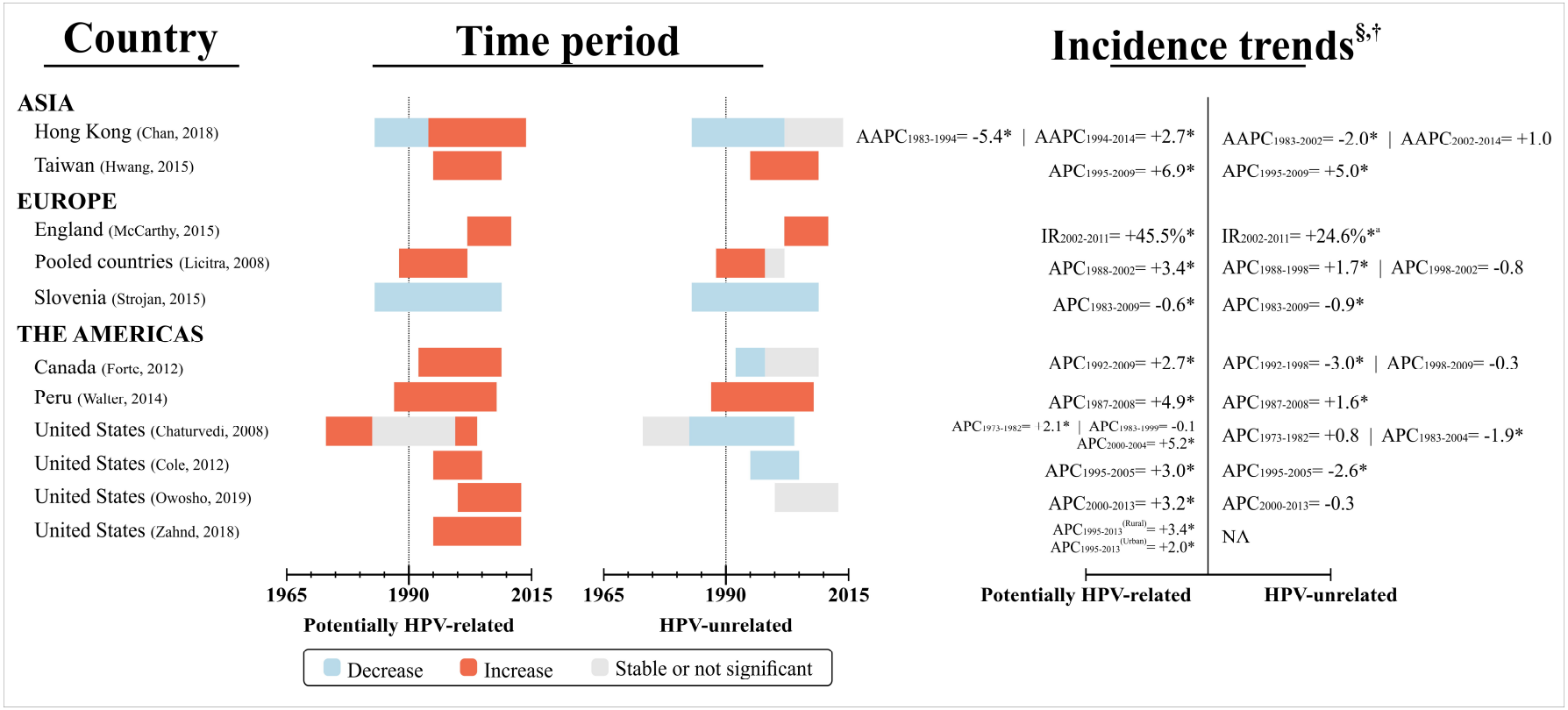
FIRST AUTHOR (YEAR)	ANATOMICAL CODES*
	C02 and C03-C06.
Chaturvedi (2008)[57]	"HPV-related": C01.9, C02.4, C09.0-C09.9, C10.0-C10.9, and C14.2. "HPV-unrelated": C02.0-C02.3, C02.5-C02.9, C03.0-C03.9, C04.0-C04.9, C05.0-C05.9, and C06.0-C06.9.
Cole (2012)[63]	"HPV-Associated Sites": C01.9, C02.4, C09.0-C09.9, C10.2-C10.9, and C14.2. "Non HPV-Associated Sites": C02.0-C02.9 (C02.4 excluded), C03.0-C03.9, C04.0-C04.9, C05.0-C05.9, C06.0-C06.9, C10.0, C10.1, C12.9, C13.0-C13.9, C14.0, C14.8, and C32.0-C32.9.
de Souza (2012)[61]	"Oropharynx": C01.9, C02.4, C05.1, C05.2, C09.0-C09.1, C09.8-C09.9, C10.0-C10.4, and C10.8-C10.9. "Oral cavity": C00.3-C00.9, C02.0-C02.3, C02.8-C02.9, C03.0-C03.1, C03.9, C04.0-C04.1, C04.8- C04.9, C05.0, C05.8-C05.9, C06.0, C06.1, C06.2, C06.8, and C06.9.
Elwood (2014)[118]	"Oropharyngeal cancers": C01.9, C02.4, C09.0-C09.9, C10.0-C10.9, and C14.2. "Oral cavity cancers": C00.3-C00.5, C02.0-C02.3, C02.8, C02.9, C03.0-C03.9, C04.0-C04.9, C05.0-C05.9, C06.0-C06.2, C06.8, and C06.9.
Forte (2012)[53]	"HPV-associated oropharyngeal cancers": C01.9, C02.4, C09.0-C09.9, C10.0-C10.9, and C14.2. "All head and neck cancers": C00.0-C14.8.
Hocking (2011)[168]	"Potentially HPV-associated cancers": C01.9, C02.4, C02.8, C09.0, C09.1, C09.8, C09.9, C10.2, C10.8, C10.9, C14.0, C14.2, and C14.8. "Comparison cancers": C02.0, C02.1, C02.2, C02.3 C02.9, C03.0, C03.1, C03.9, C04.0, C04.1, C04.8, C04.9, C05.0, C05.1, C05.2, C05.8, C05.9, C06.0, C06.1, C06.2, C06.8, C06.9, C10.0, C10.1, C10.3, C32.0, C32.1, C32.2, C32.3, C32.8, and C32.9.

FIRST AUTHOR (YEAR)	ANATOMICAL CODES*
Hwang (2015)[169]	"HPV-related sites" (ICD-O-3): C01, C02.4, C02.8, C09.0, C09.1, C09.8, C09.9, C10.2, C10.8, C10.9, C14.0, C14.2, and C14.8. "HPV-unrelated sites" (ICD-O-3): C02.0, C02.1, C02.2, C02.3, C02.9, C03.0, C03.1, C03.9, C04.0, C04.1, C04.8, C04.9, C05.0, C05.1, C05.2, C05.8, C05.9, C06.0, C06.1, C06.2, C06.8, C06.9, C10.0, C10.1, C10.3, C12, C13.0, C13.1, C13.2, C13.8, C13.9, C32.0, C32.1, C32.2, C32.3, C32.8, and C32.9. "HPV-related sites" (ICD-O-FT): 146.1, 146.2, 146.0, 146.0, 149.1, 141.0, 141.6, 141.8, 146.6, 146.8, 146.9, 149.0, 149.8, and 149.9. "HPV-unrelated sites" (ICD-O-FT): 141.1, 141.2, 141.3, 141.4, 141.9, 143.0, 143.1, 143.8, 143.9, 144.0, 144.1, 144.8, 144.9, 145.2, 145.0, 145.1, 145.6, 145.9, 148.0, 148.1, 148.2, 148.3, 148.8, 148.9, 161.0, 161.1, 161.2, 161.3, 161.8, 161.9, 145.3, 145.4, 145.5, 145.5, 146.3, 146.4, and 146.7.
Jéhannin-Ligier (2017)[129]	"Potentially HPV-related cancers": C01.9, C02.4, C09, C10 and C14.2. "HPV-unrelated cancers": C00, C02 (except C02.4), C03, C04, C05, C06, C12, C13, C14 (except C14.2), and C32.
Kurdgelashvili (2013)[59]	“Potentially HPV-related head and neck sites”: C01.9, C02.4, C09.0-C09.9, C10.0-C10.9, and C14.2.
Lam (2015)[47]	“HPV-related”: C01.9, C02.4, C05.1-C05.2, C09.0-C09.1, C09.8-C09.9, C10.0-C10.4, C10.8-C10.9, and C14.2. “HPV-unrelated”: C02.0-C02.3, C02.8-C02.9, C03.0-C03.1, C03.9, C04.0-C04.1, C04.8-C04.9, C05.0, C05.8-C05.9, C06.0-C06.2, and C06.8-C06.9.
Licitra (2008)[71]	“HPV-related”: C01.9, C02.4, C09.0-C09.9, C10.0-C10.9, and C14.2. HPV-unrelated”: C02.0-C023, C02.5-C02.9, C03.0-C03.9, C04.0-C04.9, C05.0-C05.9, and C06.0-C06.9.
Louie (2015)[170]	“HPV-related head and neck cancers”: C01, C09, and C10. "HPV-non-related HNCs”: "All other HNCs were considered HPV-non-related HNCs".
McCarthy (2015)[70]	"Potentially HPV-associated cancers": C01, C09, and C10. "Oral cavity cancer":

FIRST AUTHOR (YEAR)	ANATOMICAL CODES*
	C00, C02-06, C12-C14. "Laryngeal cancers": C32. "All HNC": C00, C01, C02-C06, C07-C08, C09, C10, C11, C12-C14, C30, C31, and C32.
Mourad (2017)[51]	"HPV-related": C09-C10. "Head and neck cancer": C00-C06, C07-C08, C09-C10, C11, C12-C14, C30, C31, and C32. "Laryngeal cancer": C32.
Nygard (2012)[60]	"HPV-related": C01 and C09-C10. "HPV-unrelated": C02-C06, C12-C13, and C32.
Oh (2014)[128]	“HPV-associated oropharyngeal cancers”: C01.9, C02.4, C02.8, C09.0, C09.1, C09.8, C09.9, C10.2, C10.8, C10.9, C14.0, C14.2, and C14.8. "Comparison sites": C02.0, C02.1, C02.2, C02.3, C02.9, C03.0, C03.1, C03.9, C04.0, C04.1, C04.8, C04.9, C05.0, C05.1, C05.2, C05.8, C05.9, C06.0, C06.1, C06.2, C06.8, C06.9, C10.0, C10.1, C10.3, C32.0, C32.1, C32.2, C32.3, C32.8, and C32.9.
Owosho (2019)[66]	"Oropharyngeal squamous cell carcinoma": C01.9, C02.4, C09.0-C09.1, and C09.8-C09.9. "Oral cavity squamous cell carcinoma": C003-C009, C02.0-C02.3, C02.8, C02.9, C03, C04, C05.0, C05.8, C05.9, and C06.
Shack (2014)[119]	"Oropharyngeal cancer": C01.9, C02.4, C02.8, C09.0-C09.9, C10.2, C10.8, C14.0, C14.2, and C14.8. "Non-HPV-associated": C000-C06.9 and C07.9-C10.9.
Shin (2013)[56]	"HPV-related": C09-C10, and C14.

FIRST AUTHOR (YEAR)	ANATOMICAL CODES*
	"HPV-unrelated": C00-C06, C01-C02, C12-C13, and C32.
Strojan (2015)[73]	"Potentially HPV-related": C01.9, C02.4, C05.1-C05.2, C09.0-C09.9, C10.0-C10.9, and C14.2. "Potentially HPV-unrelated": C32 and all other cancers in the code range C000-148 were included (lip, tongue, gum, floor of mouth, palate, other oral cavity, hypopharynx, pharynx, and larynx) according to Licitra et al (2008).[71]
Svahn (2016)[171]	"HPV-associated": C01.9, C02.4, C05.1, C05.2, C09, C10.0-C10.3, C10.8, C10.9, C14.0, and C14.2.
van Monsjou (2015)[172]	"Squamous cell carcinoma of the oral tongue": C02.0-C02.3 "Squamous cell carcinoma of the oral cavity excluding oral tongue": C03, C04, C05.0, and C06. "Squamous cell carcinoma of oropharynx": C01, C02.4, C05.1, C05.2, C09, and C10.
Walter (2014)[68]	"HPV-related sites": C01.9, C02.4, C05.1-C05.2, C09.0-C09.9, C10.0-C10.9, and C14.2. "HPV-unrelated sites": C02.0-C02.3, C02.8, C03.0-C03.9, C04.0-C04.9, C05.0, C05.8, C06.0-C06.9, C07.9-C08.9, C11.0-C11.9, C13.0-C13.9, C30.0-C31.9, and C32.
Zahnd (2018)[67]	“Oropharyngeal SCC”: C01.9, C02.4, C02.8, C05.1, C05.2, C09.0, C09.1, C09.8, C09.9, C10.0, C10.1, C10.2, C10.3, C10.4, C10.8, C10.9, C14.0, C14.2, and C14.8.
Zumsteg (2016)[173]	“Oropharyngeal squamous cell carcinomas”: C01.9, C02.4, C05.1, C05.2, C09.0-C09.1, C09.8-C09.9, C10.0, C10.2-C10.3, C10.8-C10.9, and C14.2. “Tobacco- and alcohol-related head and neck cancers”: C00.0-C00.9, C02.0-C02.3, C03.0-C03.1, C03.9, C04.0-C04.9, C05.0, C06.0, C06.1, C06.2, C12.9-C13.9, and C32.0-C32.9.

Abbreviations: HNC: head and neck cancer; HPV: human papillomavirus; ICD-O-FT: International Classification of Diseases for Oncology, Field Trial Edition; ICD-O-3: International Classification of Diseases for Oncology, Third Edition; and SCC: Squamous cell carcinoma.



Supplementary Figure 1. Stratified overall incidence trends for HPV-related and -unrelated HNC subsites presenting at least the anatomical codes C01 or C01.9 and C09, 1965-2015.

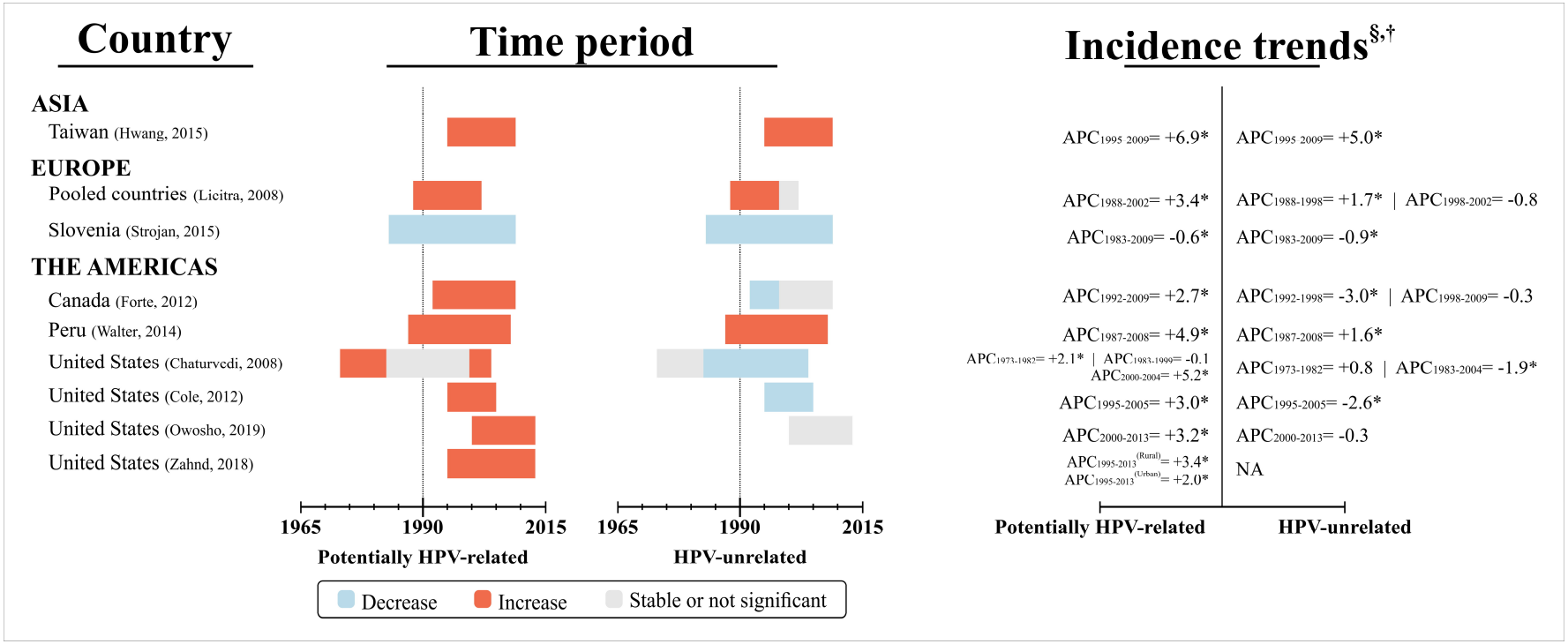
§ Data were rounded to one decimal place.

† The studies had different standard populations (see Table 1).

* Statistically significant.

a Oral cavity subsites (Supplementary Table 2).

Abbreviations: AAPC: average annual percent change; APC: annual percentage change; IR: incidence rate; and NA: Not available.



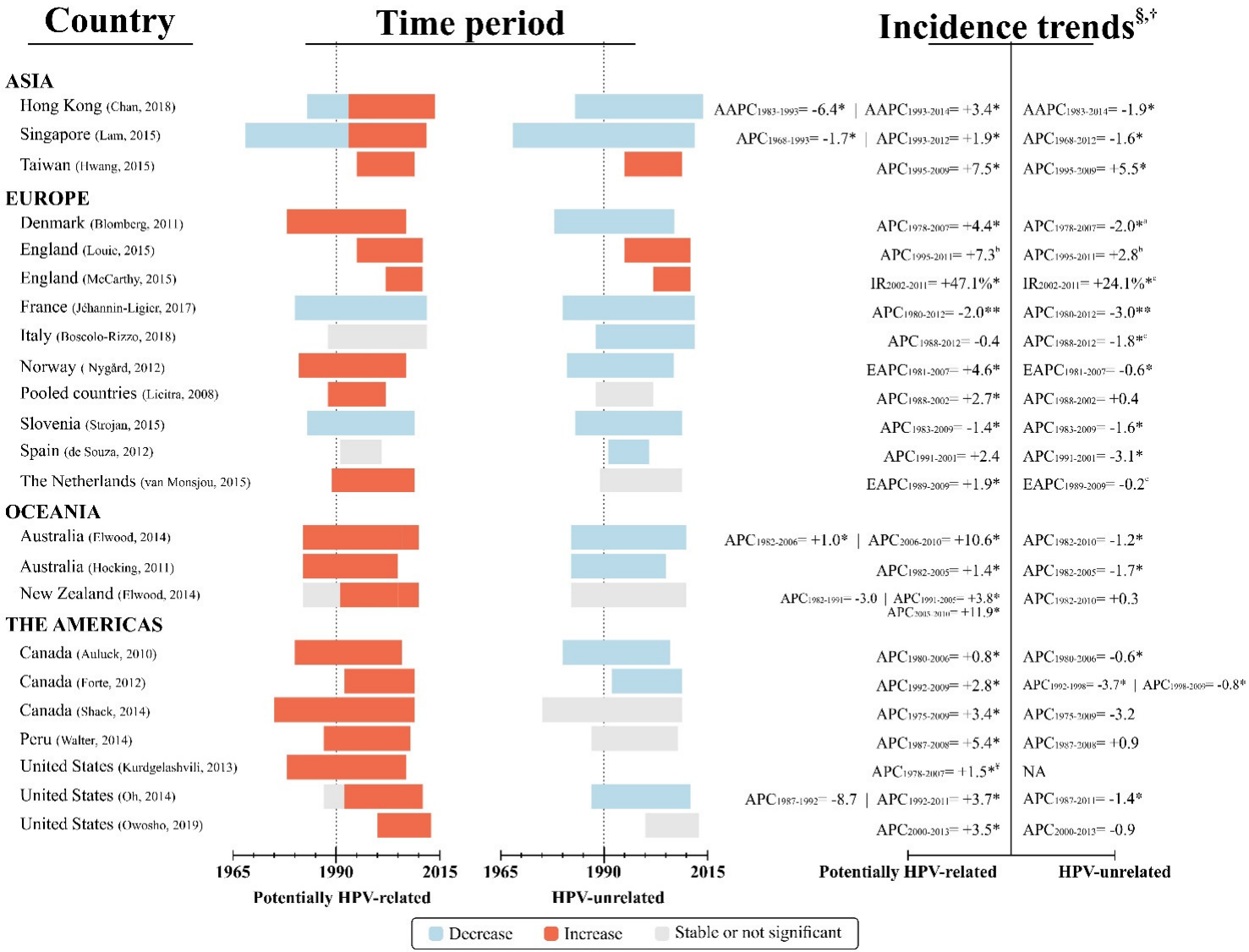
Supplementary Figure 2. Stratified overall incidence trends for HPV-related and -unrelated HNC subsites presenting at least the anatomical codes C01 or C01.9 and C09 plus squamous cell carcinoma diagnoses, 1965-2015.

§ Data were rounded to one decimal place.

† The studies had different standard populations (see Table 1).

* Statistically significant.

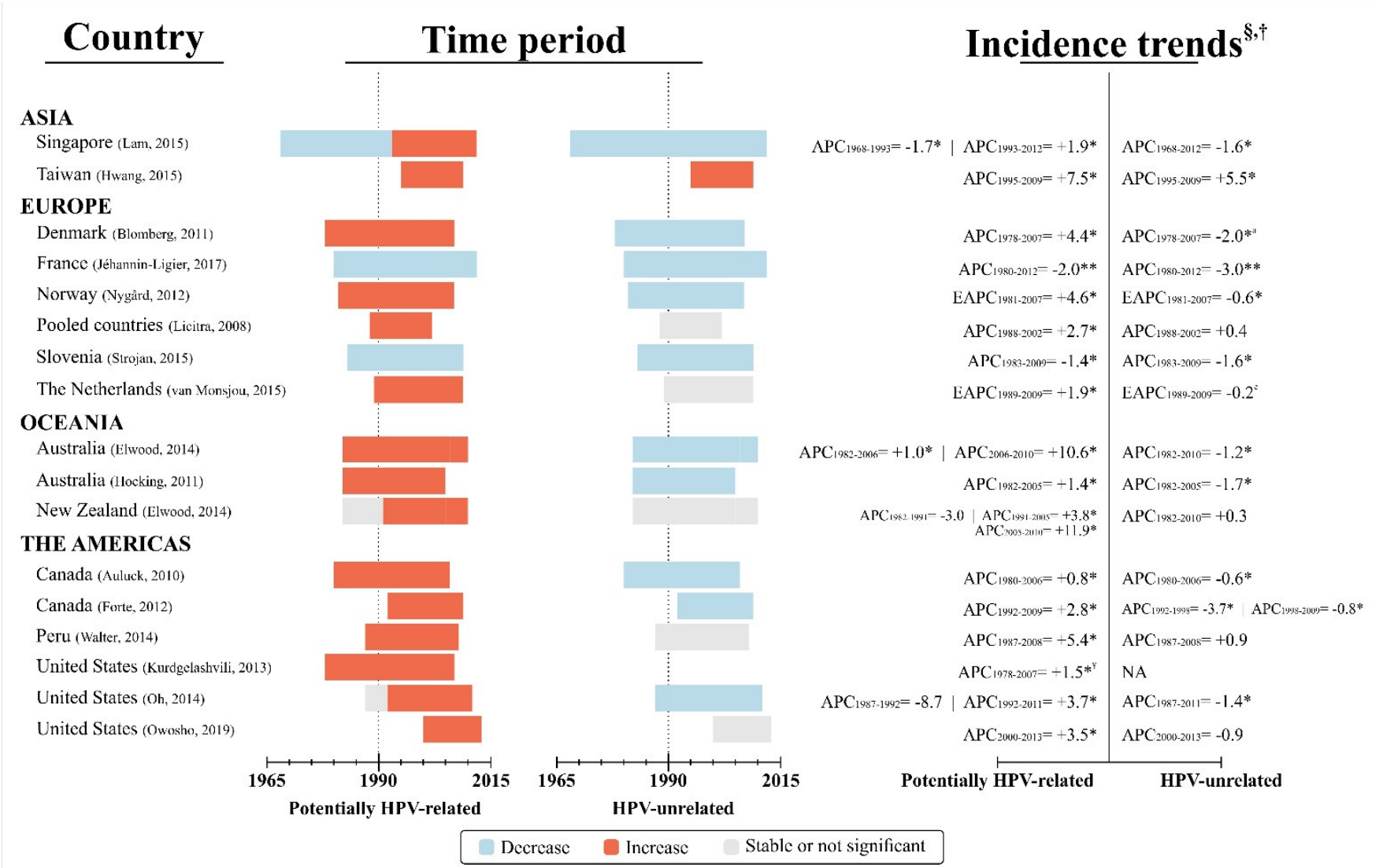
Abbreviations: AAPC: average annual percent change; APC: annual percentage change; and NA: Not available.



Supplementary Figure 3. Stratified incidence trends for HPV-related and -unrelated HNC subsites in males presenting at least the anatomical codes C01 or C01.9 and C09, 1965-2015.

§ Data were rounded to one decimal place.
† The studies had different standard populations (see Table 1).
¥ Only invasive cancers were considered.
* Statistically significant.
** Authors failed to report whether results were significant or not.
[a] Subsites potentially unrelated to HPV (Supplementary Table 2).
[b] Deemed oral cavity, excluding lip and hard palate (Supplementary Table 2). Also, authors failed to report whether results were significant or not.
[c] Oral cavity subsites (Supplementary Table 2).

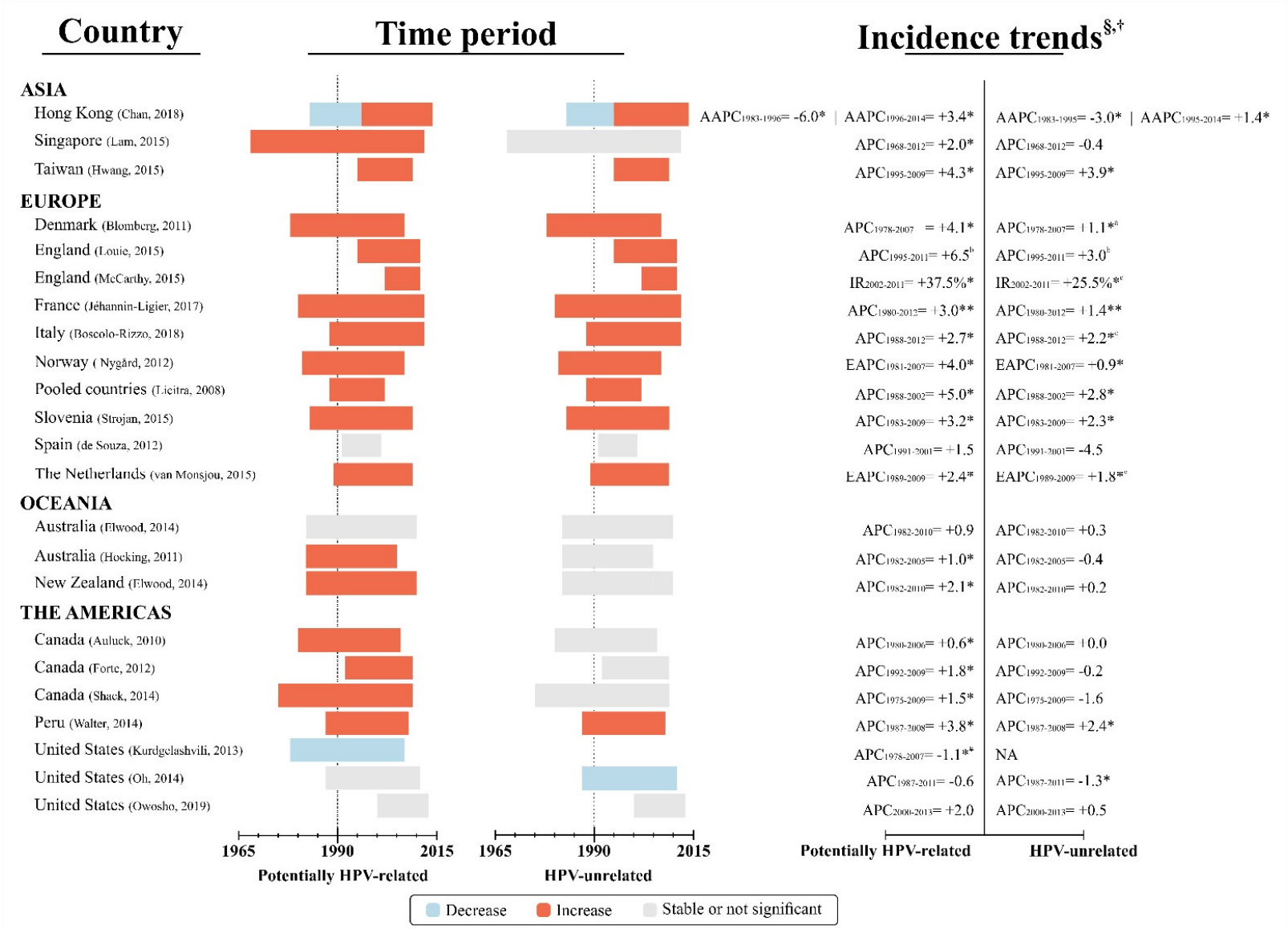
Abbreviations: AAPC: average annual percent change; APC: annual percentage change; EAPC: estimated annual percentage change; IR: incidence rate; and NA: Not available.



Supplementary Figure 4. Stratified incidence trends for HPV-related and -unrelated HNC subsites in males presenting at least the anatomical codes C01 or C01.9 and C09 plus squamous cell carcinoma diagnoses, 1965-2015.

§ Data were rounded to one decimal place.
† The studies had different standard populations (see Table 1).
¥ Only invasive cancers were considered.
* Statistically significant.
** Authors failed to report whether results were significant or not.
[a] Subsites potentially unrelated to HPV (Supplementary Table 2).

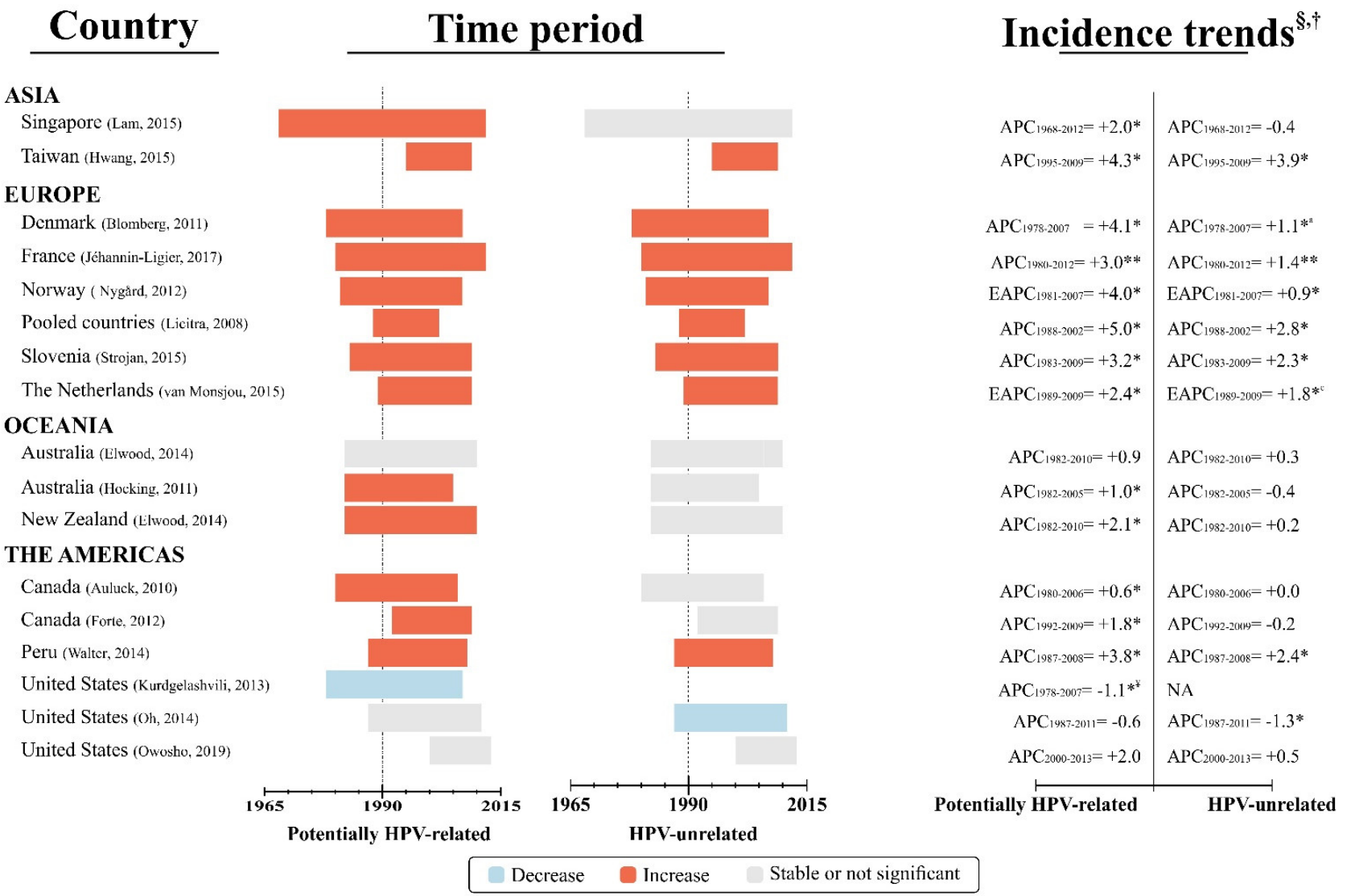
Abbreviations: AAPC: average annual percent change; APC: annual percentage change; EAPC: estimated annual percentage change; IR: incidence rate; and NA: Not available.



Supplementary Figure 5. Stratified incidence trends for HPV-related and -unrelated HNC subsites in females presenting at least the anatomical codes C01 or C01.9 and C09, 1965-2015.

§ Data were rounded to one decimal place.
† The studies had different standard populations (see Table 1).
¥ Only invasive cancers were considered.
* Statistically significant.
**Authors failed to report whether results were significant or not.
[a] Subsites potentially unrelated to HPV (Supplementary Table 2).
[b] Deemed oral cavity, excluding lip and hard palate (Supplementary Table 2). Also, authors failed to report whether results were significant or not.
[c] Oral cavity subsites (Supplementary Table 2).

Abbreviations: AAPC: average annual percent change; APC: annual percentage change; EAPC: estimated annual percentage change; IR: incidence rate; and NA: Not available.



Supplementary Figure 6. Stratified incidence trends for HPV-related and -unrelated HNC subsites in females presenting at least the anatomical codes C01 or C01.9 and C09 plus squamous cell carcinoma diagnoses, 1965-2015.

§ Data were rounded to one decimal place.
† The studies had different standard populations (see Table 1).
¥ Only invasive cancers were considered.
* Statistically significant.
** Authors failed to report whether results were significant or not.
[a] Subsites potentially unrelated to HPV (Supplementary Table 2).

Abbreviations: AAPC: average annual percent change; APC: annual percentage change; EAPC: estimated annual percentage change; IR: incidence rate; and NA: Not available.

5.2 Manuscrito 2

Esse artigo foi submetido e publicado na revista PlosOne (Qualis: A1) (Fator de impacto: 2,776) (Anexo I) (Figura 12).

Figura 12 – Carta com a decisão final sobre o aceite do artigo.

Date: Apr 24 2020 09:39AM
To: "Fabrício dos Santos Menezes" fabriciomenezes@msn.com
cc: "Maria do Rosário Dias de Oliveira Latorre" mdrddola@usp.br, "Gleice Margarete de Souza Conceição" gleice@usp.br, "Maria Paula Curado" mp.curado@accamargo.org.br, "José Leopoldo Ferreira Antunes" leopoldo@usp.br, "Tatiana Natasha Toporcov" toporcov@usp.br
From: "PLOS ONE" plosone@plos.org
Subject: PONE-D-20-01575R1: Final Decision Being Processed

The emerging risk of oropharyngeal and oral cavity cancer in HPV-related subsites in young people in Brazil
PONE-D-20-01575R1

Dear Dr. Menezes,

We are pleased to inform you that your manuscript has been judged scientifically suitable for publication and will be formally accepted for publication once it complies with all outstanding technical requirements.

Within one week, you will receive an e-mail containing information on the amendments required prior to publication. When all required modifications have been addressed, you will receive a formal acceptance letter and your manuscript will proceed to our production department and be scheduled for publication.

Shortly after the formal acceptance letter is sent, an invoice for payment will follow. To ensure an efficient production and billing process, please log into Editorial Manager at https://www.editorialmanager.com/pone/, click the "Update My Information" link at the top of the page, and update your user information. If you have any billing related questions, please contact our Author Billing department directly at authorbilling@plos.org.

If your institution or institutions have a press office, please notify them about your upcoming paper to enable them to help maximize its impact. If they will be preparing press materials for this manuscript, you must inform our press team as soon as possible and no later than 48 hours after receiving the formal acceptance. Your manuscript will remain under strict press embargo until 2 pm Eastern Time on the date of publication. For more information, please contact onepress@plos.org.

With kind regards,

Xuefeng Liu
Academic Editor
PLOS ONE

Fonte: Plos One.

The emerging risk of oropharyngeal and oral cavity cancer in HPV-related subsites in young people in Brazil

Fabrício dos Santos Menezes[1,ƶ,#a,*], Maria do Rosário Dias de Oliveira Latorre[ƶ], Gleice Margarete de Souza Conceição[ƶ], Maria Paula Curado[3,4], José Leopoldo Ferreira Antunes[ƶ], and Tatiana Natasha Toporcov[ƶ].

[1] Department of Health Education, Federal University of Sergipe, Lagarto, Sergipe, Brazil

[ƶ] Department of Epidemiology, School of Public Health, University of São Paulo, São Paulo City, São Paulo State, Brazil

[3] Department of Epidemiology, International Research Center, A.C. Camargo Cancer Center, São Paulo City, São Paulo State, Brazil

[4] International Prevention Research Institute, Ecully, France

[#a]Current Address: Department of Health Education, Federal University of Sergipe, Lagarto, Sergipe, Brazil.

* Corresponding author

E-mail: fabriciomenezes@usp.br (FSM)

Abstract

Human papillomavirus (HPV) is responsible for the rise in the incidence of cancer in the oropharynx, tonsils, and base of the tongue (i.e., HPV-related subsites). HPV triggered the changes in the epidemiology of oropharyngeal and oral cavity cancer (OPC/OCC) in Asia, Europe, North America, and Oceania. Hence, the incidence of cancer in HPV-related subsites is augmenting, while that in other HPV-unrelated subsites is decreasing. In South America, although the incidence of HPV-positive tumors has gradually increased, there is an atypically low prevalence of HPV in people with OPC/OCC. To clarify whether this dramatic shift in incidence trends also occurred in this population, we estimated the burden of HPV on the incidence trends of OPCs/OCCs in São Paulo city in Brazil. In this population-based study, we categorized OPCs/OCCs by HPV-related and HPV-unrelated subsites. We used Poisson regression to assess the age-standardized incidence rates (ASRs) stratified by sex and age groups, as well as to examine the age-period-cohort effects. There were 15,391 cases of OPCs/OCCs diagnosed in HPV-related (n= 5,898; 38.3%) and HPV-unrelated (n= 9,493; 61.7%) subsites. Overall, the ASRs decreased for most subsites, for both sexes and for all age groups, except for HPV-related OPC/OCC in young males and females, which increased by 3.8% and 8.6% per year, respectively. In the birth-cohort-effect analysis, we identified an increasing risk for HPV-related OPC/OCC in both sexes in recent birth cohorts; however, this risk was sharply decreased in HPV-unrelated subsites. Our data demonstrate an emerging risk for HPV-related OPC/OCC in young people, which supports prophylactic HPV vaccination in this group.

Introduction

Human papillomavirus (HPV) is an oncogenic virus that is sexually transmitted, and it is the cause of an estimated 630,000 new cancers each year worldwide [1]. There is a causal association between HPV and oropharyngeal and oral cavity cancers (OPCs/OCCs) [2]. In addition to the unique carcinogenesis pathway [3] and HPV DNA identified in tumors [4], HPV-positive OPCs/OCCs are associated with clinical and epidemiological features, such as a young age at diagnosis, high-risk sexual behaviors [5,6], and enhanced survival rates [7], which distinguish these cancers from their HPV-negative counterparts.

In the mid-2000s, there was a striking rise, from 40.5% to 72.2%, in the overall HPV prevalence of oropharyngeal tumors [4]. Likewise, oropharyngeal and oral cavity subsites strongly associated with HPV infection (hereafter referred to as HPV-related subsites) have increased in both sexes in Asia [8], Oceania [9,10], and North America [11–13], whereas HPV-unrelated subsites have decreased, similar to the prevalence of smoking [14] and lung cancer incidence [15]. There is a global concern regarding the changing epidemiology of OPC/OCC. However, little information is available on the burden of this “virus-related cancer epidemic” in South America [16]; this information is urgently needed because South America has the highest prevalence of oral HPV in healthy individuals worldwide [17]. In Brazil, studies found a low prevalence of HPV in oropharynx tumors ranging from 4.4% to 8.8% [18–20]. Conversely, patients from a private hospital had an HPV positivity rate of 59.1% [21], which demonstrates the HPV heterogeneity in the country. Due to these discrepancies in the prevalence of HPV, it is crucial to monitor these subsites to clarify whether this dramatic shift in incidence trends observed worldwide also affects this population.

To the best of our knowledge, no population-based study has focused on the burden of HPV associated with OPC/OCC incidence in Brazil. Prophylactic HPV vaccinations were introduced in 2014 in an effort to hasten a decrease in HPV prevalence, but its need in oral cavity and oropharyngeal subsites at the population level was unknown. For these reasons, we assessed the incidence trends of OPC/OCC in HPV-related and HPV-unrelated subsites over the 15 years prior to large-scale HPV immunization in São Paulo city.

Materials and methods

Data source

The Research Ethics Committee (nº 83218318.8.0000.5421) and the Technical Advisory Committee of the Population-based Cancer Registry in the city of São Paulo (RCBP-SP) approved our investigation. We accessed data on the RCBP-SP repository in July 2018 [22]. All datasets were fully anonymized before using them.

This population-based study included new cases of OPC/OCC diagnosed between 1997 and 2013 in the RCBP-SP database. In São Paulo city, the RCBP-SP records cancer data of more than 12 million residents from 301 sources, including hospitals, clinics, and death investigation services; this database is one of the oldest and largest cancer registries in Latin America [23].

Classification of anatomic sites

To investigate the potential role of HPV in the burden of OPC/OCC, we classified anatomical codes as a proxy for HPV exposure based on robust scientific evidence [4,8,24–27] because cancer registries do not contain information on HPV DNA testing from tumors [25,28,29]. Hence, HPV-related subsites comprised individuals with the following subsites: base of the tongue (C01), tonsil (C02.4, C09.0-C09.1, and C09.8-C09.9), oropharynx (C10.0-C10.4 and C10.8-C10.9), soft palate and uvula (C05.1-C05.2), and Waldeyer's ring (C14.2). Likewise, HPV-unrelated subsites comprised individuals with other parts of the tongue (C02.0-C02.3 and C02.8-C02.9), gums (C03.0-C03.1 and C03.9), mouth (C04.0-C04.1, C04.8-C04.9, C06.0-C06.2, and C06.8-C06.9), and hard palate (C05.0, and C05.8-C05.9). According to Chaturvedi et al. (2013), we included all histological codes because approximately 95% of head and neck cancers are squamous cell carcinomas [15].

Statistical analyses

The incidence rates were further age-standardized per 100,000 persons using the direct method, the World Health Organization (WHO) standard population [30], and data provided by the SEADE Foundation [31].

For the incidence trend analysis, we adjusted Poisson regression models by sex. The dependent variable was the annual incidence, and the explanatory variables were the HPV group (HPV-related or HPV-unrelated subsites), age group (≤39, 40-59, and 60+ years), and time (years). We used as offset the population size according to the age group and year. With the models, we estimated the incidence rates and the annual percent change (APC; 95% confidence interval [CI]) for each segment (i.e., tumor classification and age group). To assess whether the trends were similar in different segments, we assessed contrasts under the general linear hypotheses [32].

Additionally, we investigated the effects of age, calendar year (period), and birth year (cohort) on incidence rates with Poisson regression to measure the relative risk [33,34]. We constructed age-period-cohort models according to 5-year age groups (from 15-19 years to 75+ years) and 5-year calendar periods (1999-2003, 2004-2008, and 2009-2013). The lowest deviance indicated the best-fitted model ($p<0.05$), and we used R version 3.5.3 (Epi package version 2.3.5) for the analyses.

Results

Over the entire study period, there were 15,391 new cases of OPC/OCC in São Paulo city. Of these cases, 5,898 occurred in HPV-related subsites (38.3%), and 9,493 occurred in HPV-unrelated subsites (61.7%). There was a marked male dominance in both HPV-related and HPV-unrelated subsites and all anatomical site groups (Table 1). Nevertheless, the proportion of cases in the HPV-related subsites in young individuals aged ≤39 years was 3-fold higher in females than in males (18.0% vs. 5.8%). Likewise, the sex ratio of the incidence decreased more in the HPV-related subsites than in the HPV-unrelated subsites, from 6.2 to 3.5 and 2.4 to 2.1, respectively.

In the temporal analysis, incidence trends decreased or remained stable for all anatomical sites, sexes, and age groups (S1 and S2 Figs). For the HPV groups, the incidence rate decreased more sharply in the HPV-unrelated subsites, from 7.4 to 3.3

per 100,000, than in the HPV-related subsites, from 4.1 to 2.6 per 100,000. Moreover, we found a dramatic increase in incidence for HPV-related subsites in young males and females, by 3.8% and 8.6% per year, respectively; in contrast, HPV-unrelated subsites had a decreased incidence rate for most sexes and age groups (Fig 1).

When we compared the inclines (β1) with the contrasts under the general linear hypotheses, we found statistically significant differences among HPV-related and HPV-unrelated subsites for young females ($p \approx 0.010$) and males ($p = 0.033$). Additionally, the incidence trends were different between individuals aged ≤39 years and older age groups in both sexes for HPV-related subsites, which indicates a distinct pattern for HPV-related and HPV-unrelated subsites in the young population.

In the age-period-cohort analysis, the incidence rates of HPV-related OPC/OCC increased in the youngest birth cohorts in both sexes, while it decreased in HPV-unrelated subsites (Fig 2). For HPV-related subsites, the risk increased for cohorts born after 1984 in females, with a sharp rise in recent cohorts of males. Conversely, the risk of HPV-unrelated OPC/OCC was decreased in recent birth cohorts in both sexes (Fig 3). In the age-period-cohort models, there was an age-cohort effect in HPV-related subsites and an age-period-cohort effect in HPV-unrelated subsites in both sexes (Table 2).

Discussion

Understanding the HPV pattern over time is critical to support prophylactic interventions focused on diminishing its harmful impacts on populations. For this reason, we performed this study to determine the burden of HPV in OPC/OCC in São Paulo city, which is the largest city in Latin America. Overall, the incidence rates decreased for most OPCs/OCCs in both sexes in all age groups, and particularly in those with HPV-unrelated subsites. However, we identified a dramatically increasing incidence trend for HPV-related OPC/OCC in young females, emphasizing the highest risk in recent birth cohorts.

Our study revealed a striking reduction in the overall incidence trends of OPC/OCC and an age-period-cohort effect in HPV-unrelated subsites. Since the 1990s, the Brazilian tobacco control policy has led to a decrease in smoking [14] and, consequently, tobacco-related cancers. In São Paulo city, the estimated prevalence of

smoking decreased in males from 23.6% to 15.6% and in females from 14.6% to 9.8% over thirteen years [35]. Indeed, these data explain our cancer incidence and the lowest risk found in individuals with HPV-unrelated sites in recent generations, which is understandable due to the critical role of tobacco in carcinogenesis [3,36] and the public policy that affects the whole population [14,35].

The lung cancer incidence is decreasing worldwide, while the OPC incidence is increasing, which suggests that HPV infection is a reason for this growth [15]. In this study, the incidence dramatically trended upward in young males and females in HPV-related subsites, particularly in recent cohorts. Our finding is analogous to data from Denmark, which demonstrated an increase in young and middle-aged males and females [37], and France, which demonstrated an increased cumulative risk in females [29]. Conversely, there was a sharp increase in all age groups in Taiwan and the United States (1995-2005) [38]. Additionally, incidence trends increased in older females in England [39], Italy [40], the Netherlands [41], and the United States [42], and there was a negative cohort effect among females in Hong Kong [43]. In summary, these controversial data demonstrate different outbreak periods of HPV infection across populations. Moreover, these results highlight the regional heterogeneity in HPV prevalence, as HPV transmission depends on high-risk sexual behaviors and the virus's circulation among individuals.

A possible cause for the increased incidence of cancer at HPV-related subsites is the changing sexual behaviors [44]. People who engage in high-risk sexual behaviors are likely to develop cancers in the oropharynx, tonsils, and base of the tongue [45]. Not only did the cases of HPV-related OPC/OCC increase similarly to the rates of genital warts and genital herpes [39], but the HPV prevalence in OPC cases also increased over time. In addition, the incidence of cancers peaked for birth cohorts born between 1943 and 1958 [46], which suggest temporal coherence. Moreover, it is biologically plausible that HPV requires more than ten years to produce a tumor [47]. In Brazil, the median age at first sexual intercourse is 16.5 and 18.5 years in males and females, respectively. Additionally, the occurrence of sexual intercourse before the age of 15 years has increased in females and especially in males, who accounted for 29.6% of men, representing the second-highest global prevalence [48]. HPV is a known cause of cervical cancers [49], and the mortality attributable to this tumor is increasing in Brazilian females aged 20 to 39 years [50]. Additionally, the average age at first diagnosis, 35.4 years, was the lowest among those of all cancer types in females

[51]. Under these circumstances, we suppose that changes in the sexual behavior of recent generations have led to an emerging burden of HPV-related diseases in Brazil, as observed in HPV-related OPC/OCC subsites in young individuals in our investigation.

Another potential reason for our findings is the prevalence of alcohol and tobacco use by the individuals with cancer in HPV-related subsites. Previous studies have reported an HPV infection rate of 6.2% in a healthy Brazilian population [52], and the detection rate of HPV16 was 4.1% in OPC patients from São Paulo [18]. Conversely, in São Paulo city, 79.6% of the subjects aged between 16 and 25 years reported high-risk sexual behavior. Consequently, HPV was detected in 52% of samples from the uterine cervix, penis, and scrotum, of which 38.8% were positive for viral strains with high-risk of progression to cancer [53]. Furthermore, smoking prevalence decreased in females [35]. For these reasons, it is plausible that alcohol and tobacco use do not fully clarify the increasing risk observed in young individuals.

Although our results are not sufficiently robust to indicate a viral epidemic in São Paulo city, they highlight the need to monitor the burden of these cancers in young populations. Considering that cancer is a time-dependent disease, we expected stable trends for individuals aged ≤ 39 years, but we found an upward trend in HPV-related OPC/OCC in young individuals. In addition, the remarkable decrease in smoking may be masking the increasing incidence in the HPV-related subsites, as this tumor classification occasionally includes tobacco-related cancers. For this reason, our data suggest that a dramatic increase in HPV-related OPC/OCC in its initial phase is occurring in the city of São Paulo. Indeed, this is a public health concern due to high survival rates and its potential magnitude, which impairs patients' quality of life and the healthcare and social security systems, particularly in developing countries, such as Brazil.

Our study had limitations that are important to its interpretation. As in other countries [25,46], cancer registries do not gather data on positive HPV DNA within tumors. Accordingly, we used anatomic sites as a proxy to categorize OPCs/OCCs as those occurring in either HPV-related or HPV-unrelated subsites. Moreover, we had no information on alcohol and tobacco use and high-risk sexual behaviors in the subjects. However, several investigations had similar limitations, especially regarding tumor classification [8,11,12,24,25,37,46,54–56]. Furthermore, this grouping had

analogous results to laboratory data results [57], suggesting it is a reliable method since HPV testing is not a standard procedure in cancer registries.

This population-based study had strengths including its generalizability and limited selection bias, which allowed us to demonstrate the emerging risk of HPV-related OPC/OCC in young males and females, whereas the risk in HPV-unrelated subsites sharply decreased. For these reasons, our data support the HPV vaccination program and the continuity of the Brazilian tobacco control policy, which has had positive effects on OPC/OCC incidence in São Paulo city. Furthermore, it is crucial to continue to specifically monitor the incidence of HPV-related OPC/OCC and to investigate vaccine effectiveness in the oropharyngeal and oral cavity subsites in the long term. Moreover, cancer control programs should broaden screening coverage in young subjects to prevent sexually transmitted infections and HPV-related cancers to minimize the increasing risk.

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Supporting information

S1 Fig. OCC/OPC incidence trends by anatomic site and sex (1997-2013).

S2 Fig. OCC/OPC incidence trends by anatomic site (1997-2013).

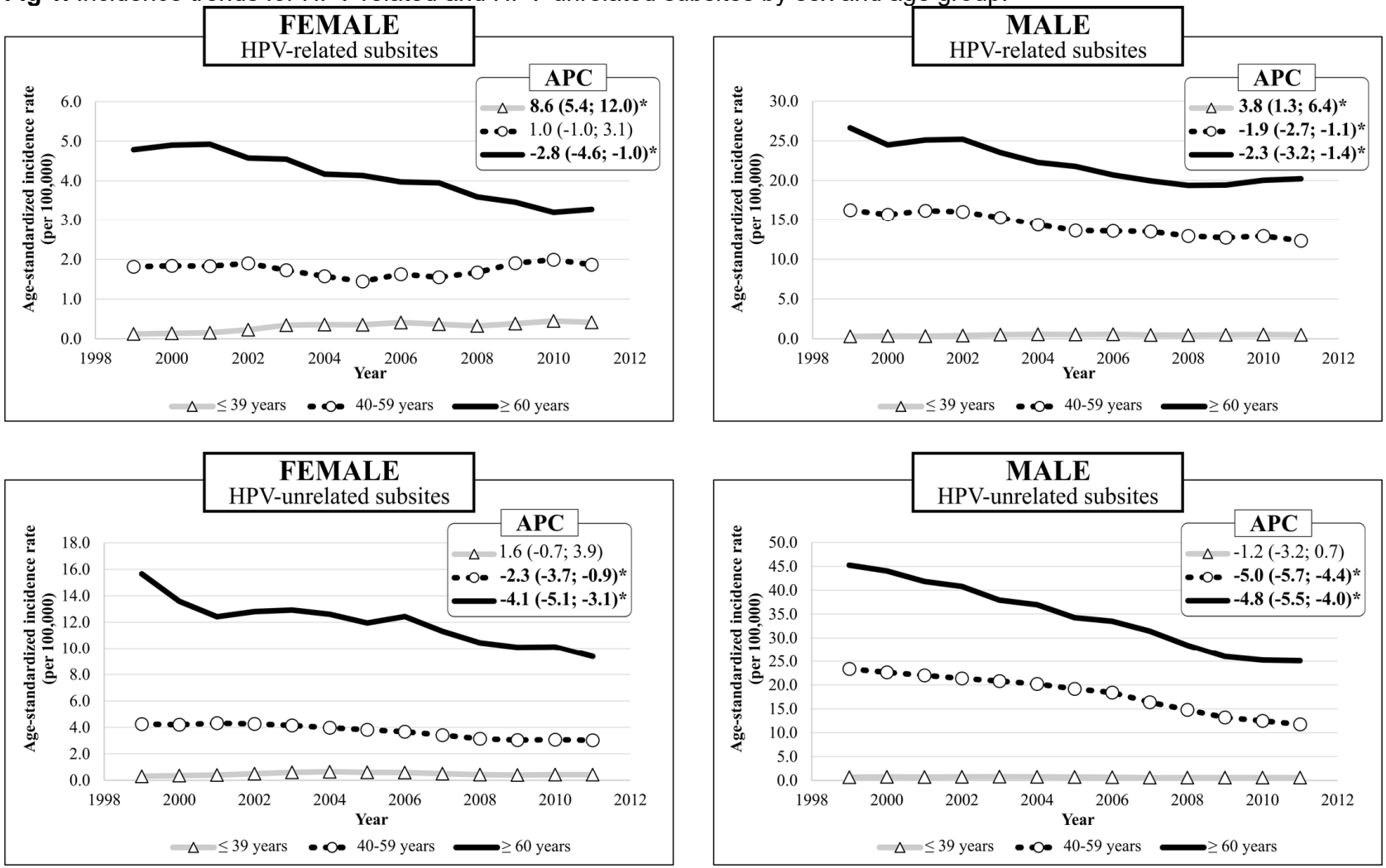
S3 Fig. [A]: Incidence trends for OCC/OPC according to HPV groups; [B]: incidence trends for OCC/OPC by sex and HPV groups; [C]: incidence trends for HPV-related OCC/OPC by age groups; and [D]: incidence trends for HPV-unrelated OCC/OPC by age groups.

Table 1. Descriptive analysis of OPC/OCC by the subsites, sex, and HPV groups.

	TOTAL	SEX		
		Male	Female	Ratio (M:F)
All OPC/OCC sites	15,391 (100.0%)	11,538	3,853	3.0
HPV-related	5,898 (38.3%)	4,801	1,097	4.4
Base of the tongue	1,287 (8.4%)	1,062	225	4.7
Oropharynx	2,275 (14.8%)	1,915	360	5.3
Tonsils	1,545 (10.0%)	1,189	356	3.3
Waldeyer's ring, soft palate and uvula	791 (5.1%)	635	156	4.1
HPV-unrelated	9,493 (61.7%)	6,737	2,756	2.4
Gums	625 (4.1%)	372	253	1.5
Hard palate	836 (5.4%)	486	350	1.4
Mouth	3,847 (25.0%)	2,810	1,037	2.7
Other parts of the tongue	4,185 (27.2%)	3,069	1,116	2.8

M:F: male:female ratio.

Fig 1. Incidence trends for HPV-related and HPV-unrelated subsites by sex and age group.[a]



APC: annual percent change; *: statistically significant APC.

[a] For better graph visualization, we applied a simple moving average of 5 years.

Fig 2. Descriptive birth cohort analysis.

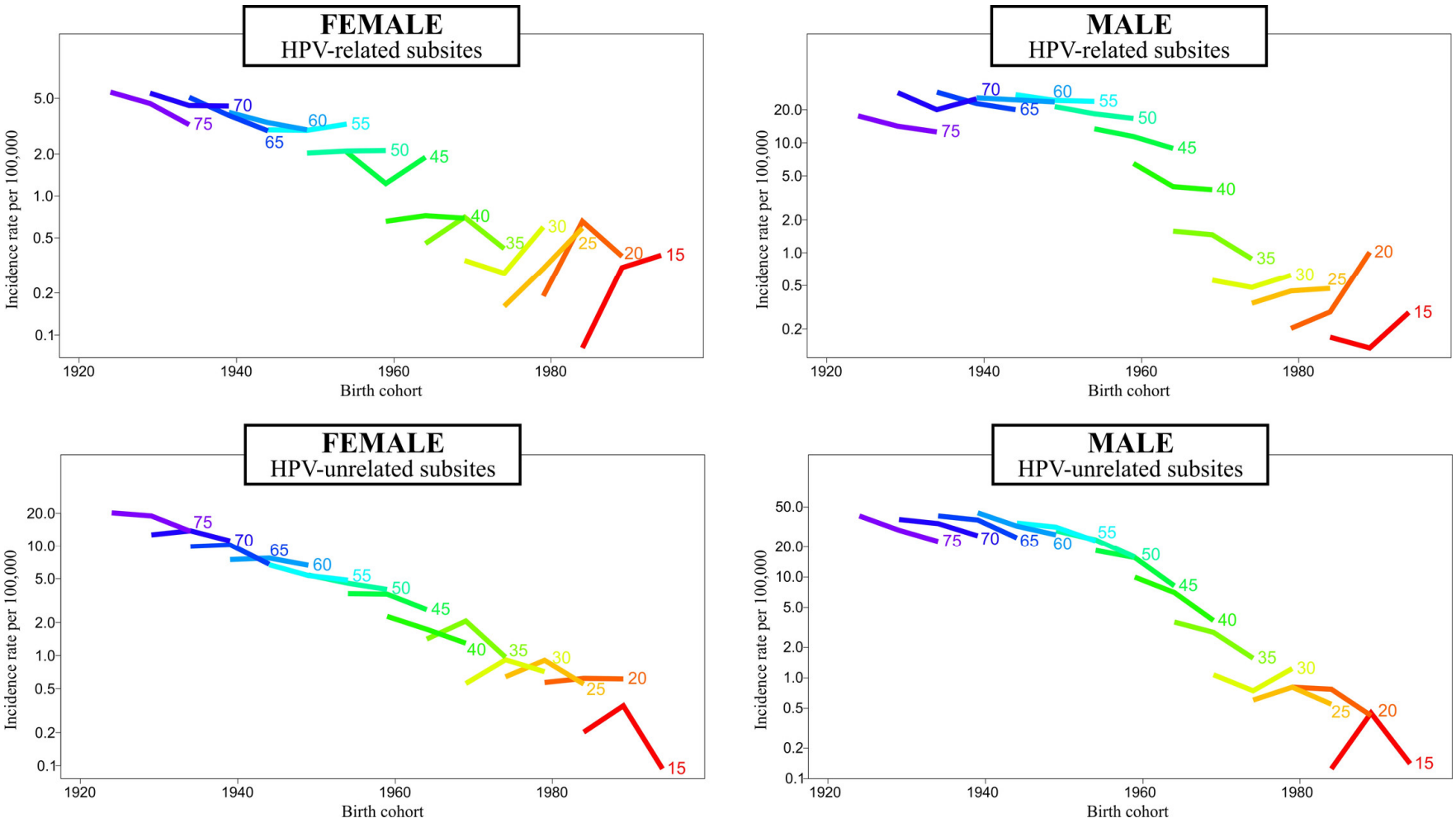


Fig 3. Age-period-cohort effect analysis.

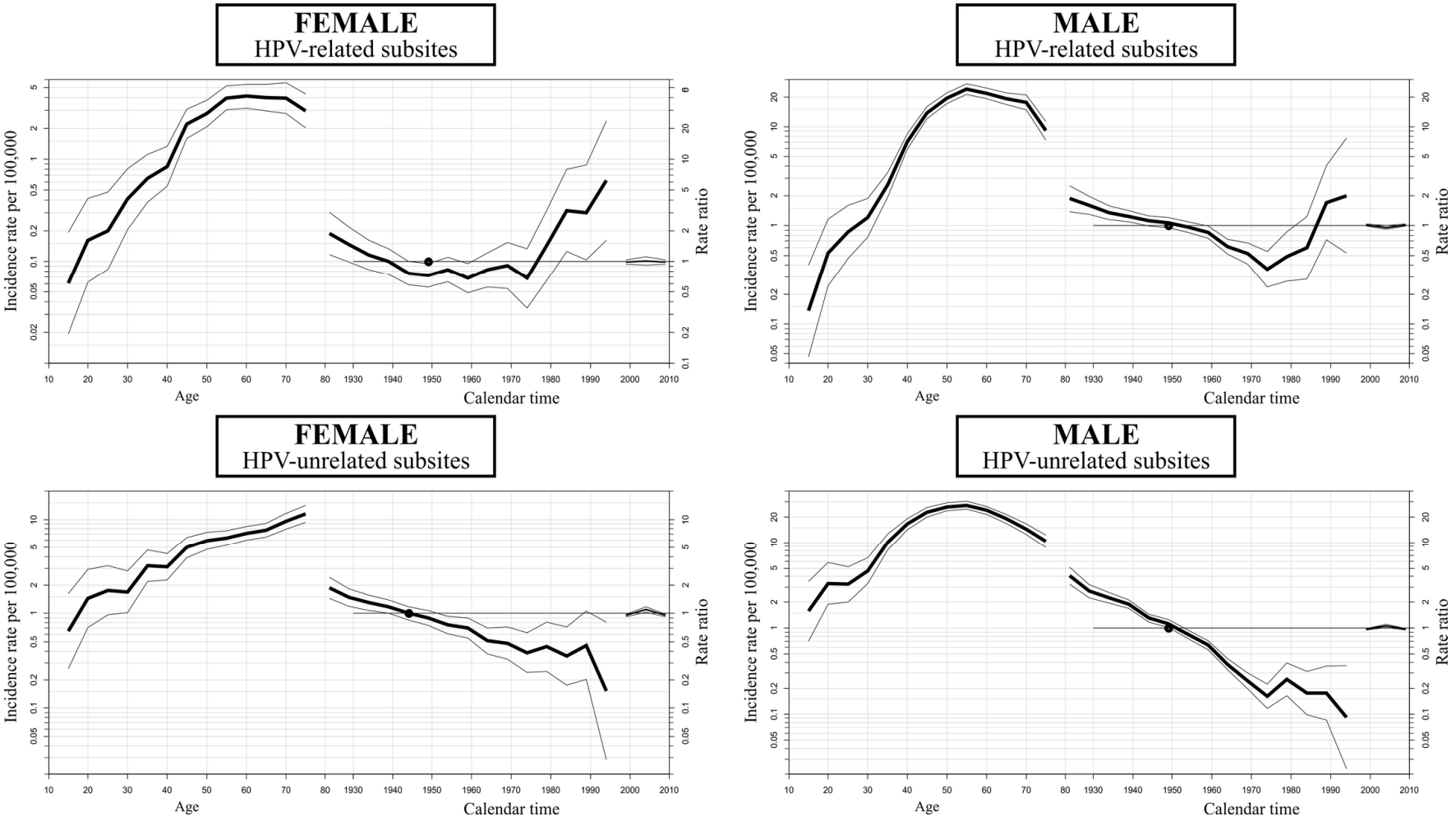
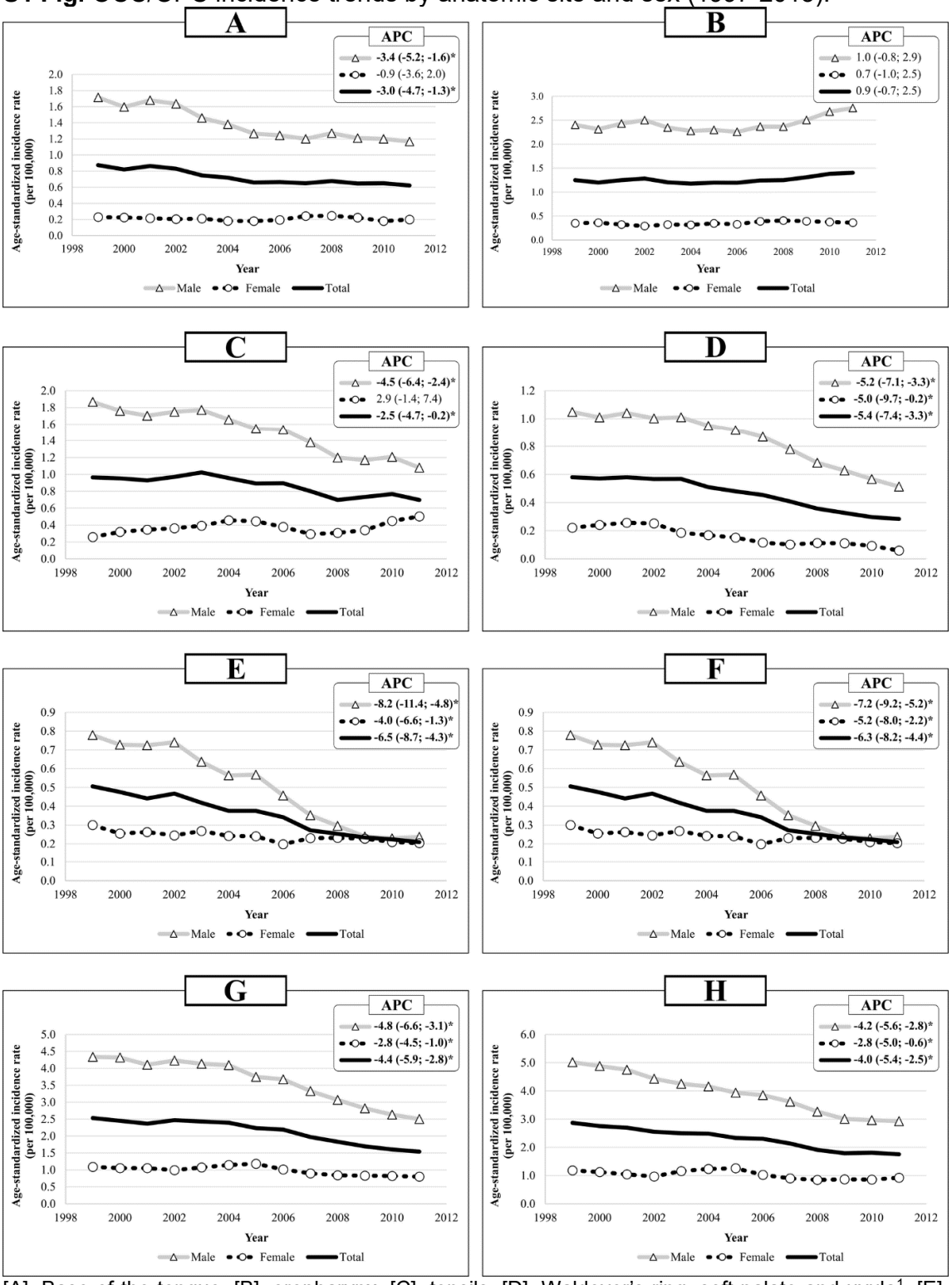


Table 2. Age-period-cohort models presented by sex and the HPV-related and HPV-unrelated subsites.

Model	Female				Male			
	Resid. Df	Resid. Dev	Deviance	p-value	Resid. Df	Resid. Dev	Deviance	p-value
HPV-related								
Age	26	43.477			26	88.034		
Age-Drift	25	42.438	1.038	0.308	25	52.329	35.705	<0.001*
Age-Cohort	12	10.832	31.607	***0.003****	12	15.429	36.900	***<0.001****
Age-Period-Cohort	11	10.776	0.055	0.814	11	12.023	3.406	0.065
Age-Period	24	42.374	-31.598	0.003*	24	48.994	-36.971	<0.001*
Age-Drift	25	42.438	-0.064	0.800	25	52.329	-3.335	0.068
HPV-unrelated								
Age	26	60.580			26	346.440		
Age-Drift	25	30.405	30.175	<0.001*	25	61.740	284.696	<0.001*
Age-Cohort	12	22.483	7.923	0.849	12	18.470	43.270	<0.001*
Age-Period-Cohort	11	13.165	9.318	***0.002****	11	8.800	9.676	***0.002****
Age-Period	24	21.008	-7.844	0.854	24	52.130	-43.329	<0.001*
Age-Drift	25	30.405	-9.397	0.002*	25	61.740	-9.618	0.002*

Df: degree of freedom; Dev: deviance; *: statistically significant.

S1 Fig. OCC/OPC incidence trends by anatomic site and sex (1997-2013).

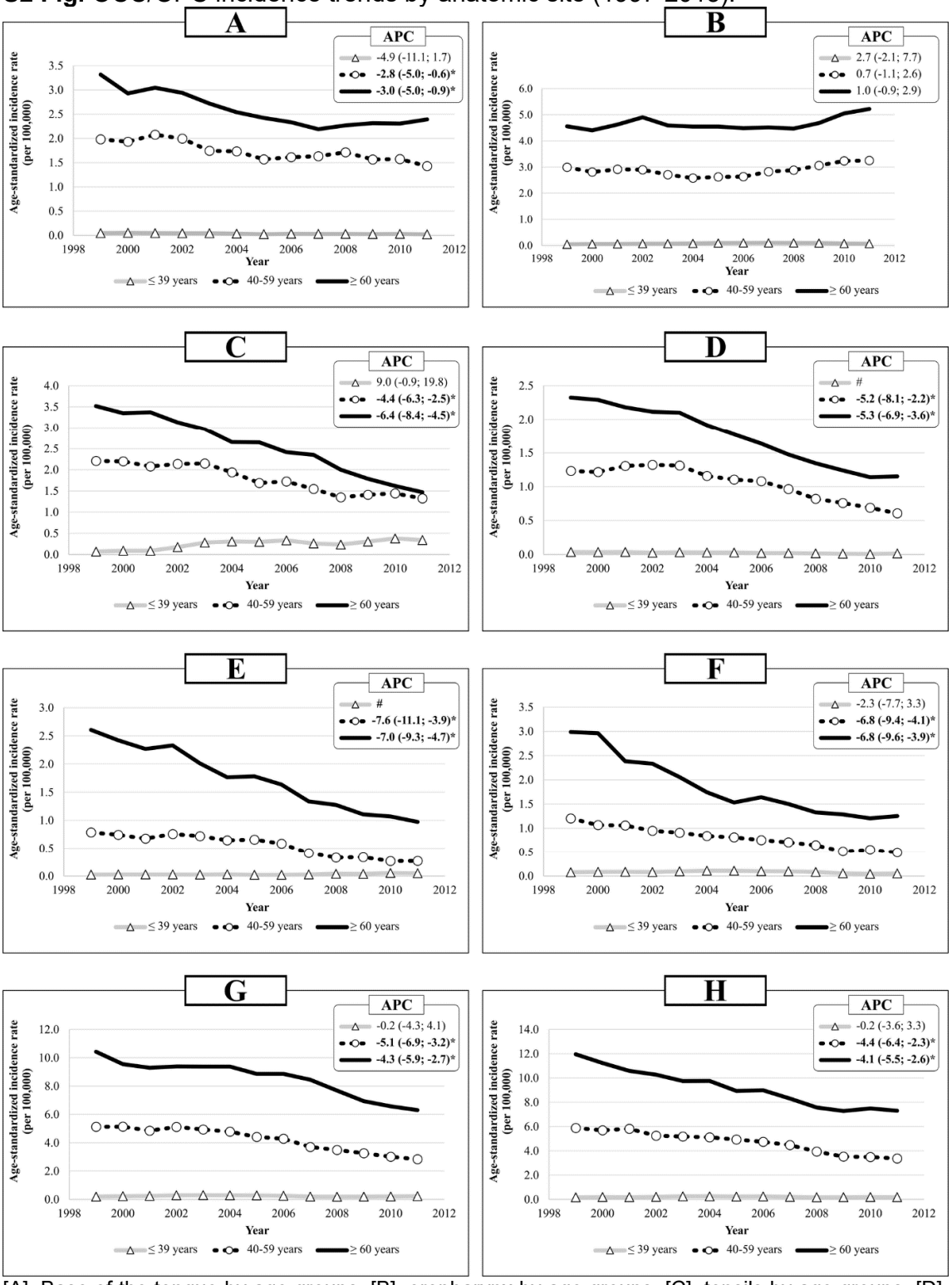


[A]: Base of the tongue; [B]: oropharynx; [C]: tonsils; [D]: Waldeyer's ring, soft palate and uvula[1]; [E]: gums; [F]: hard palate; [G]: mouth; and [H]: other parts of the tongue.[a,b]

APC: annual percent change; *: statistically significant APC (95% CI).
[a] For better graph visualization, we applied the simple moving average of 5 years.
[b] We analyzed these data with joinpoint regression models.

[1] As there were 11 cases of cancer in Waldeyer's ring, they were combined with the cases of cancer in the soft palate and uvula.

S2 Fig. OCC/OPC incidence trends by anatomic site (1997-2013).

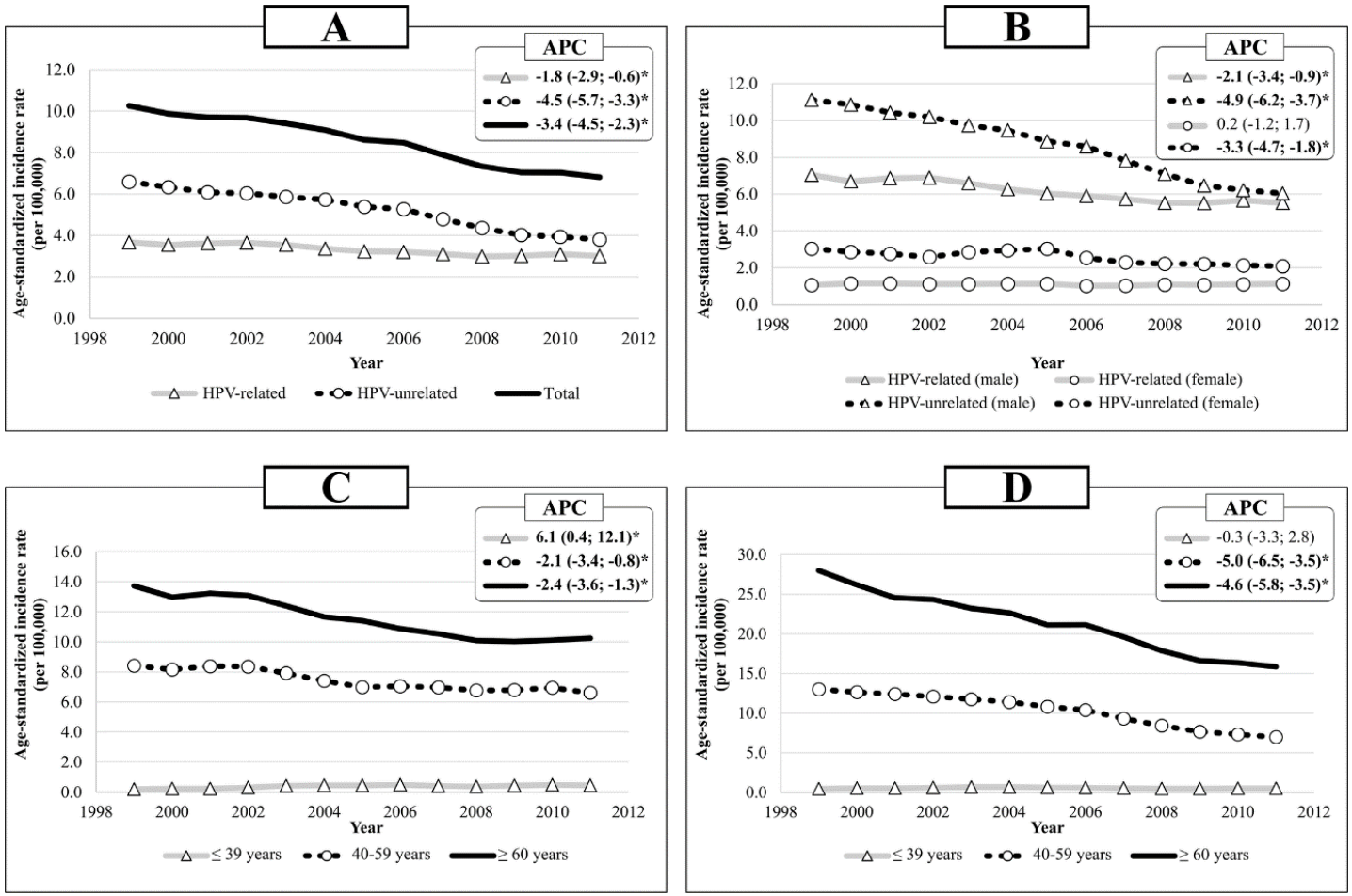


[A]: Base of the tongue by age groups; [B]: oropharynx by age groups; [C]: tonsils by age groups; [D]: Waldeyer's ring, soft palate and uvula[1] by age groups; [E]: gums by age groups; [F]: hard palate by age groups; [G]: mouth by age groups; and [H]: other parts of the tongue by age groups.[a,b]

APC: annual percent change; *: statistically significant APC (95% CI).
[a] For better graph visualization, we applied the simple moving average of 5 years.

[b] We analyzed these data with joinpoint regression models.
[1] As there were 11 cases of cancer in Waldeyer's ring, these cases were combined with the cases of cancer in the soft palate and uvula.
There were insufficient cases for analysis.

S3 Fig. [A]: Incidence trends for OCC/OPC according to HPV groups; [B]: incidence trends for OCC/OPC by sex and HPV groups; [C]: incidence trends for HPV-related OCC/OPC by age groups; and [D]: incidence trends for HPV-unrelated OCC/OPC by age groups.[a,b]



APC: annual percent change; *: statistically significant APC (95% CI).

[a] For better graph visualization, we applied a simple moving average of 5 years.

[b] We analyzed these data with joinpoint regression models.

5.3 Manuscrito 3

Esse artigo será submetido para uma revista internacional, indexada e classificada até o quarto estrato do Qualis da CAPES.

Survival inequalities in head and neck cancers according to HPV-related subsites

Fabrício dos Santos Menezes[1,2,a,*], Stela Verzinhasse Peres[3], José Leopoldo Ferreira Antunes[2], and Tatiana Natasha Toporcov[2].

[1]Department of Health Education, Federal University of Sergipe, Lagarto, Brazil;

[2]Department of Epidemiology, School of Public Health, University of São Paulo, São Paulo, Brazil;

[2]Oncocentro Foundation of São Paulo (FOSP), São Paulo, Brazil.

[a]Current Address: Department of Health Education, Federal University of Sergipe, Lagarto, Sergipe, Brazil.

* Corresponding author

E-mail: fabriciomenezes@usp.br (FSM)

Abstract

It is unclear whether human papillomavirus (HPV) impacts survival in head and neck subsites under universal health coverage (UHC) within high-income concentration background. Hence, we investigated whether the socioeconomic status (SES) impaired survival in HPV-related subsites or oropharynx cancers (OPC), oral cavity cancers (OCC), and larynx cancers (LC) in Brazilian patients. This hospital-based cohort study included cases diagnosed between 2000 and 2018. We assessed the 5-year overall survival (OS) by Kaplan-Meier curves, log-rank tests, and Cox proportional hazard models. Age-standardized 5-year relative survival (RS) was estimated using the Pohar Perme estimator. Also, we examined survival differences between social gradients across periods of diagnosis. We identified 37,191 cases in OPC (n= 12,238), OCC (n= 12,858), and LC (n= 12,095). Five-year RS were 24.4%, 34.1%, and 44.9% in OPC, OCC, and LC, respectively. In multiple Cox regression, the highest risk of death occurred in the most vulnerable social strata for all subsites – i.e., illiterates or public funded healthcare patients, adjusted for age group, gender, clinical staging, and treatments. Disparities increased over time by 34.9% in OPC due to the rising survival rates in the highest SES, whereas it reduced by 10.2% and 29.6% in OCC and LC. The potential of inequities is more significant for HPV-related subsites than in OCC, and LC. It is urgent to tackle disparities to improve prognosis in highly unequal countries.

Introduction

Head and neck cancers (HNCs) are a varied group of tumors with distinct prognoses that include oropharynx cancers (OPC), oral cavity cancers (OCC), and larynx cancers (LC).[1] There is a causal association between socioeconomic status (SES) and these subsites,[2–6] which poses a global concern due to their role in preventable deaths. Although the cancer prognosis has improved in high-income countries,[1] inequities increased both between and within populations.[2,3] Cancer inequalities are a multidimensional social phenomenon related to income, schooling, smoking, alcohol use, diet,[4] and access to healthcare services,[7,8] which leads to late-stage diagnosis and worse survival rates. Nevertheless, in highly unequal countries, this issue is not entirely explained by classical risk factors due to unknown modulating effects.[4] Hence, the elucidation of the SES role on the survival of these countries could guide interventions to narrow health disparities improving the prognosis.

Brazil is a continental country with one of the highest income concentration worldwide,[9] presenting the leading incidence rate for head and neck subsites in Central and South America.[10] Since the 1990s, as a constitutional right, Brazil has increasing universal health coverage (UHC) through a unified health system (Sistema Único de Saúde [SUS]).[11] Despite the implementation of primary healthcare and oral health programs, inequities in healthcare utilization persisted. The public sector healthcare system is the primary source of healthcare for low-income groups and those without private insurance, whereas high-income patients often access private sector services.[11] Although the effect of these inequities in survival are unclear, these asymmetries presumably influence the hazard of death, once the highest mortality rates occurred in deprived and economically unequal areas.[12]

The progress in cancer control depends on the understanding in-depth of how socioeconomic drivers impact on survival outcomes. Cancer survival disparities have widened over time,[5,13,14] but it is unknown whether human papillomavirus (HPV) may affect survival outcomes taking into account the UHC under a high-income concentration. Hence, we investigated whether inequalities impaired survival in HPV-related subsites (OPC), OCC, and LC in Brazilian patients, assessing changes in the prognosis over time between social gradients.

Methods

Study design and data sources

This hospital-based cohort study consisted of cases from 76 hospitals recorded between 2000 and 2018 and followed-up until December, 31, 2019 at São Paulo State, Brazil. Our sample were obtained from Hospital-based Cancer Registries provided by the Oncocentro Foundation of São Paulo (FOSP). The state of São Paulo locates in the southeast region of Brazil and has more than 44 million residents. It comprises 645 municipalities organized by seventeen regional departments of health (RDH) to better provision of health-care services for the population.

All cases of cancer were limited to the following topography codes of the International Classification of Disease for Oncology version-3 (ICD-O-3): oropharynx or HPV-related subsites (C01.9, C02.4, C05.1-C05.2, C09.0-C09.1, C09.8-C09.9, C10.0-C10.4, C10.8-C10.9, and C14.2), oral cavity (C02.0-C02.3, C02.8-C02.9, C03.0-C03.1, C03.9, C04.0-C04.1, C04.8-C04.9, C05.0, C05.8-C05.9, C06.0-C06.2, and C06.8-C06.9), and larynx (C32). We restricted the analyses to squamous cell histologies (ICD-O-3 codes: 8050 to 8076, 8078, 8083, 8084, and 8094). Also, this investigation included only São Paulo State residents aged ≥15 years at diagnosis. Cases without follow-up, presenting previous treatments, and carcinomas *in situ* were excluded.

We deemed patient- and contextual-level factors to assess the role of the SES on survival. The education level and the sector of healthcare assistance were considered as individual socioeconomic markers. At the contextual level, the Municipal Human Development Index (HDI) related to 2010 was obtained on the website of the Human Development Atlas in Brazil, provided by the United Nations Development Programme. The HDI is the geometric mean of normalized indicators assembling three dimensions of human development: longevity, education, and income.[15] Additionally, the Seade Foundation associated with governmental agencies and regional councils of health professionals (e.g., medicine and dentistry) provided complementary information.[16] For instance, the mean number of dentists (per 2,000 inhabitants) and doctors (per 100,000 inhabitants) from 2000 to 2018; the average gross domestic product (GDP) per capita between 2002 to 2017; and the mean amount of hospital

beds (per 1,000 inhabitants) from 2008 to 2018. We used all available information on contextual variables according to the study period, and we grouped it into tertiles in survival analysis.

We classified the clinical staging according to the 5th, 6th, and 7th versions of the TNM staging system. Hence, we grouped the period of diagnosis to consider these changes over time, adjusting for age group and sex. Further, we measured the magnitude of the difference in OS between the highest and lowest tertiles of the HDI for each subsite to compare the late (2000-2005) and the recent (2014-2018) periods.

Missing values

Education level and the sector of healthcare assistance had a completeness of 75.2% e 51.9%, respectively. Hence, we conducted multiple imputations by chained equations (MICE) once the missing-data were missing at random.[17] In the imputation model, we included the outcome variable (vital status) plus age and other predictor variables selected by chi-square test and logistic regression models, such as clinical staging, the period of diagnosis, and treatments (chemotherapy, radiotherapy, and surgery). A total of 50 imputed datasets were created,[18] and the relative efficiency was higher than 0.99 in all analyses.

Statistical analysis

Frequencies, percentages, and median were calculated to describe our cohort. For continuous variables, we assessed the normality and homoscedasticity through the Shapiro-Wilks test and Levene's test, respectively. Accordingly, the Kruskal-Wallis test or chi-square test was conducted to verify differences across subsites. This investigation considered the 5-year overall survival (OS) as the period from diagnosis to death from any cause. Individuals alive after five years were censored. In survival analysis, we used Kaplan-Meier curves to illustrate the OS and the log-rank test to assess the equality of survival functions. For each subsite, prognostic and contextual factors were investigated using Cox proportional hazards models to calculate the hazard ratio (HR). In multiple analyses, we examined the

education level and the sector of healthcare assistance, adjusted for age group, gender, clinical staging, and treatments (chemotherapy, radiotherapy, and surgery).

Age-standardized 5-year relative survival (RS) was calculated using the Pohar Perme net survival estimator[19,20] and the International Cancer Survival Standard (ICSS) 1.[21] Net survival considers the probability of surviving after adjusting for other causes of death – i.e., that the competing risks of death are higher for older individuals than those younger. For the estimates of population life tables, we used data provided by the Brazilian National Institute of Geography and Statistics (IBGE) stratified by sex, age, and year.[22]

We generated maps using QGIS software version 3.10.2 to depict georeferenced information on the HDI and OS. In the sensitivity analysis, we conducted a complete-case analysis for two variables with imputed values. Besides, we carried out multilevel mixed-effects survival models with a Weibull distribution to test the risk of death related to the HDI on OS. We fitted different three-level models involving hospital-level, municipality-level, and RDH-level random effects. All analyses were adjusted for socioeconomic factors (education level and sector of healthcare assistance) and prognostic factors (age group, gender, clinical staging, and treatments).

We conducted statistical analysis using Stata software, version 14.0 (Stata Corporation, College Station, Texas, USA). All hypothesis tests were two-sided, and p-values < .05 indicated statistical significance. The Research Ethics Committee approved this study (protocol nº 83218318.8.0000.5421).

Results

Over nineteen years, there were 816,393 cancers diagnosed in São Paulo State residents. Of these, 37,191 cases occurred in oropharynx or HPV-related subsites (n= 12,238), oral cavity (n= 12,858), and larynx (n= 12,095) subsites (Figure 1). The male:female ratio was 8.3, 3.9, and 7.2 in OPC, OCC, and LC (Table 1). Although HPV-related subsites (OPC) had younger patients than those with OCC and LC (p< 0.001), the median survival of 16 months for oropharynx was lower than the oral cavity (21 months) and larynx subsites (34 months). OPC had more deaths (n= 8,583; 70.1%) than OCC (n= 8,049; 62.6%) and LC (n= 6,566; 54.3%) (p< 0.001),

revealing through Kaplan-Meier curves the lowest survival rate. Likewise, age-standardized 5-year RS rates were 24.4% (95% CI 22.0-26.8), 34.1% (95% CI 31.7-36.6%), and 44.9% (95% CI 42.8-47.1) for oropharynx, oral cavity, and larynx subsites, respectively (Figure 2). The OPC diagnosis was more delayed than the OCC and LC, in which 81.6% of cases had the III/IV clinical staging (Table 1) mainly in the first tertile of the HDI (p=0.032) (Supplementary Table 1).

There were disparities in survival at the patient-level factors. The education level, which had a negative dose-response relationship, and public healthcare assistance rose the risk of death for all cancers (Table 1 and Figure 2). However, these socioeconomic factors predisposed more to poor prognosis in the oropharynx and larynx subsites than the oral cavity subsites. For instance, public healthcare assistance rose the risk of death by 61% and 62% in HPV-related subsites (OPC) and LC, whereas it accounted for 31% in OCC in comparison with private healthcare assistance. These results were adjusted for age group, education level, gender, clinical staging, and treatments (chemotherapy, radiotherapy, and surgery) (Table 2).

Area-based socioeconomic factors

We identified differences across subsites comparing the cases by contextual factors. For oropharynx subsites, people living in municipalities with more limited access to doctors and dentists augmented their risk of death by 13% and 9% in comparison with those in cities better provided by these health professionals. In OCC, the poorest prognostic occurred for individuals from towns with the fewer number of dentists and hospital beds than municipalities with superior healthcare assistance. For both OPC and OCC, the hazard of death increased for residents from cities with the lowest municipal HDI by 15% and 16%, respectively. Conversely, LC had no significant results at the contextual factors (Table 1).

There were significant regional disparities in patients' prognosis across RDH at São Paulo State. In comparison with Greater São Paulo RDH, individuals treated at Campinas RDH demonstrated a reduced risk in all tumors, while those from Sorocaba RDH rose the risk of death by 22% and 18% for the oral cavity and larynx subsites, respectively (Supplementary Table 2) (Figure 3).

Survival differences across periods of diagnosis

There were improvements in survival across diagnosis periods in some subsites. In comparison with cases recorded from 2000 to 2005, the hazard of death decreased in the most recent period of diagnosis in HPV-related subsites (OPC) and OCC (Supplementary Table 3). Further, we compared survival rates by the highest and lowest HDI adjusted for age and sex. The magnitude of percent differences in 5-year OS diminished between periods for the oral cavity and larynx subsites by 10.2% and 29.6%, respectively. Conversely, these disparities increased by 34.9% in HPV-related subsites due to the rising survival rates in the highest tertile of the HDI (Figure 4).

Sensitivity analysis

Complete-case analysis has reinforced the significant role played by the education level and the sector of healthcare assistance on patients' survival (Supplementary Tables 4-5). In all multilevel survival models, the HDI was significant only for HPV-related subsites after controlling for age group, education level, gender, sector of healthcare assistance, clinical staging, and treatments (chemotherapy, radiotherapy, and surgery) (Supplementary Tables 6-8). These results confirmed the impact of social disparities at the individual- and contextual-level on patients' prognosis, especially for HPV-related subsites.

Discussion

This large study is the first to report a comparative analysis of the survival for HPV-related subsites (OPC), OCC, and LC in Brazilian patients. Here we demonstrated that socioeconomic inequalities are a prognostic factor in the survival of these subsites, once the highest risk of death was observed in patients poorly educated and using the public healthcare assistance. Further, this investigation identified regional asymmetries underscoring pernicious inequities in human development and

their effect on cancer mortality. In HPV-related subsites (OPC), survival disparities were a result of the combined individual- and contextual-level SES factors, exacerbated by the late-stage diagnosis. Moreover, in the oropharynx the prognosis improved only in the highest SES, likely due to HPV infection, whereas survival inequalities narrowed in OCC and LC. The UHC has contributed for reducing survival gaps; however, to tackle socioeconomic disparities is crucial to improve patients' prognosis, especially in a highly unequal country such as Brazil.

Survival outcomes are not a democratic phenomenon. This study had worse survival rates than Europe as a whole,[1] and inequities occurred without an equal distribution among social gradients and geographic regions. Worldwide, absolute gaps in survival persist both between and within countries. In European countries, the 5-year RS broadly ranged for oropharynx and tonsil cancers (16.2-57.1%), OCC (19.1-60.9%), and LC (42.8-77.5%).[1] Likewise, socioeconomic survival inequalities were found between affluent and deprived patients in Canada[5] and Singapore,[2] as well as in our analysis. These disparities in cancer prognosis are reasonable once the low SES significantly increased the risk of cancer irrespective of the SES of the country.[23] However, the lack of health care resources to earlier diagnosis and treatment results in worse outcomes in low- and middle-income countries,[24] especially in the most deprived socioeconomic gradients, as we demonstrated in this investigation.

Low educational attainment and public healthcare assistance were predictors of adverse survival outcomes, irrespective of head and neck subsite. The major reasons for these cancer inequalities are due to variations in lifestyle and access to healthcare services. As shown in this study, there is an inverse association between education level and cancer mortality. The education level increases the risk of cancer due to alcohol use, smoking, and diets low in fruit and vegetables in poorly educated patients.[4] In parallel, it contributes to health illiteracy,[25] which allied to low-income conditions commonly observed in patients using public health services,[11] reduces the access to healthcare assistance[7,8] and the likelihood to seek them.[26] Additionally, high-income patients using the private-sector health-care system have access to timeliness technological resources to prior diagnosis and tailored therapeutics by specialists. Hence, these unequal conditions triggered by socioeconomic disparities led to markable cancer survival inequalities between patients.

The improvements in the prognosis in HPV-related subsites (OPC) were restricted to the highest SES, widening survival inequalities. The HPV-attributable

proportions in cancers may elucidate this finding once HPV-positive HNCs are common in affluent groups.[3] Besides, these tumors have higher survival rates, and a better response to radiotherapy treatment,[27] than HPV-negative cancers.[27] In Brazil, there is a rising risk of HPV-related subsites in HNCs,[28] and patients from a private hospital had an HPV prevalence of 59.1%.[29] Conversely, our sample comprises mainly underprivileged patients, and studies enrolling cases from public hospitals found an HPV detection of 4.4-8.8% in OPC,[30–32] which explains the survival rates observed in the lowest SES. Hence, these findings reinforce that socioeconomic factors still play a role more significant in the survival of oropharynx subsites than HPV in Brazil.

Furthermore, this study found heterogeneities in survival due to differences in the effect of socioeconomic conditions across subsites. Social disparities impaired more significantly HPV-related subsites (OPC) than OCC and LC, and there are several reasons endorsing this finding. First, oropharynx subsites had worse survival rates than other subsites, despite the youngest cohort of patients. Second, OPC had more cases with an increased size of the tumor, regional lymph nodes, and distant metastasis than OCC and LC, revealing a sharp late-stage diagnosis. It may occur because oropharynx subsites have a challenging clinical assessment due to asymptomatic cancers on less visible sites.[33] Also, oropharynx subsites had more male cases than any other tumor, which may reflect in care-seeking behavior, once men have fewer access to health facilities than women in Brazil.[34] Additionally, the lack of literacy under social deprivation seems to exacerbate these previous conditions increasing the hazard of death. In this work, higher SES was related to better prognosis for HPV-related subsites. Also, we demonstrated worse survival rates associated with underprivileged living conditions measured by the HDI. The life expectancy and per capita income are used to calculate this proxy. However, OPC occurred commonly in adults and GDP per capita had no significance across subsites, which led us to suppose that those data did not impact the HDI. Accordingly, we presuppose that the educational level of the adult population and the educational flow of young people had a major influence on patients diagnosed with OPC. This finding is consistent with educational attainment results, contributing to explain the geographic variations in survival. Therefore, we hypothesized that the absence of literacy at the individual- and contextual levels, combined with clinical features and barriers in access to health services, led to delayed diagnosis and worse survival in HPV-related subsites.

UHC alone may not eliminate health disparities within the unequal background. Brazil has provided free cancer treatments for the entire population,[11] limiting up to sixty days the time length between cancer diagnosis and treatment.[35] Besides, the state of São Paulo established a regionalization of the healthcare network and facilities to improve cancer care.[36] However, we observed that socioeconomic issues unleashed by the high-income concentration impacted survival in HNCs. Although survival inequalities narrowed over time in OCC and LC, we noticed that most vulnerable social strata publicly funded had poorer outcomes than those using the private sector healthcare system. Also, we revealed that 30 years of UHC was not enough to extinguish health poverty traps evidenced by individual and regional asymmetries in survival rates. It is possibly related to the insufficient funding for SUS to scale UHC, especially under recent fiscal policies of austerity.[11] Therefore, equitable public policies are urgent to provide equal opportunities for disadvantaged individuals to ensure fair and affordable cancer care for all patients.

This study had limitations that are important to its interpretation. The mechanisms by which the SES impact survival in HNCs are difficult to measure due to unknown risk factors and pathways that turn it a challenge for researchers.[4,5] However, studies have used the insurance status,[6,37,38] education,[39] and area-based variables[2,3,5,40] to assess survival inequalities. Although the choice of variables used to measure the SES varies broadly,[41] these investigations were consistent in pointing to survival disparities, as we observed in our analysis. Hospital-based data do not collect information on the SES routinely. Accordingly, we used contextual variables and multiple imputations to recover missing data, which reached a high relative efficiency in all analyses due to the high dataset completeness. Notwithstanding our sample had not statewide representativeness, this large study had a high heterogeneity comprising 98.3% of the municipalities from the state of São Paulo. We used net survival analysis to provide reliable measures once hospital-based cases have better survival rates than population-based data. Moreover, we had a lack of information on alcohol and tobacco use. However, these risk factors do not fully explain the education effect in OPC in unequal countries,[4] which reinforced our major results.

Socioeconomic inequalities pose as a challenge to improve the prognosis in Brazilian patients. Cancer prevention should consider living conditions and improvements in health literacy and care-seeking attitudes to avoid delayed diagnosis and worse survival rates. Further, enough health expenditure is needed to address

disparities that affect cancer prevention through early diagnosis and timely referral to treatment focused on the most vulnerable populations and subsites. In order to achieve progress in cancer control, public policies should tackle regional variations and inequities across social gradients, providing social justice in healthcare access to fulfill the Brazilian constitutional principles.

Acknowledgments

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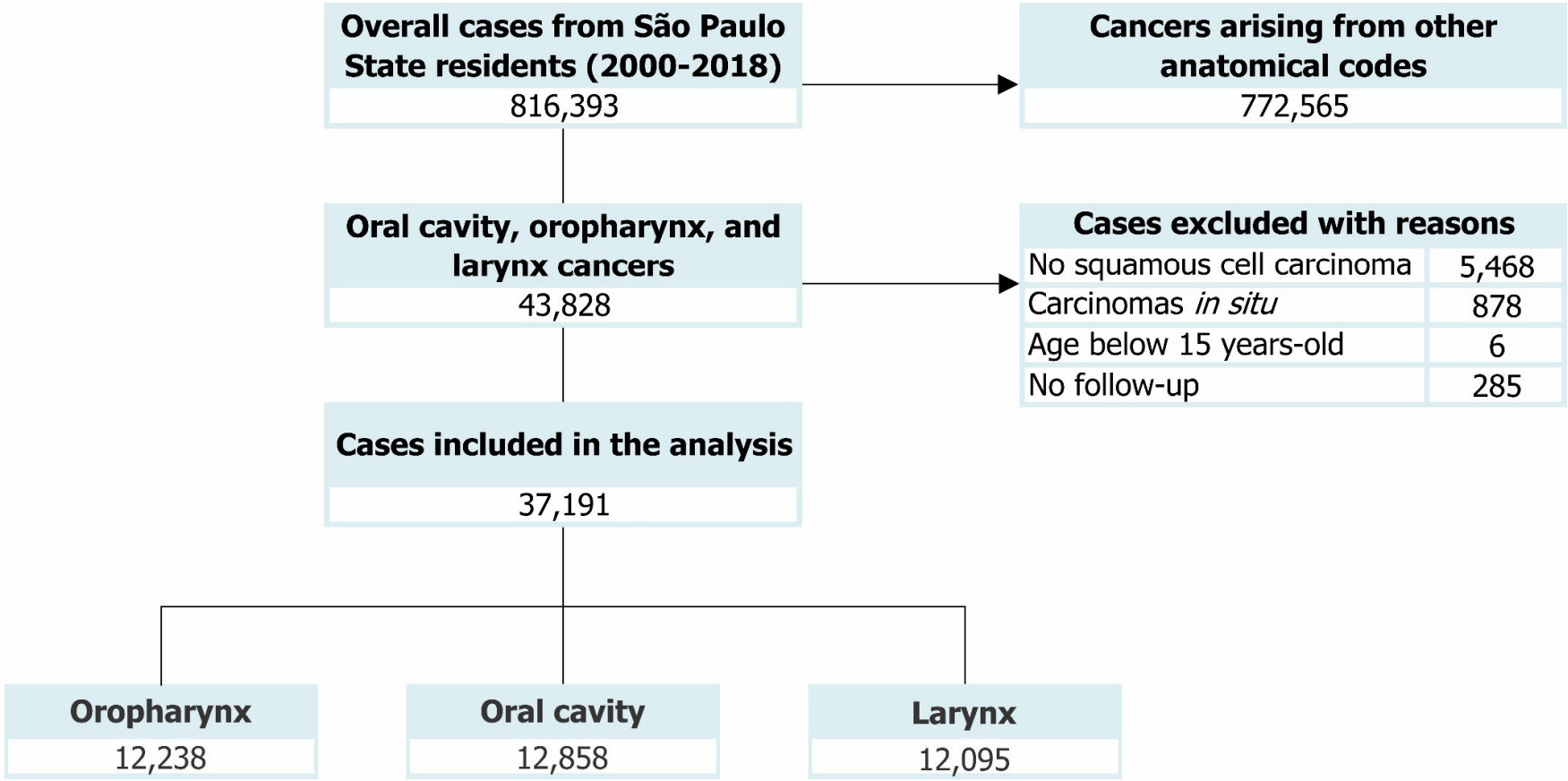

Figure 1. Flow diagram showing the selection of eligible patients for inclusion in the study.
† Oropharynx included HPV-related subsites.

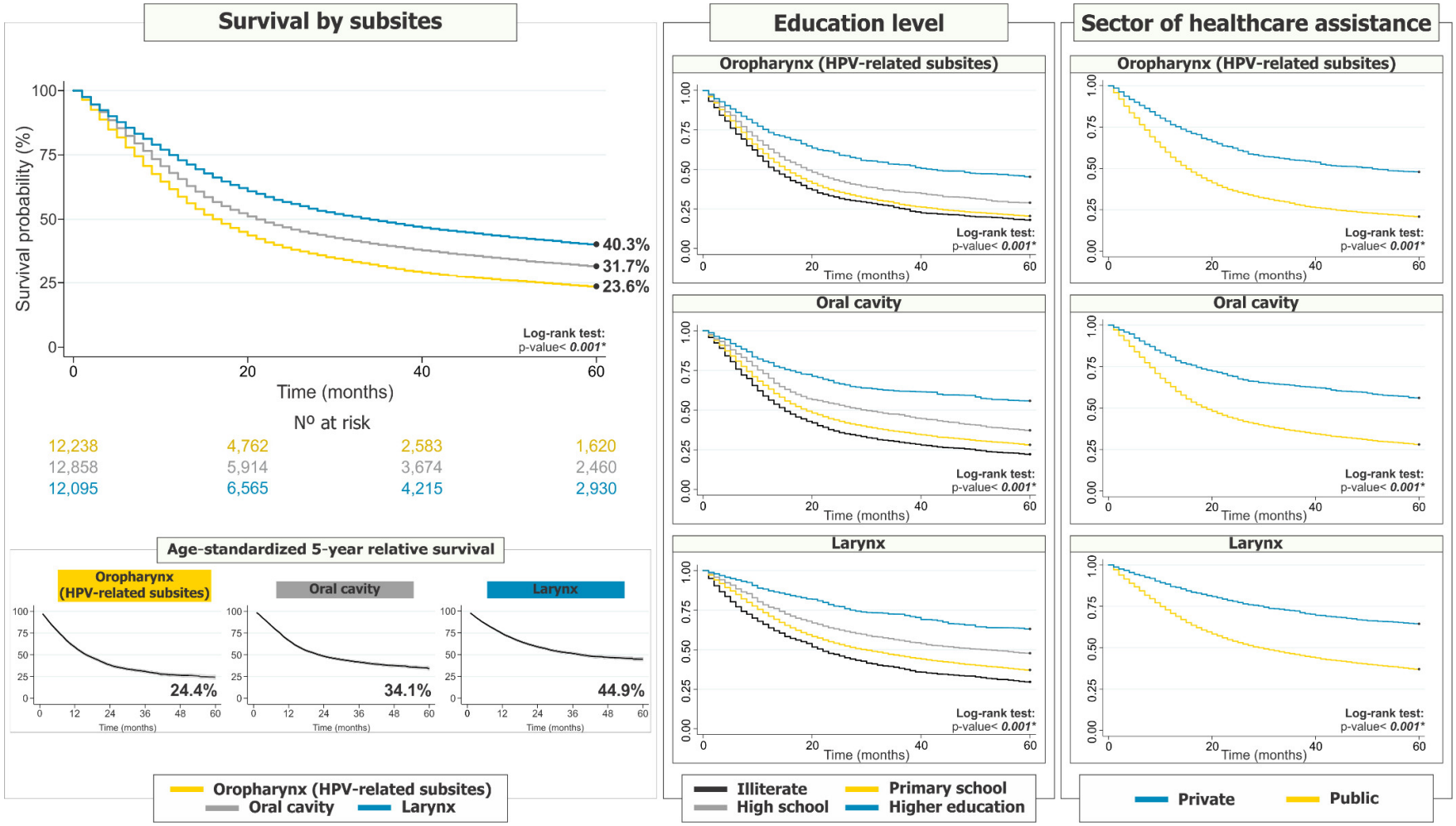

Figure 2. Net survival and Kaplan-Meier curves for 5-year overall survival by subsites, education level, and sector of healthcare assistance.
* Statistically significant.

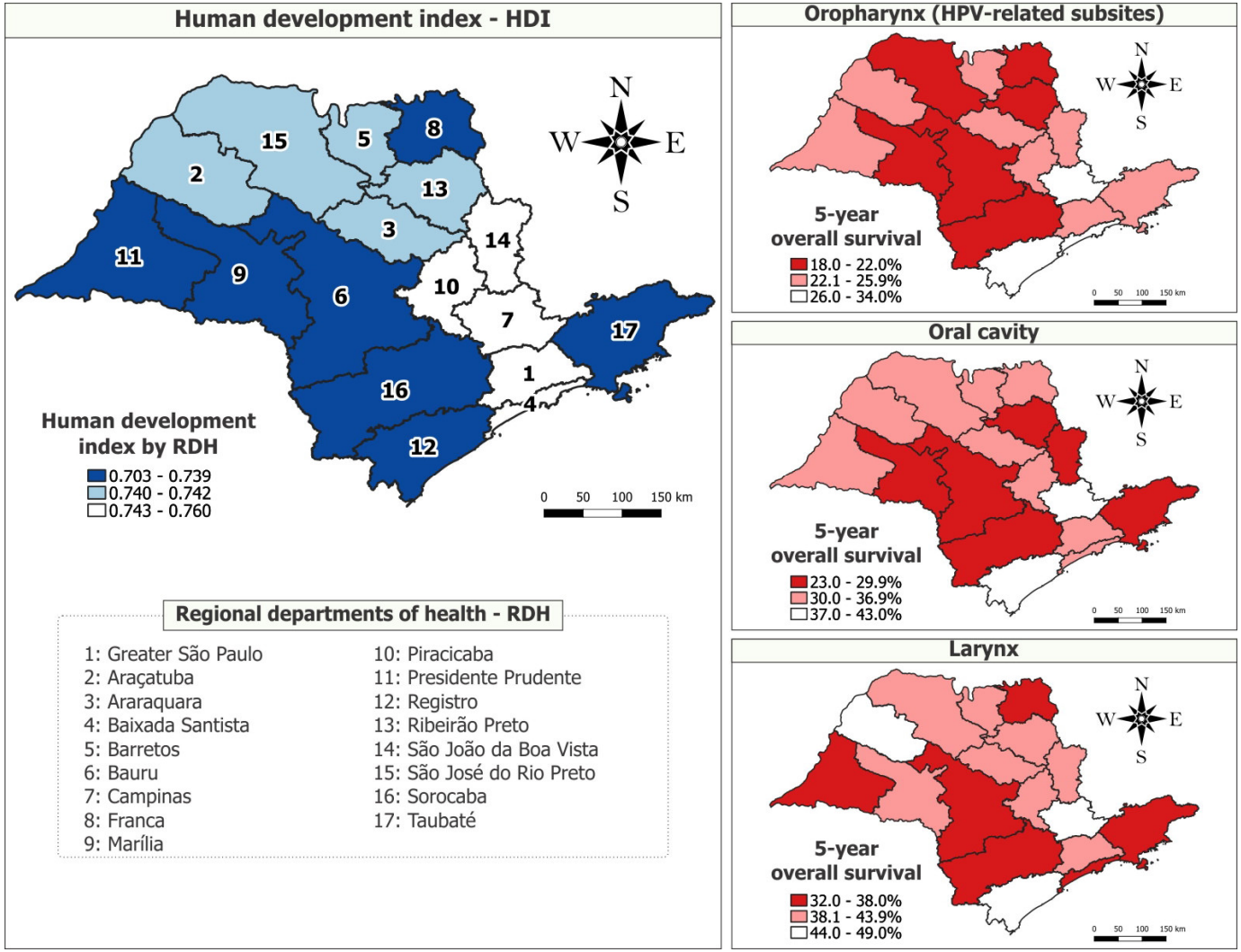

Figure 3. Human development index and 5-year overall survival for oropharynx, oral cavity, and larynx subsites by regional departments of health from São Paulo State.
* Statistically significant.

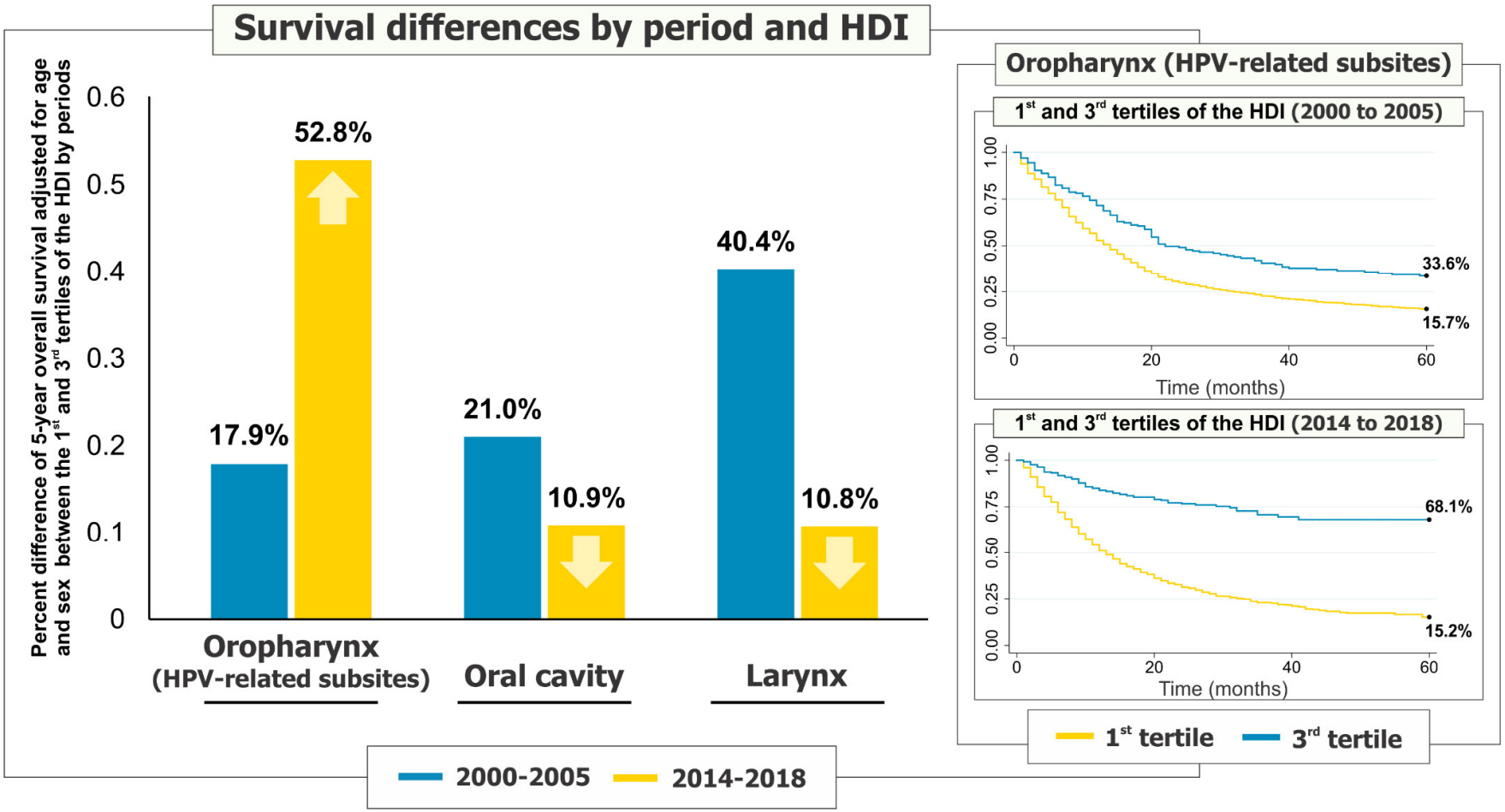

Figure 4. Percent difference of survival between the 1st and 3rd tertiles of the HDI across the initial and recent periods, adjusted for age and sex.

* Statistically significant.
** Data were rounded to one decimal place.

Table 1. Characteristics of patients, age-standardized 5-year relative survival, 5-year overall survival, and univariate analysis by oropharynx, oral cavity, and larynx subsites.

	Oropharynx (HPV-related subsites)				Oral cavity				Larynx			
	n (%)	RS (95% CI)	OS (95% CI)	HR (95% CI)	n (%)	RS (95% CI)	OS (95% CI)	HR (95% CI)	n (%)	RS (95% CI)	OS (95% CI)	HR (95% CI)
Sociodemographic characteristics												
Age group (median age)		(57 years)				(59 years)				(61 years)		
15-44 years	952 (7.8)	24.7% (23.9-25.5)	24.5% (21.6-27.5)	Ref.	1,130 (8.8)	38.6% (37.8-39.4)	38.4% (35.4-41.5)	Ref.	586 (4.8)	40.8% (39.6-41.9)	40.3% (36.1-44.5)	Ref.
45-54 years	3,705 (30.3)	25.9% (25.3-26.4)	25.1% (23.6-26.7)	0.98 (0.90; 1.06)	3,420 (26.6)	33.3% (32.7-34.0)	32.2% (30.6-33.9)	**1.18 (1.08; 1.29)**	2,805 (23.2)	42.2% (41.5-42.9)	40.9% (38.9-42.8)	0.93 (0.82; 1.04)
55-64 years	4,438 (36.3)	26.1% (25.4-26.9)	24.3% (22.9-25.8)	0.97 (0.89; 1.05)	4,191 (32.6)	35.0% (34.2-35.9)	32.6% (31.0-34.1)	**1.13 (1.03; 1.23)**	4,274 (35.3)	46.3% (45.4-47.1)	43.0% (41.4-44.7)	**0.85 (0.76; 0.96)**
65-74 years	2,322 (19.0)	26.1% (24.9-27.4)	22.4% (20.5-24.4)	1.03 (0.95; 1.13)	2,580 (20.1)	36.5% (35.3-37.8)	31.2% (29.2-33.3)	**1.20 (1.09; 1.31)**	3,157 (26.1)	46.8% (45.5-48.0)	39.6% (37.7-41.5)	0.92 (0.81; 1.03)
+75 years	821 (6.7)	23.1% (18.9-27.6)	13.4% (10.6-16.4)	**1.36 (1.22; 1.52)**	1,537 (12.0)	32.1% (27.9-36.4)	23.6% (21.3-26.0)	**1.54 (1.40; 1.71)**	1,273 (10.5)	46.0% (42.2-49.6)	30.3% (27.4-33.3)	**1.19 (1.05; 1.36)**
Education level[a]												
Higher education	339 (3.7)	45.7% (32.7-57.7)	45.4% (44.5-46.3)	Ref.	438 (4.5)	59.9% (49.2-69.0)	55.8% (55.0-56.6)	Ref.	368 (4.1)	69.4% (56.5-79.1)	63.1% (62.3-63.9)	Ref.
High school	1,080 (11.7)	25.1% (18.5-32.3)	29.0% (28.6-29.5)	**1.66 (1.40; 1.98)**	1,181 (12.1)	35.2% (29.5-41.0)	37.2% (36.7-37.7)	**1.55 (1.32; 1.82)**	1,064 (11.8)	52.1% (43.2-60.2)	47.7% (47.2-48.2)	**1.71 (1.40; 2.08)**
Primary school[b]	7,073 (76.9)	24.0% (21.1-27.1)	20.6% (20.4-20.8)	**2.04 (1.74; 2.40)**	7,239 (74.1)	35.8% (32.3-39.3)	28.1% (27.9-28.3)	**1.94 (1.68; 2.24)**	6,859 (76.2)	45.3% (42.0-48.5)	37.2% (37.0-37.4)	**2.12 (1.76; 2.54)**
Illiterate	706 (7.7)	24.2% (19.1-29.7)	18.2% (17.7-18.6)	**2.30 (1.92; 2.76)**	912 (9.3)	26.6% (20.4-33.2)	22.2% (21.7-22.6)	**2.36 (2.01; 2.76)**	711 (7.9)	36.4% (30.4-42.5)	29.6% (29.1-30.1)	**2.60 (2.13; 3.19)**
Gender												
Female	1,315 (10.8)	28.5% (22.8-34.5)	33.2% (30.3-36.0)	Ref.	2,621 (20.4)	38.4% (32.6-44.1)	39.2% (37.1-41.2)	Ref.	1,483 (12.3)	48.8% (43.5-53.9)	50.2% (47.3-52.9)	Ref.
Male	10,923 (89.3)	25.2% (23.0-27.4)	22.5% (21.6-23.3)	**1.32 (1.22; 1.42)**	10,237 (79.6)	34.1% (31.9-36.3)	29.9% (28.9-30.8)	**1.26 (1.19; 1.33)**	10,612 (87.7)	44.9% (42.5-47.2)	38.9% (37.8-39.9)	**1.36 (1.25; 1.47)**
Period of diagnosis												
2000-2005	3,004 (24.6)	24.7% (20.9-28.7)	22.4% (20.8-23.9)	Ref.	3,747 (29.1)	34.2% (31.0-37.4)	30.7% (29.1-32.2)	Ref.	3,457 (28.6)	47.4% (43.5-51.3)	40.5% (38.9-42.2)	Ref.
2006-2013	5,711 (46.7)	22.4% (19.0-26.0)	23.5% (22.3-24.7)	0.97 (0.92; 1.02)	5,753 (44.7)	33.4% (28.5-38.3)	32.3% (31.1-33.6)	**0.94 (0.89; 0.99)**	5,545 (45.9)	43.9% (41.0-46.8)	40.1% (38.8-41.5)	1.01 (0.95; 1.07)
2014-2018	3,523 (28.8)	31.2% (26.5-36.0)	23.9% (21.0-26.9)	**0.91 (0.85; 0.97)**	3,358 (26.1)	37.1% (32.1-42.1)	30.1% (26.8-33.5)	0.95 (0.89; 1.01)	3,093 (25.6)	46.4% (41.2-51.4)	39.4% (36.0-42.7)	1.01 (0.94; 1.08)
Access to health-care services												
Sector of healthcare assistance[a]												
Private	394 (5.8)	53.6% (41.2-64.6)	47.9% (47.1-48.7)	Ref.	521 (8.0)	64.0% (55.0-71.7)	56.1% (55.5-56.8)	Ref.	408 (6.8)	72.5% (58.8-82.3)	64.4% (63.8-65.1)	Ref.
Public	6,371 (94.2)	28.5% (25.7-31.5)	20.9% (20.8-21.1)	**2.15 (1.84; 2.51)**	6,024 (92.0)	37.1% (33.9-40.4)	28.1% (27.9-28.2)	**1.98 (1.73; 2.28)**	5,587 (93.2)	47.0% (43.9-50.1)	37.0% (36.9-37.2)	**2.34 (1.95; 2.80)**
Oncology assistance												
CACON	8,117 (68.0)	26.2% (23.8-28.7)	23.6% (22.6-24.6)	Ref.	8,753 (70.1)	35.3% (32.5-38.1)	32.5% (31.4-33.6)	Ref.	8,013 (68.7)	46.2% (43.7-48.7)	41.5% (40.3-42.6)	Ref.
UNACON	3,822 (32.0)	23.2% (18.4-28.3)	22.8% (21.2-24.3)	0.98 (0.93; 1.03)	3,726 (29.9)	34.5% (29.9-39.1)	29.9% (28.2-31.6)	1.04 (0.99; 1.09)	3,646 (31.3)	41.7% (36.0-47.3)	37.3% (35.5-39.0)	**1.11 (1.05; 1.17)**
Clinical features												
Clinical staging												

	Oropharynx (HPV-related subsites)				Oral cavity				Larynx			
	n (%)	RS (95% CI)	OS (95% CI)	HR (95% CI)	n (%)	RS (95% CI)	OS (95% CI)	HR (95% CI)	n (%)	RS (95% CI)	OS (95% CI)	HR (95% CI)
I	727 (5.9)	49.7% (40.6-58.1)	47.5% (43.2-51.6)	Ref.	1,629 (12.7)	68.8% (61.5-74.9)	62.8% (60.1-65.4)	Ref.	1,991 (16.5)	80.8% (74.6-85.6)	68.5% (66.1-70.7)	Ref.
II	998 (8.2)	49.3% (40.8-57.3)	43.0% (39.6-46.5)	1.11 (0.96; 1.28)	1,860 (14.5)	50.8% (44.4-56.9)	51.0% (48.4-53.4)	**1.44 (1.29; 1.61)**	1,516 (12.5)	70.9% (65.8-75.5)	57.8% (55.0-60.4)	**1.51 (1.34; 1.71)**
III	2,051 (16.8)	35.3% (30.9-39.8)	33.3% (31.1-35.6)	**1.49 (1.32; 1.69)**	2,106 (16.4)	39.1% (35.0-43.1)	35.0% (32.7-37.2)	**2.34 (2.11; 2.60)**	2,654 (21.9)	44.6% (40.2-48.9)	44.5% (42.4-46.6)	**2.23 (2.01; 2.47)**
IV	7,933 (64.8)	17.3% (14.7-20.1)	16.9% (16.0-17.9)	**2.60 (2.31; 2.91)**	6,824 (53.1)	21.8% (19.7-24.0)	18.5% (17.5-19.5)	**4.04 (3.68; 4.43)**	5,408 (44.7)	23.8% (21.2-26.4)	24.2% (23.0-25.5)	**4.17 (3.80; 4.58)**
No clinical staging	529 (4.3)	16.4% (10.8-23.0)	16.5% (12.9-20.3)	**3.07 (2.64; 3.57)**	439 (3.4)	24.6% (18.5-31.2)	26.0% (21.4-30.9)	**3.83 (3.30; 4.45)**	526 (4.4)	30.0% (23.8-36.4)	26.6% (22.2-31.2)	**4.40 (3.82; 5.08)**
TNM staging system												
Primary tumor (T)												
T_1	1,058 (9.2)	50.0% (42.1-57.5)	45.6% (42.1-49.0)	Ref.	1,927 (15.6)	65.9% (59.8-71.4)	59.3% (56.7-61.7)	Ref.	2,178 (19.0)	78.2% (72.3-83.0)	66.6% (64.3-68.8)	Ref.
T_2	2,171 (18.8)	43.9% (37.1-50.5)	38.1% (35.7-40.4)	**1.20 (1.08; 1.33)**	2,889 (23.4)	45.3% (39.6-50.7)	44.7% (42.6-46.6)	**1.55 (1.41; 1.70)**	2,218 (19.3)	60.9% (56.4-65.0)	51.1% (48.8-53.3)	**1.74 (1.57; 1.93)**
T_3	3,053 (26.4)	24.5% (21.3-27.9)	24.9% (23.2-26.6)	**1.78 (1.61; 1.96)**	2,273 (18.4)	31.1% (27.1-35.0)	27.2% (25.2-29.2)	**2.66 (2.42; 2.91)**	3,212 (28.0)	37.1% (33.2-40.9)	37.5% (35.7-39.4)	**2.55 (2.32; 2.80)**
T_4	5,277 (45.7)	13.1% (9.7-16.9)	13.8% (12.7-14.8)	**2.74 (2.49; 3.02)**	5,262 (42.6)	20.4% (18.1-22.8)	17.4% (16.2-18.5)	**3.78 (3.48; 4.11)**	3,858 (33.7)	24.6% (21.3-28.0)	24.1% (22.6-25.6)	**3.94 (3.60; 4.31)**
Regional lymph nodes (N)												
N_0	3,595 (31.0)	35.8% (30.5-41.2)	35.0% (33.3-36.8)	Ref.	5,860 (47.4)	49.0% (45.0-52.9)	45.7% (44.3-47.1)	Ref.	6,642 (57.7)	61.3% (58.2-64.2)	53.7% (52.4-55.0)	Ref.
N_1	2,015 (17.4)	30.8% (25.8-36.0)	27.4% (25.2-29.6)	**1.25 (1.17; 1.34)**	2,173 (17.6)	29.8% (26.0-33.8)	28.9% (26.8-31.0)	**1.61 (1.51; 1.71)**	1,424 (12.4)	34.3% (29.2-39.3)	34.0% (31.3-36.7)	**1.78 (1.65; 1.93)**
N_2	4,261 (36.7)	19.4% (16.3-22.7)	18.3% (17.0-19.7)	**1.70 (1.60; 1.80)**	3,413 (27.6)	18.4% (15.5-21.5)	17.3% (15.9-18.7)	**2.38 (2.25; 2.51)**	2,505 (21.8)	23.1% (19.6-26.8)	23.3% (21.4-25.1)	**2.44 (2.30; 2.59)**
N_3	1,741 (15.0)	10.7% (7.1-15.2)	11.0% (9.4-12.7)	**2.48 (2.32; 2.65)**	918 (7.4)	8.1% (4.6-12.8)	6.0% (4.4-7.8)	**4.24 (3.92; 4.59)**	933 (8.1)	6.9% (4.5-10.0)	8.9% (7.0-11.1)	**4.46 (4.12; 4.83)**
Distant metastasis (M)												
M_0	11,138 (95.1)	26.4% (23.8-29.1)	24.8% (23.9-25.7)	Ref.	12,060 (97.1)	35.8% (33.2-38.3)	32.6% (31.7-33.5)	Ref.	11,198 (96.8)	47.5% (45.2-49.8)	41.9% (40.9-42.9)	Ref.
M_1	571 (4.9)	#	6.2% (4.1-8.8)	**2.07 (1.89; 2.27)**	360 (2.9)	10.2% (4.2-19.2)	8.0% (5.2-11.6)	**2.32 (2.07; 2.61)**	371 (3.2)	#	6.7% (4.1-10.3)	**3.17 (2.83; 3.56)**
Treatment												
Chemotherapy												
No	5,082 (41.5)	23.4% (19.0-28.0)	23.6% (22.3-24.9)	Ref.	7,918 (61.6)	41.0% (38.2-43.8)	38.0% (36.8-39.1)	Ref.	6,971 (57.6)	51.9% (49.2-54.5)	45.3% (44.0-46.6)	Ref.
Yes	7,156 (58.5)	26.1% (22.9-29.4)	23.6% (22.5-24.7)	**0.82 (0.78; 0.85)**	4,940 (38.4)	23.4% (20.2-26.8)	22.0% (20.7-23.2)	**1.36 (1.30; 1.43)**	5,124 (42.4)	34.9% (31.4-38.5)	33.7% (32.3-35.1)	**1.24 (1.18; 1.31)**
Radiotherapy												
Yes	7,896 (64.5)	27.8% (25.0-30.6)	25.0% (23.9-26.0)	Ref.	6,904 (53.7)	32.3% (29.5-35.1)	28.3% (27.1-29.4)	Ref.	7,231 (59.8)	47.7% (44.7-50.7)	41.1% (39.8-42.3)	Ref.
No	4,342 (35.5)	20.4% (16.1-25.2)	21.0% (19.6-22.5)	**1.41 (1.35; 1.47)**	5,954 (46.3)	38.2% (34.3-42.1)	36.1% (34.8-37.5)	**0.92 (0.88; 0.96)**	4,864 (40.2)	42.0% (38.9-45.1)	39.2% (37.6-40.7)	**1.24 (1.18; 1.30)**
Surgery												
Yes	3,417 (27.9)	40.6% (33.6-47.5)	38.4% (36.6-40.2)	Ref.	7,197 (56.0)	49.0% (45.4-52.6)	45.4% (44.1-46.6)	Ref.	5,507 (45.5)	57.6% (54.2-60.9)	51.1% (49.6-52.5)	Ref.
No	8,821 (72.1)	19.2% (17.0-21.5)	17.5% (16.6-18.4)	**2.05 (1.94; 2.16)**	5,661 (44.0)	15.0% (13.0-17.2)	13.2% (12.2-14.3)	**2.90 (2.78; 3.04)**	6,588 (54.5)	35.2% (32.3-38.3)	30.8% (29.5-32.0)	**1.95 (1.86; 2.06)**

	Oropharynx (HPV-related subsites)				Oral cavity				Larynx			
	n (%)	RS (95% CI)	OS (95% CI)	HR (95% CI)	n (%)	RS (95% CI)	OS (95% CI)	HR (95% CI)	n (%)	RS (95% CI)	OS (95% CI)	HR (95% CI)
Contextual factors												
Dentists (per 2,000 inhab.)												
3rd tertile	2,067 (16.9)	31.6% (25.3-38.1)	24.9% (22.8-27.0)	Ref.	2,017 (15.7)	34.0% (27.1-40.9)	33.0% (30.7-35.2)	Ref.	1,926 (15.9)	49.4% (44.7-54.0)	40.4% (38.0-42.8)	Ref.
2nd tertile	6,107 (49.9)	23.4% (20.0-26.9)	23.8% (22.6-25.0)	1.06 (0.99; 1.12)	6,470 (50.3)	35.8% (33.2-38.4)	32.4% (31.2-33.7)	1.05 (0.98; 1.12)	6,203 (51.3)	46.3% (43.0-49.5)	40.9% (39.6-42.3)	1.01 (0.94; 1.08)
1st tertile	4,064 (33.2)	24.8% (21.3-28.3)	22.7% (21.2-24.1)	**1.09 (1.02; 1.16)**	4,371 (34.0)	34.6% (30.9-38.3)	30.0% (28.5-31.5)	**1.09 (1.02; 1.17)**	3,966 (32.8)	41.6% (38.0-45.2)	39.1% (37.4-40.8)	1.05 (0.97; 1.13)
Doctors (per 100,000 inhab.)												
3rd tertile	984 (8.1)	29.8% (20.4-39.7)	26.1% (23.0-29.3)	Ref.	1,024 (8.0)	31.4% (21.9-41.2)	32.9% (29.7-36.2)	Ref.	995 (8.3)	42.9% (36.3-49.3)	38.1% (34.7-41.4)	Ref.
2nd tertile	7,094 (58.4)	24.5% (21.3-27.9)	23.6% (22.5-24.7)	**1.13 (1.04; 1.23)**	7,401 (58.0)	36.1% (33.5-38.7)	32.2% (31.1-33.4)	1.04 (0.95; 1.13)	7,017 (58.5)	47.1% (43.9-50.2)	40.6% (39.3-41.8)	0.96 (0.87; 1.05)
1st tertile	4,063 (33.5)	24.7% (21.3-28.2)	23.0% (21.5-24.5)	**1.13 (1.04; 1.24)**	4,330 (34.0)	33.6% (29.6-37.7)	30.5% (29.0-32.1)	1.06 (0.97; 1.16)	3,983 (33.2)	43.0% (39.5-46.4)	40.3% (38.6-42.0)	0.95 (0.87; 1.05)
GDP *per capita*												
3rd tertile	856 (7.0)	25.9% (19.5-32.8)	24.0% (20.8-27.3)	Ref.	840 (6.6)	36.5% (29.8-43.1)	32.4% (29.0-35.9)	Ref.	802 (6.6)	47.8% (39.8-55.2)	41.3% (37.4-45.1)	Ref.
2nd tertile	7,190 (58.9)	25.2% (22.0-28.5)	24.7% (23.6-25.8)	0.95 (0.87; 1.04)	7,626 (59.4)	35.7% (32.4-39.1)	32.4% (31.2-33.5)	0.99 (0.91; 1.09)	7,335 (60.8)	46.1% (43.3-48.9)	40.2% (39.0-41.4)	1.05 (0.95; 1.16)
1st tertile	4,156 (34.1)	24.7% (21.5-28.0)	21.5% (20.1-22.9)	1.02 (0.93; 1.11)	4,365 (34.0)	32.9% (29.8-36.1)	30.4% (28.9-31.9)	1.03 (0.94; 1.13)	3,934 (32.6)	43.7% (40.0-47.3)	40.2% (38.5-41.9)	1.04 (0.93; 1.15)
Hospital beds (per 1,000 inhab.)												
3rd tertile	3,152 (27.3)	27.4% (23.2-31.7)	24.1% (22.4-25.8)	Ref.	3,189 (26.3)	32.6% (26.9-38.3)	32.8% (31.0-34.6)	Ref.	3,077 (27.1)	43.5% (39.0-48.0)	39.5% (37.6-41.4)	Ref.
2nd tertile	4,467 (38.7)	23.8% (19.7-28.2)	23.2% (21.8-24.6)	**1.09 (1.03; 1.15)**	4,919 (40.5)	38.1% (34.9-41.3)	32.7% (31.3-34.1)	1.05 (0.99; 1.11)	4,499 (39.6)	48.0% (44.7-51.3)	40.8% (39.2-42.3)	1.00 (0.94; 1.07)
1st tertile	3,917 (34.0)	25.4% (22.0-29.0)	24.1% (22.6-25.7)	1.05 (0.99; 1.11)	4,029 (33.2)	33.0% (29.7-36.2)	30.0% (28.4-31.6)	**1.08 (1.02; 1.15)**	3,799 (33.4)	45.7% (42.2-49.1)	39.9% (38.2-41.6)	1.01 (0.95; 1.08)
Human development index												
3rd tertile	713 (5.8)	33.8% (25.5-42.2)	27.4% (23.7-31.2)	Ref.	713 (5.6)	36.6% (25.7-47.6)	36.6% (32.6-40.6)	Ref.	609 (5.0)	45.8% (30.3-60.1)	42.8% (38.2-47.3)	Ref.
2nd tertile	7,373 (60.3)	25.2% (22.1-28.4)	24.1% (23.0-25.2)	1.09 (0.99; 1.20)	7,827 (60.9)	35.9% (33.4-38.4)	31.9% (30.8-33.0)	**1.14 (1.03; 1.27)**	7,512 (62.1)	47.6% (45.1-50.0)	40.3% (39.1-41.5)	1.11 (0.98; 1.25)
1st tertile	4,152 (33.9)	23.9% (20.7-27.3)	22.1% (20.7-23.5)	**1.15 (1.04; 1.27)**	4,318 (33.6)	33.8% (30.4-37.3)	30.6% (29.0-32.1)	**1.16 (1.05; 1.29)**	3,974 (32.9)	41.5% (37.9-45.1)	39.8% (38.1-41.5)	1.12 (0.99; 1.26)

CACON: Center of Reference in High Complexity of Oncology; CI: confidence interval; GDP: gross domestic product; HR: hazard ratio; INHAB.: inhabitants; OS: 5-year overall survival; Ref.: Reference; RS: age-standardized 5-year relative survival; UNACON: Unit of High Complexity in Oncology.

[a] We used multiple imputation data to calculate the HR, which had a relative efficiency >0.99 for all models.
[b] This category comprises the completed plus uncompleted primary school.
There were insufficient cases for 5-year net survival analysis.
* Statistically significant.
** Data were rounded to one decimal place.
*** For each subsite, the tertiles were grouped as follows. For oropharynx subsites, dentists per 2,000 inhabitants (1st: 0.17 to 2.78; 2nd: 2.79 to 4.57; and 3rd: 4.64 to 9.02); doctors per 100,000 inhabitants (1st: 0.04 to 1.22; 2nd: 1.22 to 4.26; and 3rd: 4.57 to 6.45); GDP per capita (1st: 5519.85 to 21486.03; 2nd: 21556.82 to 38403.00; and 3rd: 38525.90 to

177397.80); hospital beds per 1,000 inhabitants (1st: 0.09 to 2.05; 2nd: 2.05 to 2.54; and 3rd: 2.56 to 30.89); and the HDI (1st: 0.639 to 0.766; 2nd: 0.767 to 0.805; and 3rd: 0.806 to 0.862). For oral cavity subsites, dentists per 2,000 inhabitants (1st: 0.17 to 2.78; 2nd: 2.79 to 4.57; and 3rd: 4.64 to 9.02); doctors per 100,000 inhabitants (1st: 0.04 to 1.22; 2nd: 1.22 to 4.26; and 3rd: 4.57 to 6.45); GDP per capita (1st: 5519.85 to 21486.03; 2nd: 21556.82 to 38403.00; and 3rd: 38525.90 to 177397.80); hospital beds per 1,000 inhabitants (1st: 0.09 to 2.05; 2nd: 2.05 to 2.54; and 3rd: 2.56 to 30.89); and the HDI (1st: 0.64 to 0.77; 2nd: 0.77 to 0.81; and 3rd: 0.81 to 0.86). For larynx subsites, dentists per 2,000 inhabitants (1st: 0.17 to 2.78; 2nd: 2.79 to 4.57; and 3rd: 4.64 to 9.02); doctors per 100,000 inhabitants (1st: 0.04 to 1.22; 2nd: 1.22 to 4.26; and 3rd: 4.57 to 6.45); GDP per capita (1st: 5519.85 to 21486.03; 2nd: 21556.82 to 38403.00; and 3rd: 38525.90 to 177397.80); hospital beds per 1,000 inhabitants (1st: 0.09 to 2.05; 2nd: 2.05 to 2.54; and 3rd: 2.56 to 30.89); and the HDI (1st: 0.66 to 0.77; 2nd: 0.77 to 0.81; and 3rd: 0.81 to 0.86).

Table 2. Multiple analysis of 5-year overall survival for oropharynx (HPV-related subsites), oral cavity, and larynx cancers.

	Oropharynx (HPV-related subsites)	**Oral cavity**	**Larynx**
	HR (95% CI)	HR (95% CI)	HR (95% CI)
Age group			
15-44 years	Ref.	Ref.	Ref.
45-54 years	0.96 (0.88; 1.05)	1.05 (0.96; 1.15)	0.93 (0.82; 1.05)
55-64 years	0.95 (0.87; 1.03)	1.05 (0.96; 1.15)	0.89 (0.79; 1.00)
65-74 years	1.02 (0.92; 1.11)	**1.17 (1.07; 1.29)**	1.03 (0.91; 1.17)
+75 years	**1.19 (1.06; 1.34)**	**1.48 (1.33; 1.65)**	**1.32 (1.15; 1.51)**
Education level[a]			
Higher education	Ref.	Ref.	Ref.
High school	**1.30 (1.08; 1.57)**	**1.23 (1.05; 1.46)**	**1.33 (1.08; 1.64)**
Primary school[b]	**1.53 (1.29; 1.82)**	**1.26 (1.08; 1.47)**	**1.47 (1.21; 1.79)**
Illiterate	**1.59 (1.31; 1.93)**	**1.43 (1.20; 1.69)**	**1.66 (1.34; 2.06)**
Gender			
Female	Ref.	Ref.	Ref.
Male	**1.30 (1.21; 1.41)**	**1.15 (1.09; 1.23)**	**1.43 (1.31; 1.56)**
Sector of healthcare assistance[a]			
Private	Ref.	Ref.	Ref.
Public	**1.61 (1.36; 1.90)**	**1.31 (1.13; 1.52)**	**1.62 (1.34; 1.96)**
Clinical staging			
I	Ref.	Ref.	Ref.
II	1.15 (0.99; 1.32)	**1.42 (1.27; 1.59)**	**1.56 (1.39; 1.77)**
III	**1.77 (1.56; 2.01)**	**2.31 (2.07; 2.57)**	**2.59 (2.33; 2.89)**
IV	**3.16 (2.80; 3.57)**	**3.81 (3.45; 4.20)**	**5.09 (4.62; 5.62)**
Treatment			
Chemotherapy			
Yes	Ref.	Ref.	Ref.
No	**1.76 (1.67; 1.85)**	**1.27 (1.20; 1.34)**	**1.32 (1.24; 1.40)**
Radiotherapy			
Yes	Ref.	Ref.	Ref.
No	**1.61 (1.53; 1.69)**	**1.41 (1.34; 1.48)**	**1.54 (1.46; 1.62)**
Surgery			
Yes	Ref.	Ref.	Ref.
No	**2.16 (2.04; 2.29)**	**2.51 (2.39; 2.65)**	**2.16 (2.05; 2.29)**

CI: confidence interval; HR: hazard ratio; Ref.: Reference.

* Statistically significant.
** Data were rounded to one decimal place.
[a] We used multiple imputation data to calculate the HR, which had a relative efficiency >0.99 for all models.
[b] This category comprised the completed plus uncompleted primary school.

Supplementary Table 1. Association between clinical staging and the HDI by subsites.

	Human development index; n (%)						p-value
	1st tertile		2nd tertile		3rd tertile		
	I/II	III/IV	I/II	III/IV	I/II	III/IV	
Oropharynx†	549 (13.6)	3,476 (86.4)	1,064 (15.2)	5,948 (84.8)	112 (16.7)	560 (83.3)	***0.032****
Oral cavity	1,213 (29.1)	2,958 (70.9)	2,072 (27.4)	5,495 (72.6)	204 (30.0)	477 (70.0)	0.079
Larynx	1,142 (29.9)	2,678 (70.1)	2,155 (30.1)	5,011 (69.9)	210 (36.0)	373 (64.0)	***0.009****

* Statistically significant.

** Data were rounded to one decimal place.

† Oropharynx included HPV-related subsites.

Supplementary Table 2. Regional health departments-level descriptive data, age-standardized 5-year relative survival, and univariate analysis of 5-year overall survival by oropharynx (HPV-related subsites), oral cavity, and larynx subsites.

	Oropharynx (HPV-related subsites)				Oral cavity				Larynx			
	n (%)	RS (95% CI)	OS (95% CI)	HR (95% CI)	n (%)	RS (95% CI)	OS (95% CI)	HR (95% CI)	n (%)	RS (95% CI)	OS (95% CI)	HR (95% CI)
(1) Greater São Paulo	4,747 (38.8)	23.1% (19.7-26.8)	23.7% (22.4-25.0)	Ref.	5,414 (42.1)	35.8% (32.5-39.1)	32.2% (30.8-33.5)	Ref.	4,959 (41.0)	46.5% (43.4-49.6)	40.0% (38.5-41.5)	Ref.
(2) Araçatuba	402 (3.3)	35.0% (25.5-44.7)	24.5% (19.9-29.3)	0.96 (0.84; 1.08)	290 (2.3)	38.9% (28.3-49.3)	33.4% (27.5-39.4)	0.90 (0.77; 1.05)	280 (2.3)	56.6% (43.8-67.5)	45.3% (38.8-51.5)	0.89 (0.75; 1.06)
(3) Araraquara	424 (3.5)	29.8% (21.4-39.1)	24.2% (19.9-28.7)	0.93 (0.82; 1.04)	384 (3.0)	28.9% (20.8-37.5)	31.0% (26.0-36.2)	0.96 (0.84; 1.10)	383 (3.2)	55.4% (45.3-64.3)	41.8% (36.3-47.1)	0.93 (0.80; 1.07)
(4) Baixada Santista	267 (2.2)	28.9% (18.1-40.7)	33.3% (26.8-40.0)	**0.74 (0.62; 0.87)**	309 (2.4)	37.4% (22.4-52.5)	34.5% (28.5-40.6)	0.90 (0.77; 1.05)	268 (2.2)	36.3% (24.2-48.5)	36.5% (30.0-43.0)	1.09 (0.92; 1.29)
(5) Barretos	362 (3.0)	21.5% (14.6-29.2)	22.1% (17.5-27.1)	0.95 (0.83; 1.08)	306 (2.4)	40.2% (30.5-49.7)	36.0% (29.9-42.1)	0.87 (0.74; 1.01)	292 (2.4)	44.0% (32.5-54.8)	40.4% (34.2-46.4)	0.97 (0.82; 1.14)
(6) Bauru	947 (7.7)	20.8% (16.0-26.2)	20.8% (18.0-23.8)	0.99 (0.91; 1.07)	1,005 (7.8)	34.4% (28.6-40.3)	29.2% (26.2-32.3)	1.02 (0.94; 1.11)	905 (7.5)	42.4% (35.9-48.6)	38.0% (34.5-41.5)	1.01 (0.92; 1.11)
(7) Campinas	1,091 (8.9)	37.3% (26.0-48.7)	32.2% (28.9-35.5)	**0.79 (0.72; 0.86)**	914 (7.1)	40.9% (33.3-48.4)	39.4% (35.7-43.0)	**0.81 (0.74; 0.89)**	920 (7.6)	52.3% (43.1-60.6)	48.9% (45.1-52.6)	**0.78 (0.70; 0.87)**
(8) Franca	240 (2.0)	#	18.0% (13.0-23.8)	1.09 (0.94; 1.27)	199 (1.6)	39.8% (25.6-53.7)	35.2% (27.9-42.6)	0.89 (0.74; 1.08)	239 (2.0)	50.2% (38.3-61.0)	35.7% (28.9-42.5)	1.05 (0.88; 1.24)
(9) Marília	485 (4.0)	29.1% (20.8-37.9)	19.9% (16.1-23.9)	1.07 (0.96; 1.19)	548 (4.3)	31.9% (23.3-40.8)	27.8% (23.7-32.0)	1.05 (0.94; 1.17)	419 (3.5)	49.0% (40.0-57.4)	42.0% (36.7-47.1)	0.98 (0.85; 1.12)
(10) Piracicaba	359 (2.9)	18.5% (9.3-30.1)	23.4% (18.5-28.7)	0.91 (0.79; 1.03)	398 (3.1)	44.0% (33.9-53.7)	31.5% (26.4-36.7)	0.91 (0.80; 1.04)	399 (3.3)	47.0% (37.4-56.1)	38.5% (33.2-43.9)	1.02 (0.89; 1.17)
(11) Presidente Prudente	194 (1.6)	#	25.3% (18.5-32.7)	0.93 (0.77; 1.12)	281 (2.2)	26.3% (20.3-32.7)	30.0% (24.0-36.2)	1.06 (0.90; 1.24)	236 (2.0)	35.2% (23.9-46.8)	33.6% (26.0-41.4)	1.14 (0.93; 1.39)
(12) Registro	26 (0.2)	#	30.1% (11.9-50.7)	0.71 (0.43; 1.18)	59 (0.5)	58.3% (39.4-73.1)	42.4% (28.0-56.1)	0.82 (0.57; 1.18)	44 (0.4)	#	46.7% (30.8-61.0)	0.91 (0.60; 1.38)
(13) Ribeirão Preto	624 (5.1)	27.7% (18.9-37.2)	20.2% (16.7-23.9)	1.03 (0.93; 1.13)	647 (5.0)	31.6% (24.1-39.3)	25.7% (22.0-29.5)	1.10 (0.99; 1.21)	625 (5.2)	44.6% (36.1-52.6)	42.4% (38.1-46.6)	0.92 (0.82; 1.03)
(14) São J. da Boa Vista	291 (2.4)	35.5% (24.2-47.0)	24.3% (18.7-30.3)	0.92 (0.79; 1.07)	298 (2.3)	36.1% (24.2-48.1)	28.5% (22.6-34.7)	0.99 (0.85; 1.15)	302 (2.5)	37.5% (27.0-48.0)	42.9% (36.3-49.4)	0.85 (0.72; 1.01)
(15) São J. do Rio Preto	987 (8.1)	20.3% (15.4-25.8)	20.4% (17.7-23.3)	1.00 (0.92; 1.09)	987 (7.7)	33.4% (28.1-38.8)	35.1% (31.8-38.5)	**0.86 (0.79; 0.94)**	1,039 (8.6)	41.3% (34.4-48.0)	39.1% (35.9-42.4)	1.01 (0.92; 1.10)
(16) Sorocaba	385 (3.2)	#	21.7% (17.4-26.3)	1.05 (0.93; 1.19)	505 (3.9)	32.0% (22.9-41.4)	23.3% (19.4-27.5)	**1.22 (1.10; 1.36)**	419 (3.5)	35.2% (26.2-44.4)	32.9% (27.9-37.9)	**1.18 (1.04; 1.35)**
(17) Taubaté	407 (3.3)	27.5% (16.9-39.2)	24.1% (19.6-28.8)	0.96 (0.85; 1.09)	314 (2.4)	31.7% (22.9-40.8)	25.0% (19.9-30.3)	**1.25 (1.09; 1.43)**	366 (3.0)	42.7% (32.4-52.5)	37.1% (31.6-42.5)	1.00 (0.87; 1.16)

CI: confidence interval; HR: hazard ratio; OS: 5-year overall survival; Ref.: Reference; RS: age-standardized 5-year relative survival.

* Statistically significant.
** Data were rounded to one decimal place.
# There were insufficient cases for net survival analysis.

Supplementary Table 3. Multiple Cox regression analysis across subsites by period of diagnosis.

	Oropharynx (HPV-related subsites)	**Oral cavity**	**Larynx**
	HR (95% CI)	HR (95% CI)	HR (95% CI)
Period of diagnosis			
2000-2005	Ref.	Ref.	Ref.
2006-2013	0.96 (0.91; 1.01)	**0.93 (0.88; 0.98)**	1.01 (0.95; 1.06)
2014-2018	**0.90 (0.84; 0.95)**	**0.93 (0.88; 0.99)**	1.00 (0.93; 1.07)
Age group	**1.06 (1.04; 1.09)**	**1.10 (1.08; 1.13)**	**1.04 (1.02; 1.07)**
Gender	**0.75 (0.70; 0.81)**	**0.76 (0.71; 0.80)**	**0.74 (0.68; 0.80)**

CI: confidence interval; HR: hazard ratio; Ref.: Reference.

* Statistically significant.

** Data were rounded to one decimal place.

Supplementary Table 4. Complete-case analysis related to univariate analysis of the 5-year overall survival for the formal education and sector of healthcare assistance by subsites.

	Oropharynx (HPV-related subsites)		**Oral cavity**		**Larynx**	
	OS	HR (95% CI)	OS	HR (95% CI)	OS	HR (95% CI)
Education level						
Higher education	47.5%	Ref.	52.5%	Ref.	61.2%	Ref.
High school	28.9%	**1.63 (1.36; 1.96)**	38.7%	**1.47 (1.25; 1.74)**	46.1%	**1.66 (1.35; 2.03)**
Primary school[a]	21.7%	**2.01 (1.70; 2.37)**	30.6%	**1.81 (1.56; 2.11)**	39.1%	**2.03 (1.68; 2.44)**
Illiterate	18.8%	**2.23 (1.86; 2.69)**	24.7%	**2.21 (1.87; 2.62)**	31.9%	**2.55 (2.07; 3.13)**
Sector of healthcare assistance						
Private	52.4%	Ref.	53.5%	Ref.	66.1%	Ref.
Public	24.5%	**2.43 (2.04; 2.89)**	33.8%	**1.86 (1.60; 2.17)**	41.6%	**2.43 (1.98; 2.99)**

CI: confidence interval; HR: hazard ratio; OS: 5-year overall survival; Ref.: Reference.
* Statistically significant.
** Data were rounded to one decimal place.
*** The total of cases per Cox models for oropharynx, oral cavity, and larynx subsites were 8,976, 9,613, and 8,840, respectively.
[a] This category comprises the completed plus uncompleted primary school.

Supplementary Table 5. Multiple analysis of the 5-year overall survival with complete-cases for the formal education and sector of healthcare assistance by subsites.

	Oropharynx (HPV-related subsites)	**Oral cavity**	**Larynx**
	HR (95% CI)	HR (95% CI)	HR (95% CI)
Age group			
15-44 years	Ref.	Ref.	Ref.
45-54 years	1.03 (0.88; 1.21)	1.06 (0.90; 1.25)	0.91 (0.73; 1.13)
55-64 years	1.00 (0.86; 1.17)	1.13 (0.96; 1.32)	0.88 (0.71; 1.09)
65-74 years	1.06 (0.90; 1.24)	**1.19 (1.01; 1.41)**	1.10 (0.88; 1.36)
+75 years	1.20 (0.98; 1.46)	**1.66 (1.38; 1.99)**	**1.36 (1.06; 1.73)**
Education level			
Higher education	Ref.	Ref.	Ref.
High school	**1.37 (1.05; 1.81)**	1.23 (0.96; 1.57)	**1.46 (1.08; 1.98)**
Primary school[a]	**1.59 (1.23; 2.06)**	1.13 (0.90; 1.43)	**1.47 (1.11; 1.96)**
Illiterate	**1.59 (1.19; 2.12)**	1.25 (0.96; 1.63)	**1.43 (1.03; 1.98)**
Gender			
Female	Ref.	Ref.	Ref.
Male	**1.27 (1.12; 1.44)**	**1.20 (1.08; 1.34)**	**1.34 (1.16; 1.55)**
Sector of healthcare assistance[a]			
Private	Ref.	Ref.	Ref.
Public	**1.66 (1.27; 2.18)**	1.12 (0.91; 1.39)	**1.80 (1.34; 2.41)**
Clinical staging			
I	Ref.	Ref.	Ref.
II	1.01 (0.81; 1.26)	**1.28 (1.06; 1.55)**	**1.54 (1.24; 1.90)**
III	**1.44 (1.17; 1.76)**	**1.88 (1.56; 2.26)**	**2.39 (1.98; 2.89)**
IV	**2.90 (2.42; 3.48)**	**3.74 (3.18; 4.39)**	**5.43 (4.58; 6.43)**
Treatment			
Chemotherapy			
Yes	Ref.	Ref.	Ref.
No	**1.81 (1.67; 1.96)**	**1.30 (1.19; 1.42)**	**1.49 (1.35; 1.64)**
Radiotherapy			
Yes	Ref.	Ref.	Ref.

	Oropharynx (HPV-related subsites)	Oral cavity	Larynx
	HR (95% CI)	HR (95% CI)	HR (95% CI)
No Surgery	**1.42 (1.31; 1.53)**	**1.36 (1.26; 1.48)**	**1.43 (1.31; 1.57)**
Yes	Ref.	Ref.	Ref.
No	**2.06 (1.87; 2.26)**	**2.50 (2.30; 2.73)**	**2.21 (2.01; 2.43)**

CI: confidence interval; HR: hazard ratio; OS: 5-year overall survival; Ref.: Reference.
* Statistically significant.
** Data were rounded to one decimal place.
*** The total of cases per Cox models for oropharynx, oral cavity, and larynx subsites were 4,676, 4,831, and 4,408, respectively.
[a] This category comprises the completed plus uncompleted primary school.

Supplementary Table 6. Multilevel survival analysis with complete cases diagnosed with OPC, OCC, and LC clustered by hospitals.

	Oropharynx (HPV-related subsites)	**Oral cavity**	**Larynx**
	HR (95% CI)	HR (95% CI)	HR (95% CI)
Age group			
15-44 years	Ref.	Ref.	Ref.
45-54 years	1.09 (0.93; 1.28)	1.05 (0.89; 1.24)	0.89 (0.71; 1.11)
55-64 years	1.06 (0.91; 1.24)	1.14 (0.97; 1.34)	0.87 (0.70; 1.08)
65-74 years	1.13 (0.96; 1.33)	**1.19 (1.00; 1.40)**	1.10 (0.88; 1.37)
+75 years	**1.28 (1.04; 1.56)**	**1.67 (1.38; 2.01)**	**1.37 (1.07; 1.75)**
Education level			
Higher education	Ref.	Ref.	Ref.
High school	1.22 (0.93; 1.61)	1.18 (0.92; 1.51)	**1.43 (1.05; 1.94)**
Primary school[a]	**1.49 (1.15; 1.94)**	1.10 (0.87; 1.39)	**1.44 (1.08; 1.92)**
Illiterate	**1.50 (1.12; 2.01)**	1.24 (0.95; 1.62)	**1.45 (1.05; 2.02)**
Gender			
Female	Ref.	Ref.	Ref.
Male	**1.33 (1.17; 1.51)**	**1.22 (1.10; 1.36)**	**1.43 (1.23; 1.65)**
Sector of healthcare assistance			
Private	Ref.	Ref.	Ref.
Public	**1.46 (1.10; 1.95)**	1.03 (0.81; 1.30)	**1.53 (1.12; 2.08)**
Clinical staging			
I	Ref.	Ref.	Ref.
II	1.09 (0.87; 1.37)	**1.45 (1.19; 1.77)**	**1.56 (1.26; 1.93)**
III	**1.57 (1.27; 1.94)**	**2.26 (1.87; 2.73)**	**2.53 (2.09; 3.06)**
IV	**3.28 (2.72; 3.97)**	**4.42 (3.74; 5.22)**	**5.82 (4.90; 6.92)**
Treatment			
Chemotherapy			
Yes	Ref.	Ref.	Ref.
No	**1.77 (1.63; 1.93)**	**1.28 (1.17; 1.41)**	**1.44 (1.30; 1.60)**
Radiotherapy			
Yes	Ref.	Ref.	Ref.
No	**1.68 (1.53; 1.84)**	**1.58 (1.44; 1.74)**	**1.63 (1.47; 1.80)**
Surgery			
Yes	Ref.	Ref.	Ref.
No	**2.38 (2.16; 2.63)**	**2.87 (2.62; 3.14)**	**2.50 (2.26; 2.78)**
Human development index			
3rd tertile	Ref.	Ref.	Ref.
2nd tertile	**1.24 (1.02; 1.51)**	1.04 (0.84; 1.28)	0.94 (0.74; 1.20)
1st tertile	**1.33 (1.09; 1.62)**	1.09 (0.88; 1.34)	1.00 (0.78; 1.27)

CI: confidence interval; HR: hazard ratio; OS: 5-year overall survival; Ref.: Reference.
* Statistically significant.
** Data were rounded to one decimal place.

*** The total of cases per multilevel survival analysis for oropharynx, oral cavity, and larynx subsites were 4,676, 4,831, and 4,408, respectively.

Supplementary Table 7. Multilevel survival analysis with complete cases diagnosed with OPC, OCC, and LC clustered by hospitals and municipalities.

	Oropharynx (HPV-related subsites)	**Oral cavity**	**Larynx**
	HR (95% CI)	HR (95% CI)	HR (95% CI)
Age group			
15-44 years	Ref.	Ref.	Ref.
45-54 years	1.09 (0.93; 1.28)	1.05 (0.89; 1.24)	0.88 (0.70; 1.11)
55-64 years	1.06 (0.90; 1.23)	1.13 (0.96; 1.33)	0.87 (0.69; 1.08)
65-74 years	1.13 (0.95; 1.33)	**1.19 (1.00; 1.41)**	1.09 (0.87; 1.36)
+75 years	**1.28 (1.04; 1.57)**	**1.68 (1.39; 2.03)**	**1.35 (1.05; 1.74)**
Education level			
Higher education	Ref.	Ref.	Ref.
High school	1.21 (0.91; 1.59)	1.20 (0.94; 1.55)	**1.44 (1.05; 1.96)**
Primary school[a]	**1.49 (1.14; 1.93)**	1.12 (0.88; 1.41)	**1.43 (1.07; 1.91)**
Illiterate	**1.50 (1.12; 2.02)**	1.26 (0.96; 1.65)	**1.43 (1.02; 1.99)**
Gender			
Female	Ref.	Ref.	Ref.
Male	**1.33 (1.17; 1.51)**	**1.23 (1.10; 1.36)**	**1.43 (1.24; 1.66)**
Sector of healthcare assistance			
Private	Ref.	Ref.	Ref.
Public	**1.48 (1.11; 1.97)**	1.04 (0.82; 1.32)	**1.55 (1.14; 2.12)**
Clinical staging			
I	Ref.	Ref.	Ref.
II	1.10 (0.87; 1.38)	**1.46 (1.20; 1.77)**	**1.56 (1.26; 1.94)**
III	**1.60 (1.29; 1.97)**	**2.29 (1.89; 2.78)**	**2.55 (2.10; 3.10)**
IV	**3.36 (2.77; 4.07)**	**4.54 (3.84; 5.36)**	**5.96 (5.00; 7.11)**
Treatment			
Chemotherapy			
Yes	Ref.	Ref.	Ref.
No	**1.78 (1.63; 1.94)**	**1.29 (1.18; 1.42)**	**1.45 (1.30; 1.61)**
Radiotherapy			
Yes	Ref.	Ref.	Ref.
No	**1.70 (1.55; 1.87)**	**1.58 (1.43; 1.73)**	**1.66 (1.49; 1.84)**
Surgery			
Yes	Ref.	Ref.	Ref.
No	**2.40 (2.18; 2.65)**	**2.88 (2.63; 3.16)**	**2.52 (2.28; 2.80)**
Human development index			
3rd tertile	Ref.	Ref.	Ref.
2nd tertile	1.26 (0.98; 1.61)	1.13 (0.88; 1.44)	0.94 (0.71; 1.24)
1st tertile	**1.38 (1.08; 1.76)**	1.15 (0.90; 1.48)	1.03 (0.78; 1.36)

CI: confidence interval; HR: hazard ratio; OS: 5-year overall survival; Ref.: Reference.
* Statistically significant.
** Data were rounded to one decimal place.
*** The total of cases per multilevel survival analysis for oropharynx, oral cavity, and larynx subsites were 4,676, 4,831, and 4,408, respectively.

Supplementary Table 8. Multilevel survival analysis with complete cases diagnosed with OPC, OCC, and LC clustered by hospitals and regional departments of health.

	Oropharynx (HPV-related subsites)	**Oral cavity**	**Larynx**
	HR (95% CI)	HR (95% CI)	HR (95% CI)
Age group			
15-44 years	Ref.	Ref.	Ref.
45-54 years	1.10 (0.94; 1.29)	1.05 (0.89; 1.23)	0.89 (0.71; 1.11)
55-64 years	1.06 (0.91; 1.24)	1.14 (0.98; 1.34)	0.87 (0.70; 1.08)
65-74 years	1.13 (0.95; 1.33)	**1.18 (1.00; 1.40)**	1.10 (0.88; 1.37)
+75 years	**1.27 (1.04; 1.56)**	**1.67 (1.39; 2.02)**	**1.37 (1.07; 1.75)**
Education level			
Higher education	Ref.	Ref.	Ref.
High school	1.22 (0.93; 1.61)	1.18 (0.92; 1.51)	**1.42 (1.05; 1.94)**
Primary school[a]	**1.50 (1.15; 1.94)**	1.10 (0.88; 1.39)	**1.43 (1.07; 1.91)**
Illiterate	**1.51 (1.12; 2.02)**	1.24 (0.95; 1.62)	**1.45 (1.05; 2.02)**
Gender			
Female	Ref.	Ref.	Ref.
Male	**1.33 (1.17; 1.51)**	**1.23 (1.10; 1.36)**	**1.43 (1.24; 1.65)**
Sector of healthcare assistance			
Private	Ref.	Ref.	Ref.
Public	**1.46 (1.10; 1.95)**	1.00 (0.79; 1.27)	**1.54 (1.13; 2.10)**
Clinical staging			
I	Ref.	Ref.	Ref.
II	1.09 (0.87; 1.37)	**1.44 (1.19; 1.75)**	**1.57 (1.26; 1.94)**
III	**1.57 (1.27; 1.94)**	**2.24 (1.86; 2.71)**	**2.54 (2.10; 3.08)**
IV	**3.29 (2.73; 3.98)**	**4.35 (3.69; 5.13)**	**5.86 (4.92; 6.97)**
Treatment			
Chemotherapy			
Yes	Ref.	Ref.	Ref.
No	**1.78 (1.63; 1.94)**	**1.26 (1.15; 1.39)**	**1.44 (1.30; 1.60)**
Radiotherapy			
Yes	Ref.	Ref.	Ref.
No	**1.69 (1.54; 1.85)**	**1.60 (1.46; 1.76)**	**1.63 (1.47; 1.81)**
Surgery			
Yes	Ref.	Ref.	Ref.
No	**2.39 (2.17; 2.63)**	**2.87 (2.62; 3.14)**	**2.51 (2.26; 2.78)**
Human development index			
3rd tertile	Ref.	Ref.	Ref.
2nd tertile	**1.24 (1.02; 1.52)**	1.02 (0.83; 1.25)	0.93 (0.73; 1.19)
1st tertile	**1.33 (1.09; 1.63)**	1.09 (0.89; 1.34)	0.99 (0.77; 1.27)

CI: confidence interval; HR: hazard ratio; OS: 5-year overall survival; Ref.: Reference.
* Statistically significant.
** Data were rounded to one decimal place.
*** The total of cases per multilevel survival analysis for oropharynx, oral cavity, and larynx subsites were 4,676, 4,831, and 4,408, respectively.

6 IMPACTOS À SAÚDE PÚBLICA/COLETIVA

Nesse estudo, identificou-se uma mudança global na epidemiologia do CCP em sítios anatômicos HPV-relacionados, que representa um desafio para clínicos, pesquisadores e formuladores de políticas públicas. Embora os CO HPV-positivos tenham uma melhor sobrevida,[14] o seu diagnóstico ocorre em pacientes mais jovens,[2] prejudicando substancialmente a qualidade de vida devido aos efeitos de longo prazo do tratamento.[174] Dessa forma, essa epidemia viral tem preocupado a saúde pública por conta da crescente magnitude e dos impactos financeiros ao sistema de saúde e à previdência social dos países afetados.

A partir dos resultados desse trabalho, tem-se a recomendação da prevenção profilática por meio da vacina para o HPV em ambos os sexos, visto que, observou-se um aumento na incidência de CCP em sítios anatômicos relacionados à exposição ao HPV. Ademais, tem-se a necessidade de realizar a vigilância epidemiológica desses carcinomas segundo a relação com o HPV para investigar os efeitos de longo prazo do uso da vacinação profilática nesses tumores.

No Brasil, nossos dados demonstraram a importância da continuidade das políticas de controle do tabaco, tendo em vista os efeitos positivos na incidência do CBO na cidade de São Paulo. Adicionalmente, sugere-se que os programas de controle e prevenção do câncer ampliem a cobertura em jovens para prevenir infecções sexualmente transmissíveis e cânceres relacionados ao HPV, minimizando-se esse risco crescente.

Na análise de sobrevida, o potencial das iniquidades foi mais significativo para sítios anatômicos relacionados ao HPV do que no câncer de boca e laringe. A prevenção do câncer deve considerar as melhorias nas condições de vida e nas ações de educação em saúde para evitar atrasos no diagnóstico. Além disso, são necessários gastos suficientes em saúde para lidar com as disparidades que afetam a prevenção do câncer por meio de diagnóstico precoce e encaminhamento oportuno para o tratamento focado nas populações mais vulneráveis. Portanto, políticas públicas equitativas são urgentes para oferecer oportunidades iguais para indivíduos desfavorecidos, a fim de garantir um tratamento justo e acessível a todos os pacientes independentemente do SES.

7 CONSIDERAÇÕES FINAIS

Mundialmente, observou-se uma significativa transformação na epidemiologia dos CCPs, que possivelmente se deve à maior exposição aos comportamentos sexuais de risco. Assim, houve um aumento na carga de cânceres em sítios anatômicos associados à exposição ao HPV, independentemente de sexo e faixa etária. Por outro lado, as ASRs reduziram para os carcinomas relacionados ao uso de álcool e tabaco.

No Brasil, embora em menor magnitude, identificaram-se resultados semelhantes. As ASRs reduziram para a maioria dos sítios anatômicos de CBO. Mas, houve uma tendência de crescimento em localizações anatômicas HPV-relacionadas em homens e mulheres jovens (≤39 anos) de 3,8%/ano e 8,6%/ano, respectivamente. Na análise do efeito idade-período-coorte, notou-se um risco crescente nas coortes de nascimento em ambos os sexos no CBO HPV-relacionado, enquanto que o risco reduziu consideravelmente no CBO HPV-não relacionado.

Em sítios anatômicos HPV-relacionados, a *net survival* ajustada por idade em cinco anos de 24,4% foi inferior à Europa. Embora tenha ocorrido uma melhora no prognóstico, ela se restringiu aos pacientes com o mais alto SES. Assim, o maior risco de morte ocorreu nos estratos sociais mais baixos, i.e., indivíduos analfabetos ou com a assistência pública de saúde, ajustado para faixa etária, sexo, estadiamento clínico e tratamentos (cirurgia, quimioterapia e radioterapia). Ademais, identificaram-se assimetrias regionais que revelaram iniquidades no desenvolvimento humano e seus efeitos na mortalidade por esse tipo de câncer. Portanto, essa pesquisa revelou que os fatores socioeconômicos apresentaram uma maior importância no prognóstico do que o HPV no Brasil.

Em paralelo, as desigualdades sociais também impactaram na sobrevida global em cinco anos dos cânceres de boca e laringe. Assim, observou-se que a cobertura universal de saúde não foi suficiente para extinguir as "*poverty traps*" em saúde evidenciadas nas taxas de sobrevida analisadas. Por tais motivos, as desigualdades socioeconômicas associadas ao crescente impacto do HPV nos CCPs representam um desafio para os sistemas de saúde. Para alcançar avanços no controle do câncer, as políticas públicas devem considerar as variações regionais e as desigualdades sociais para proporcionar justiça social no acesso à saúde, de acordo com os princípios constitucionais brasileiros.

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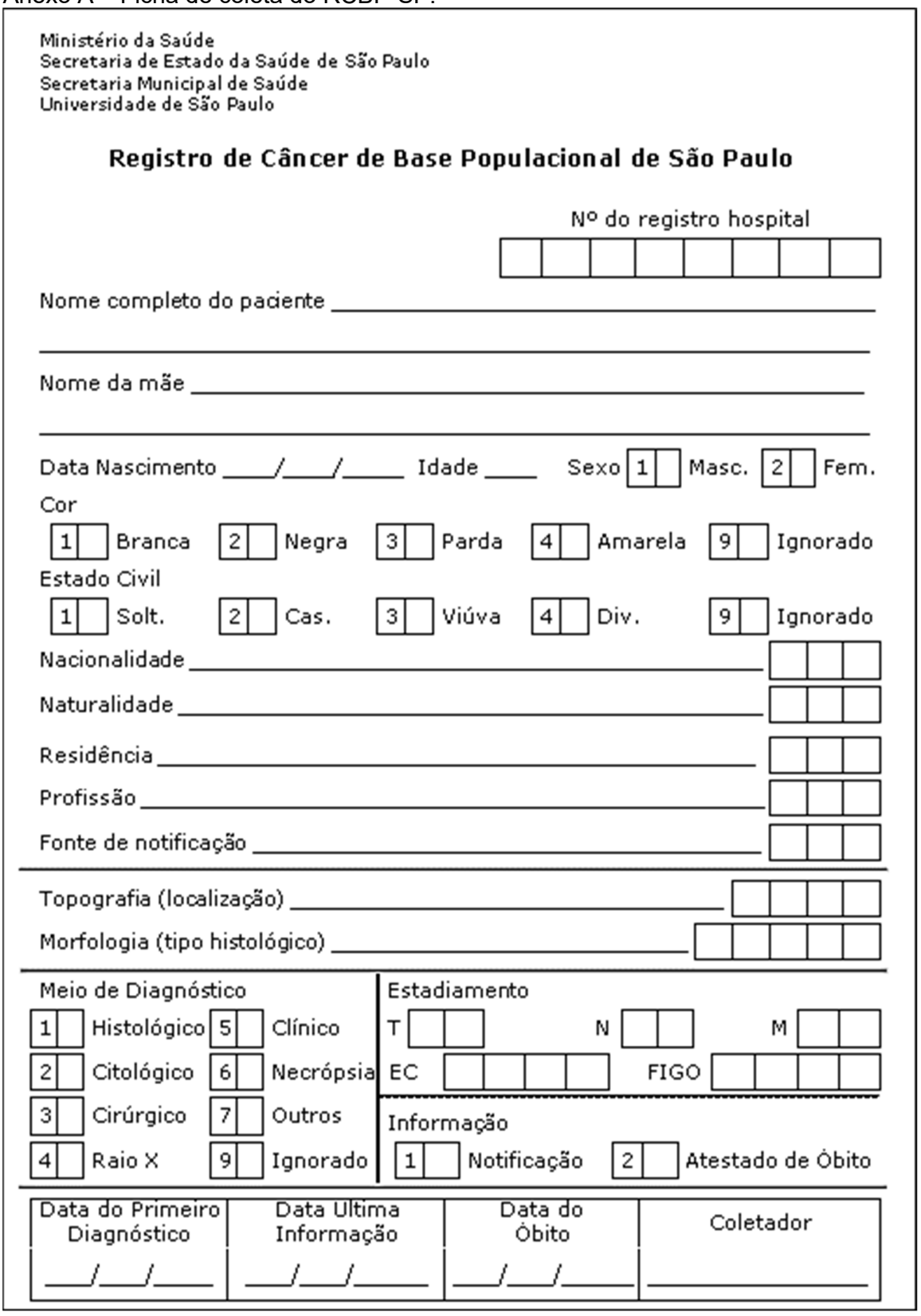
Anexo A – Ficha de coleta do RCBP-SP.



Ministério da Saúde
Secretaria de Estado da Saúde de São Paulo
Secretaria Municipal de Saúde
Universidade de São Paulo

Registro de Câncer de Base Populacional de São Paulo

Nº do registro hospital

Nome completo do paciente _____

_____

Nome da mãe _____

_____

Data Nascimento ____/____/_____ Idade ____ Sexo 1 Masc. 2 Fem.

Cor

1 Branca 2 Negra 3 Parda 4 Amarela 9 Ignorado

Estado Civil

1 Solt. 2 Cas. 3 Viúva 4 Div. 9 Ignorado

Nacionalidade _____

Naturalidade _____

Residência _____

Profissão _____

Fonte de notificação _____

Topografia (localização) _____

Morfologia (tipo histológico) _____

Meio de Diagnóstico

1 Histológico 5 Clínico
2 Citológico 6 Necrópsia
3 Cirúrgico 7 Outros
4 Raio X 9 Ignorado

Estadiamento

T N M
EC FIGO

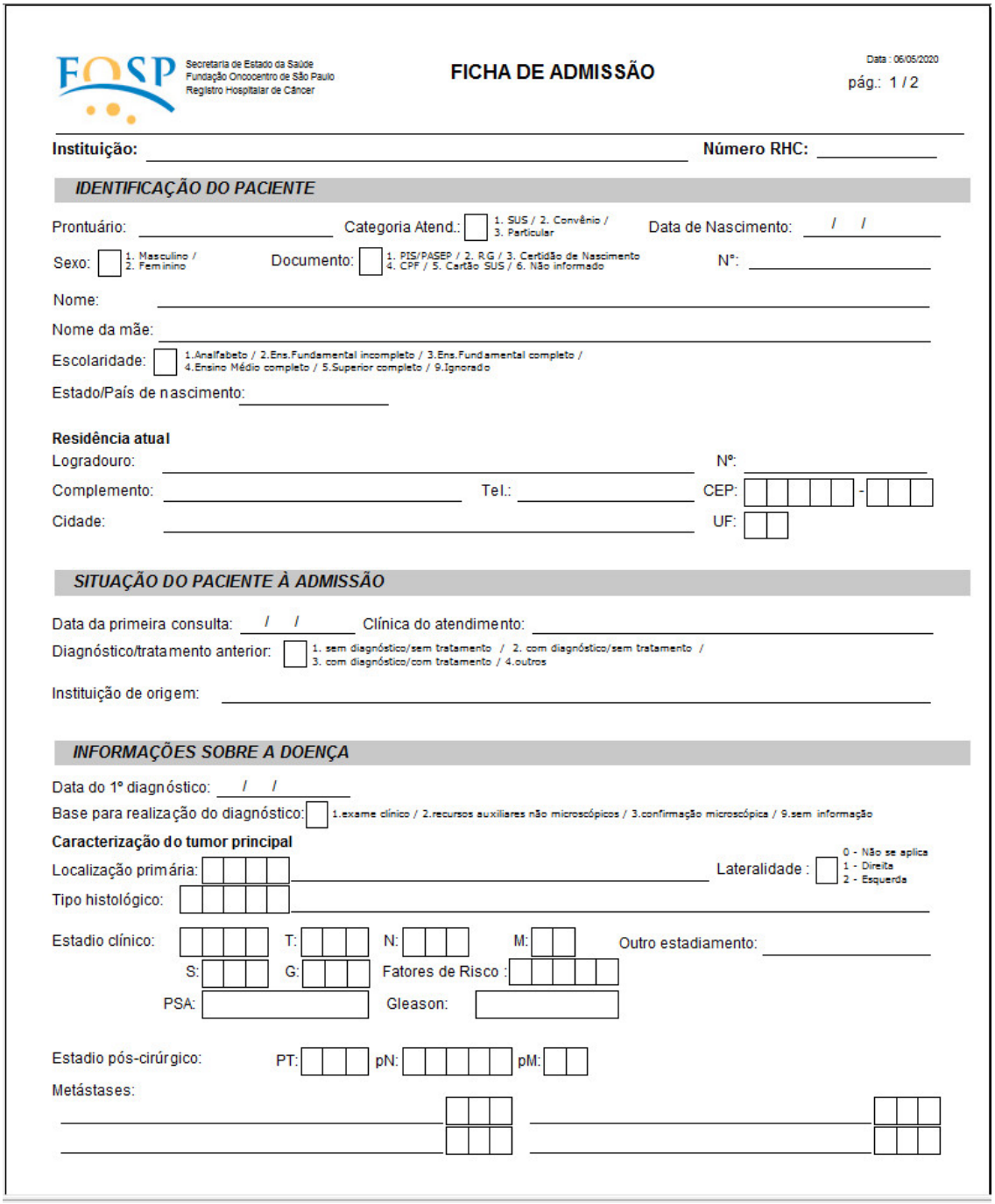
Informação

1 Notificação 2 Atestado de Óbito

Data do Primeiro Diagnóstico	Data Ultima Informação	Data do Óbito	Coletador
___/___/_____	___/___/_____	___/___/_____	_____

Fonte: Registro de Câncer de Base Populacional do Município de São Paulo.

Anexo B – Ficha de coleta da FOSP.



FOSP
Secretaria de Estado da Saúde
Fundação Oncocentro de São Paulo
Registro Hospitalar de Câncer

FICHA DE ADMISSÃO

Data : 06/05/2020
pág.: 1 / 2

Instituição: _____ **Número RHC:** _____

IDENTIFICAÇÃO DO PACIENTE

Prontuário: _____ Categoria Atend.: ☐ 1. SUS / 2. Convênio / 3. Particular Data de Nascimento: / /

Sexo: ☐ 1. Masculino / 2. Feminino Documento: ☐ 1. PIS/PASEP / 2. RG / 3. Certidão de Nascimento 4. CPF / 5. Cartão SUS / 6. Não informado N°: _____

Nome: _____

Nome da mãe: _____

Escolaridade: ☐ 1.Analfabeto / 2.Ens.Fundamental incompleto / 3.Ens.Fundamental completo / 4.Ensino Médio completo / 5.Superior completo / 9.Ignorado

Estado/País de nascimento: _____

Residência atual

Logradouro: _____ N°: _____

Complemento: _____ Tel.: _____ CEP: ☐☐☐☐☐-☐☐☐

Cidade: _____ UF: ☐☐

SITUAÇÃO DO PACIENTE À ADMISSÃO

Data da primeira consulta: / / Clínica do atendimento: _____

Diagnóstico/tratamento anterior: ☐ 1. sem diagnóstico/sem tratamento / 2. com diagnóstico/sem tratamento / 3. com diagnóstico/com tratamento / 4.outros

Instituição de origem: _____

INFORMAÇÕES SOBRE A DOENÇA

Data do 1° diagnóstico: / /

Base para realização do diagnóstico: ☐ 1.exame clínico / 2.recursos auxiliares não microscópicos / 3.confirmação microscópica / 9.sem informação

Caracterização do tumor principal

Localização primária: ☐☐☐☐ _____ Lateralidade : ☐ 0 - Não se aplica 1 - Direita 2 - Esquerda

Tipo histológico: ☐☐☐☐ _____

Estadio clínico: ☐☐☐☐ T: ☐☐☐ N: ☐☐☐ M: ☐☐ Outro estadiamento: _____

S: ☐☐☐ G: ☐☐☐ Fatores de Risco : ☐☐☐☐☐

PSA: ☐☐☐☐☐ Gleason: ☐☐☐☐

Estadio pós-cirúrgico: PT: ☐☐☐ pN: ☐☐☐☐☐ pM: ☐☐

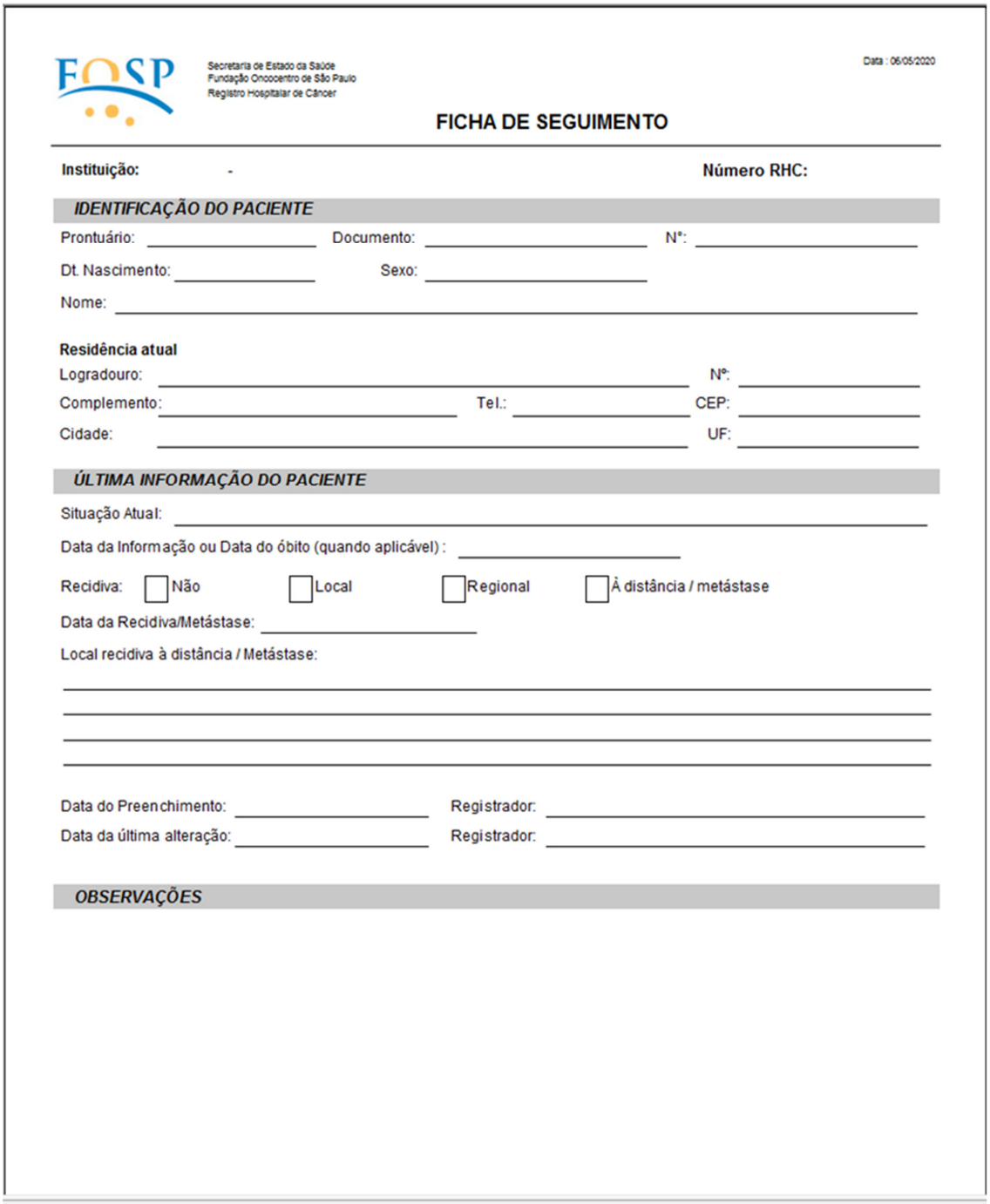
Metástases:

_____ ☐☐☐ _____ ☐☐☐

_____ ☐☐☐ _____ ☐☐☐

Fonte: Fundação Oncocentro de São Paulo (FOSP).

Anexo B – Ficha de coleta da FOSP (continuação).



Secretaria de Estado da Saúde
Fundação Oncocentro de São Paulo
Registro Hospitalar de Câncer

Data : 06/05/2020

FICHA DE SEGUIMENTO

Instituição: - **Número RHC:**

IDENTIFICAÇÃO DO PACIENTE

Prontuário: _____ Documento: _____ N°: _____

Dt. Nascimento: _____ Sexo: _____

Nome: _____

Residência atual

Logradouro: _____ N°: _____

Complemento: _____ Tel.: _____ CEP: _____

Cidade: _____ UF: _____

ÚLTIMA INFORMAÇÃO DO PACIENTE

Situação Atual: _____

Data da Informação ou Data do óbito (quando aplicável) : _____

Recidiva: ☐ Não ☐ Local ☐ Regional ☐ À distância / metástase

Data da Recidiva/Metástase: _____

Local recidiva à distância / Metástase:

_____

_____

_____

_____

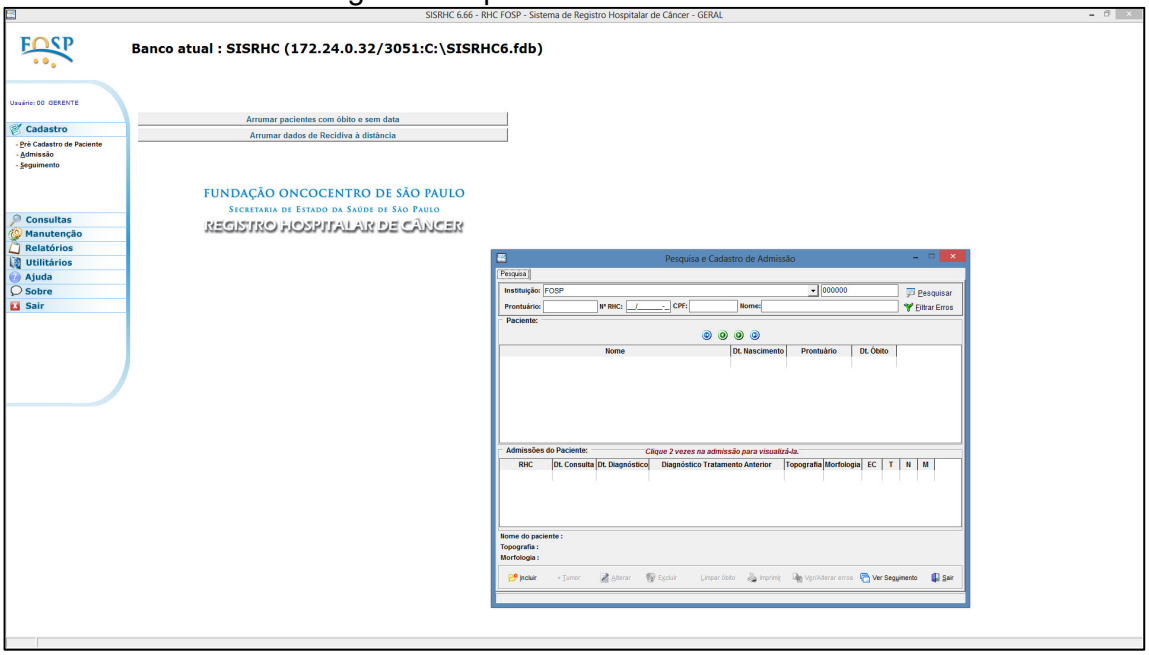
Data do Preenchimento: _____ Registrador: _____

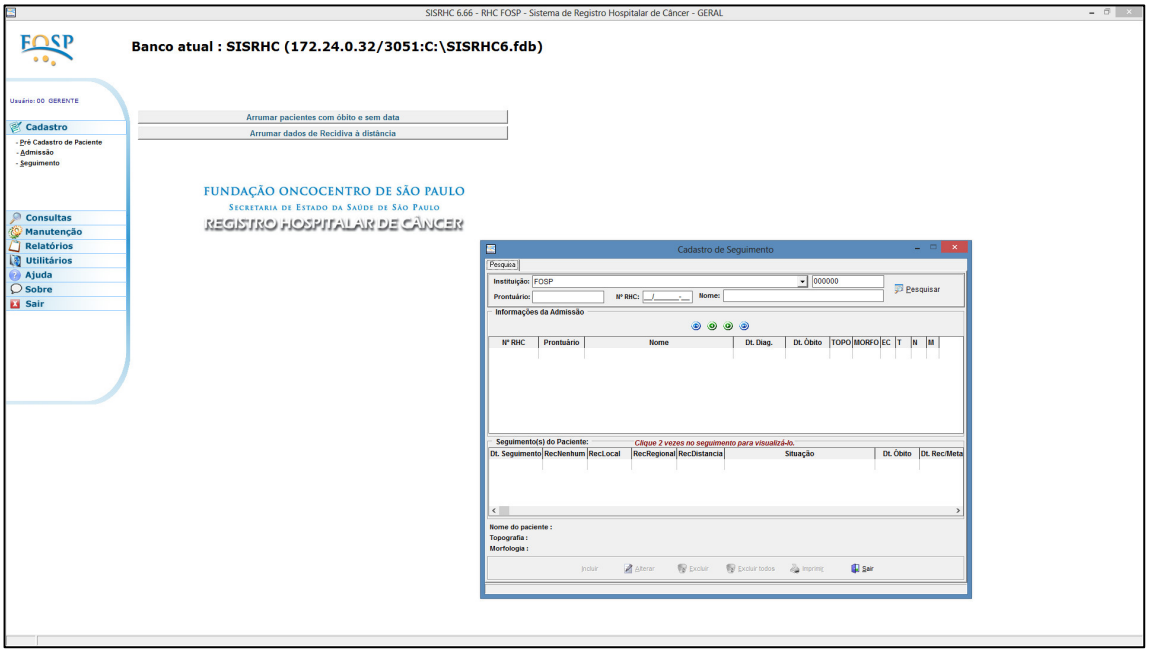
Data da última alteração: _____ Registrador: _____

OBSERVAÇÕES

Fonte: Fundação Oncocentro de São Paulo (FOSP).

Anexo C – Sistema de Registro Hospitalar de Câncer da FOSP.





Fonte: Fundação Oncocentro de São Paulo (FOSP).

Anexo D – Parecer com a aprovação pelo Comitê Técnico Assessor do RCBP-SP.

RCBP-SP

Universidade de São Paulo – USP
Faculdade de Saúde Pública – FSP
Registro de Câncer de Base Populacional de São Paulo – RCBP SP

São Paulo, 24 de abril de 2018.

Prezado Fabrício dos Santos Menezes,

Informamos que o projeto de pesquisa intitulado "Epidemiologia do câncer de boca e orofaringe segundo relação com HPV no município de São Paulo, 1997 a 2014" foi aprovado ad referendum pelo Comitê Técnico Assessor do Registro de Câncer de Base Populacional de São Paulo em 24/04/2018.

Atenciosamente,

Maria do Rosário Dias de Oliveira Latorre
Coordenadora do RCBP-SP

Av Dr. Arnaldo, 715 – Cerqueira César – CEP: 01246-904 - São Paulo - SP
Tel: (11) 3061-7799 / e-mail: rcancer@fsp.usp.br

Fonte: Registro de Câncer de Base Populacional do Município de São Paulo.

Anexo E – Análise técnica do projeto de pesquisa pelo RCBP-SP.

UNIVERSIDADE DE SÃO PAULO
FACULDADE DE SAÚDE PÚBLICA
Departamento de Epidemiologia
Av. Dr. Arnaldo, 715 Pinheiros
CEP: 01246-904 São Paulo/SP
Fone: (11) 3061-7747
jmpsouza@usp.br

Sra. Adriana de Souza
Coordenadora Administrativa do RCBP SP

Foi-me pedido parecer sobre o uso da base de dados do Registro de Câncer pelo pesquisador Fabrício dos Santos Menezes, professor da Universidade Federal de Sergipe - UFS, aluno da orientadora Tatiana Natasha Toporcov, do HEP, projeto "Epidemiologia do câncer de boca e orofaringe segundo relação com HPV no município de São Paulo, 1997 a 2014".

O projeto (apesar de um pouco ambicioso) é claro, muito bem estruturado, podendo trazer boa contribuição para ampliar os conhecimentos desta área. Eventualmente também possa originar um manual didático para eventual curso sobre o assunto, com ênfase na parte estatística. Quanto ao orçamento, julgo que a impressora solicitada deva ser multicromática e com previsão dos respectivos cartuchos coloridos, além de mais papel.

Meu parecer é favorável.

São Paulo, 25 de janeiro de 2018

José Maria Pacheco de Souza
Professor Titular (aposentado)
Professor Sênior

Fonte: Registro de Câncer de Base Populacional do Município de São Paulo.

Anexo F – Parecer de aprovação do projeto de pesquisa pelo CEP.

USP - FACULDADE DE SAÚDE PÚBLICA DA UNIVERSIDADE DE SÃO PAULO - FSP/USP

PARECER CONSUBSTANCIADO DO CEP

DADOS DO PROJETO DE PESQUISA

Título da Pesquisa: EPIDEMIOLOGIA DO CÂNCER DE BOCA E OROFARINGE SEGUNDO RELAÇÃO COM HPV NO MUNICÍPIO DE SÃO PAULO

Pesquisador: FABRICIO DOS SANTOS MENEZES

Área Temática:

Versão: 2

CAAE: 83218318.8.0000.5421

Instituição Proponente: Faculdade de Saúde Pública da Universidade de São Paulo - FSP/USP

Patrocinador Principal: Financiamento Próprio

DADOS DO PARECER

Número do Parecer: 2.675.477

Apresentação do Projeto:

Trata-se de um projeto de pesquisa que envolve os desenhos de estudo ecológico e de coorte sobre câncer de boca e de orofaringe no município de São Paulo, de acordo com os sítios anatômicos HPV-relacionados, o sexo e a faixa etária.

Esta é a 2a versão apresentada, sendo que a pendência anterior foi a apresentação dos documentos sobre apoio à pesquisa (termo anuência) por parte do RCBP-SP e do
PRO-AIM (Município de São Paulo).
Nesta versão, foram apresentados os documentos do RCBP-SP e uma justificativa sobre o dados do PRO-AIM, de que são dados de acesso público por meio do TabNet e, portanto, não necessitariam análise ética do CEP.

Objetivo da Pesquisa:

Analisar a tendência temporal, o efeito idade-período-coorte, a análise de sobrevida e a distribuição espacial dos casos e óbitos de câncer de boca e de orofaringe, de acordo com os sítios anatômicos HPV relacionados, o sexo e a faixa etária no município de São Paulo no período de 1997 a 2014.

Endereço: Av. Doutor Arnaldo, 715
Bairro: Cerqueira Cesar **CEP:** 01.246-904
UF: SP **Município:** SAO PAULO
Telefone: (11)3061-7779 **Fax:** (11)3061-7779 **E-mail:** coep@fsp.usp.br

Fonte: Comitê de Ética em Pesquisa da Faculdade de Saúde Pública da Universidade de São Paulo.

Anexo F – Parecer de aprovação do projeto de pesquisa pelo CEP (continuação).

USP - FACULDADE DE SAÚDE PÚBLICA DA UNIVERSIDADE DE SÃO PAULO - FSP/USP

Continuação do Parecer: 2.675.477

- Justificativa

Conforme o projeto detalhado, os dados serão disponibilizados sem nenhuma identificação dos sujeitos da pesquisa. A análise espacial será realizada a partir dos distritos administrativos do município de São Paulo.

Conclusões ou Pendências e Lista de Inadequações:

Pela aprovação

Considerações Finais a critério do CEP:

Este parecer foi elaborado baseado nos documentos abaixo relacionados:

Tipo Documento	Arquivo	Postagem	Autor	Situação
Informações Básicas do Projeto	PB_INFORMAÇÕES_BÁSICAS_DO_PROJETO_1056409.pdf	30/04/2018 13:56:50		Aceito
Outros	JUSTIFICATIVA_CEP.pdf	30/04/2018 13:56:17	FABRICIO DOS SANTOS MENEZES	Aceito
Declaração de Instituição e Infraestrutura	Parecer_RCBP_SP_Suplemento.pdf	30/04/2018 13:38:53	FABRICIO DOS SANTOS MENEZES	Aceito
Declaração de Instituição e Infraestrutura	Aprovacao_Projeto_RCBP_SP.pdf	30/04/2018 13:36:48	FABRICIO DOS SANTOS MENEZES	Aceito
Projeto Detalhado / Brochura Investigador	Projeto20180129.pdf	29/01/2018 11:57:59	FABRICIO DOS SANTOS MENEZES	Aceito
Folha de Rosto	Folha_de_Rosto.pdf	29/01/2018 11:50:46	FABRICIO DOS SANTOS MENEZES	Aceito

Situação do Parecer:

Aprovado

Necessita Apreciação da CONEP:

Não

Endereço: Av. Doutor Arnaldo, 715
Bairro: Cerqueira Cesar **CEP:** 01.246-904
UF: SP **Município:** SAO PAULO
Telefone: (11)3061-7779 **Fax:** (11)3061-7779 **E-mail:** coep@fsp.usp.br

Fonte: Comitê de Ética em Pesquisa da Faculdade de Saúde Pública da Universidade de São Paulo.

Anexo G – Aprovação da emenda do projeto de pesquisa pelo CEP.

USP - FACULDADE DE SAÚDE PÚBLICA DA UNIVERSIDADE DE SÃO PAULO - FSP/USP

Plataforma Brasil

PARECER CONSUBSTANCIADO DO CEP

DADOS DA EMENDA

Título da Pesquisa: EPIDEMIOLOGIA DO CÂNCER DE BOCA, OROFARINGE E LARINGE SEGUNDO RELAÇÃO COM O HPV NO ESTADO DE SÃO PAULO

Pesquisador: FABRICIO DOS SANTOS MENEZES

Área Temática:

Versão: 3

CAAE: 83218318.8.0000.5421

Instituição Proponente: Faculdade de Saúde Pública da Universidade de São Paulo - FSP/USP

Patrocinador Principal: Financiamento Próprio

DADOS DO PARECER

Número do Parecer: 3.733.544

Apresentação do Projeto:

Trata-se de uma emenda de projeto previamente aprovado pelo CEP/FSP sob o nº CAAE: 83218318.8.0000.5421.

As alterações são a inserção da análise de sobrevida do câncer de laringe, além do câncer de boca e orofaringe, assim como de englobar os pacientes cadastrados no Registro Hospitalar de Câncer do Estado de São Paulo da Fundação Oncocentro de São Paulo (FOSP).

O banco de dados da FOSP é de acesso público e não nominal, encontrando-se disponível a partir do site http://www.fosp.saude.sp.gov.br. Além disso, a FOSP declara que tais informações podem ser utilizadas por pesquisadores para a elaboração de artigos, projetos e demais estudos (declaração anexada na plataforma).

Objetivo da Pesquisa:

Analisar a tendência temporal, o efeito idade-período-coorte, a análise de sobrevida e a distribuição espacial dos casos no município e no estado de São Paulo.

i. Descrever os coeficientes de incidência (1997-2014) e de mortalidade (1997-2014) por câncer de boca e de orofaringe no município de São Paulo, de acordo com os sítios anatômicos HPV-relacionados, o sexo e a faixa etária.

ii. Analisar a tendência temporal dos coeficientes de incidência (1997-2014) e de mortalidade (1997-2014) por câncer de boca e de orofaringe no município de São Paulo, segundo sítios

Endereço: Av. Doutor Arnaldo, 715
Bairro: Cerqueira Cesar **CEP:** 01.246-904
UF: SP **Município:** SAO PAULO
Telefone: (11)3061-7779 **Fax:** (11)3061-7779 **E-mail:** coep@fsp.usp.br

Fonte: Comitê de Ética em Pesquisa da Faculdade de Saúde Pública da Universidade de São Paulo.

Anexo G – Aprovação da emenda do projeto de pesquisa pelo CEP (continuação).

USP - FACULDADE DE SAÚDE PÚBLICA DA UNIVERSIDADE DE SÃO PAULO - FSP/USP

Plataforma Brasil

Continuação do Parecer: 3.733.544

Informações Básicas do Projeto	PB_INFORMAÇÕES_BÁSICAS_1458417_E1.pdf	23/10/2019 16:33:07		Aceito
Outros	Variaveis_FOSP_2019.pdf	23/10/2019 16:28:14	FABRICIO DOS SANTOS MENEZES	Aceito
Declaração de Instituição e Infraestrutura	FOSP_declaracao_base_dados_disponibilizadas.pdf	23/10/2019 16:25:58	FABRICIO DOS SANTOS MENEZES	Aceito
Projeto Detalhado / Brochura Investigador	Projeto_CEP_alterado.pdf	23/10/2019 16:24:45	FABRICIO DOS SANTOS MENEZES	Aceito
Outros	CARTA_CEP.pdf	23/10/2019 16:19:18	FABRICIO DOS SANTOS MENEZES	Aceito
Declaração de Instituição e Infraestrutura	Parecer_RCBP_SP_Suplemento.pdf	30/04/2018 13:38:53	FABRICIO DOS SANTOS MENEZES	Aceito
Declaração de Instituição e Infraestrutura	Aprovacao_Projeto_RCBP_SP.pdf	30/04/2018 13:36:48	FABRICIO DOS SANTOS MENEZES	Aceito
Folha de Rosto	Folha_de_Rosto.pdf	29/01/2018 11:50:46	FABRICIO DOS SANTOS MENEZES	Aceito

Situação do Parecer:
Aprovado

Necessita Apreciação da CONEP:
Não

SAO PAULO, 28 de Novembro de 2019

Assinado por:
José Leopoldo Ferreira Antunes
(Coordenador(a))

Endereço: Av. Doutor Arnaldo, 715
Bairro: Cerqueira Cesar **CEP:** 01.246-904
UF: SP **Município:** SAO PAULO
Telefone: (11)3061-7779 **Fax:** (11)3061-7779 **E-mail:** coep@fsp.usp.br

Fonte: Comitê de Ética em Pesquisa da Faculdade de Saúde Pública da Universidade de São Paulo.

Anexo H – Confirmação da submissão para o periódico European Journal of Epidemiology.

EJEP-D-20-01033 - Submission Confirmation

European Journal of Epidemiology (EJEP) <em@editorialmanager.com>
Seg, 13/07/2020 16:42
Para: Fabrício dos Santos Menezes <fabriciomenezes@msn.com>

Dear Professor Menezes,

Thank you for submitting your manuscript, Global incidence trends in head and neck cancer for HPV-related and -unrelated subsites: A systematic review of population-based studies, to European Journal of Epidemiology.

During the review process, you can keep track of the status of your manuscript by accessing the Journal's website.

Your username is: fsmenezes

If you forgot your password, you can click the 'Send Login Details' link on the EM Login page at https://nam04.safelinks.protection.outlook.com/?url=https%3A%2F%2Fwww.editorialmanager.com%2Fejep%2F&data=02%7C01%7C%7C219f21568f404154878208d82764dcac%7C84df9e7fe9f640afb435aaaaaaaaaaaa%7C1%7C0%7C637302661428595944&sdata=77QluzRotSnPyCgvwYFE%2Bp7U6vtY9xQg18ccuoSTtjO%3D&reserved=0.

The submission id is: EJEP-D-20-01033

Please refer to this number in any future correspondence.

Should you require any further assistance please feel free to e-mail the Editorial Office by clicking on "Contact Us" in the menu bar at the top of the screen.

With kind regards,
Springer Journals Editorial Office
European Journal of Epidemiology

Fonte: American Journal of Epidemiology.

Anexo I – Publicação do segundo artigo da tese.

PLOS ONE

RESEARCH ARTICLE

The emerging risk of oropharyngeal and oral cavity cancer in HPV-related subsites in young people in Brazil

Fabrício dos Santos Menezes[1,2¤]*, Maria do Rosário Dias de Oliveira Latorre[2], Gleice Margarete de Souza Conceição[2], Maria Paula Curado[3,4], José Leopoldo Ferreira Antunes[2], Tatiana Natasha Toporcov[2]

1 Department of Health Education, Federal University of Sergipe, Lagarto, Sergipe, Brazil, **2** Department of Epidemiology, School of Public Health, University of São Paulo, São Paulo City, São Paulo State, Brazil, **3** Department of Epidemiology, International Research Center, A.C. Camargo Cancer Center, São Paulo City, São Paulo State, Brazil, **4** International Prevention Research Institute, Ecully, France

¤ Current address: Department of Health Education, Federal University of Sergipe, Lagarto, Sergipe, Brazil
* fabriciomenezes@usp.br

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Abstract

Human papillomavirus (HPV) is responsible for the rise in the incidence of cancer in the oropharynx, tonsils, and base of the tongue (i.e., HPV-related subsites). HPV triggered the changes in the epidemiology of oropharyngeal and oral cavity cancer (OPC/OCC) in Asia, Europe, North America, and Oceania. Hence, the incidence of cancer in HPV-related subsites is augmenting, while that in other HPV-unrelated subsites is decreasing. In South America, although the incidence of HPV-positive tumors has gradually increased, there is an atypically low prevalence of HPV in people with OPC/OCC. To clarify whether this dramatic shift in incidence trends also occurred in this population, we estimated the burden of HPV on the incidence trends of OPCs/OCCs in São Paulo city in Brazil. In this population-based study, we categorized OPCs/OCCs by HPV-related and HPV-unrelated subsites. We used Poisson regression to assess the age-standardized incidence rates (ASRs) stratified by sex and age groups, as well as to examine the age-period-cohort effects. There were 15,391 cases of OPCs/OCCs diagnosed in HPV-related (n = 5,898; 38.3%) and HPV-unrelated (n = 9,493; 61.7%) subsites. Overall, the ASRs decreased for most subsites, for both sexes and for all age groups, except for HPV-related OPC/OCC in young males and females, which increased by 3.8% and 8.6% per year, respectively. In the birth-cohort-effect analysis, we identified an increasing risk for HPV-related OPC/OCC in both sexes in recent birth cohorts; however, this risk was sharply decreased in HPV-unrelated subsites. Our data demonstrate an emerging risk for HPV-related OPC/OCC in young people, which supports prophylactic HPV vaccination in this group.

Fonte: Plos One.[23]

Anexo J – Currículo Lattes do autor da tese.

Fabricio dos Santos Menezes

Endereço para acessar este CV: http://lattes.cnpq.br/2015871187034203
ID Lattes: **2015871187034203**
Última atualização do currículo em 21/05/2020

Fabrício dos Santos Menezes é Professor Adjunto do Departamento de Educação em Saúde da Universidade Federal de Sergipe (UFS). Atualmente, realiza o Doutorado em Epidemiologia na Faculdade de Saúde Pública da Universidade de São Paulo (USP). Anteriormente, graduou-se como cirurgião-dentista na Universidade Estadual de Feira de Santana (UEFS) e foi bolsista do Programa de Educação Tutorial (PET) vinculado ao Ministério da Educação (MEC). Em 2018, foi selecionado para participar da 10ª coorte do "Public Health Collaborative Course in Brazil" organizado pela Universidade de Harvard (EUA). Durante a sua carreira, atuou como avaliador ad hoc, em ações de coordenação e Programa de Residência, assim como obteve importantes premiações e publicações nacionais e internacionais. No desenvolvimento de pesquisas, ele tem interesse em estudos sobre epidemiologia, câncer de cabeça e pescoço, desigualdades no acesso aos serviços de saúde, odontologia legal, bioética e educação em saúde. Além disso, ele é pai de um bebê de 1 ano e 11 meses. E-mail: fabriciomenezes@msn.com
(Texto informado pelo autor)

Identificação

Nome	Fabricio dos Santos Menezes
Nome em citações bibliográficas	MENEZES, F. S.;DOS SANTOS MENEZES, FABRÍCIO
Lattes iD	http://lattes.cnpq.br/2015871187034203

Endereço

Endereço Profissional	Universidade Federal de Sergipe. UNIVERSIDADE FEDERAL DE SERGIPE - UFS. Campus Universitário Prof. Antônio Garcia Filho. Avenida Universitária Governador Marcelo Déda Chagas, 330. Bairro Jardim Campo Novo. Centro 49400000 - Lagarto, SE - Brasil Telefone: (79) 36322071 URL da Homepage: www.ufs.br

Formação acadêmica/titulação

2017	Doutorado em andamento em Epidemiologia na Faculdade de Saúde Pública da USP. Universidade de São Paulo, USP, Brasil. Orientador: Profa. Dra. Tatiana Natasha Toporcov.
2012 - 2013	Mestrado em Ciências da Saude (Conceito CAPES 5). Universidade Federal de Sergipe, UFS, Brasil. Título: CÁRIE DENTÁRIA EM PACIENTES COM ANEMIA FALCIFORME EM UMA COORTE BRASILEIRA,Ano de Obtenção: 2013. Orientador: Profa. Dra. Rosana Cipolotti.
2011 - 2013	Especialização em Especialização em Odontologia do Trabalho. (Carga Horária: 605h). COPH, Bauru - SP, COPH, Brasil. Título: A OCUPAÇÃO COMO FATOR DE RISCO PARA O CÂNCER DE BOCA. Orientador: Profa. Fernanda Pataro Marsola Razera.
2010 - 2010	Aperfeiçoamento em ODONTOLOGIA LEGAL. (Carga Horária: 100h). Programa de educação continuada, PEC, Brasil. Título: .. Ano de finalização: 2010.
2006 - 2011	Graduação em Odontologia. Universidade Estadual de Feira de Santana, UEFS, Brasil. Título: Análise comparativa das características histológicas e clínico-epidemiológicas dos granulomas piogênicos da boca em uma população brasileira / Comparative analyse of histological and clinico-epidemiological features of oral PG in a brazilian population. Orientador: Márcio Campos Oliveira. Bolsista do(a): Ministério da Educação, MEC, Brasil.

Fonte: Plataforma Lattes.[175]

Anexo L – Currículo Lattes da orientadora.

Tatiana Natasha Toporcov

Endereço para acessar este CV: http://lattes.cnpq.br/5345064895953228
ID Lattes: **5345064895953228**
Última atualização do currículo em 13/11/2019

Cirurgiã-dentista com doutorado direto em Ciências odontológicas (concentração em odontologia social) pela Faculdade de Odontologia da USP, pós doutorada em Epidemiologia pela Faculdade de Saúde Pública da USP. Atualmente é Professora Doutora do Departamento de Epidemiologia da Faculdade de Saúde Pública da USP. Tem experiência na área de Epidemiologia das Doenças e Agravos Não Transmissíveis, com ênfase em Epidemiologia do Câncer, atuando principalmente em estudos descritivos e pesquisas sobre fatores de risco e fatores prognósticos. **(Texto informado pelo autor)**

Identificação

Nome Tatiana Natasha Toporcov
Nome em citações bibliográficas TOPORCOV, T. N.;Toporcov, Tatiana Natasha;TOPORCOV, T.N.;TOPORCOV, TATIANA;TOPORCOV, TATIANA N.;Toporcov, TN;Toporcov, TT
Lattes iD http://lattes.cnpq.br/5345064895953228

Endereço

Endereço Profissional Universidade de São Paulo, Faculdade de Saúde Pública.
Av. Dr. Arnaldo, 715
01246-904 - Sao Paulo, SP - Brasil
Telefone: (11) 30617920
URL da Homepage: http://www.fsp.usp.br

Formação acadêmica/titulação

2006 - 2010 Doutorado em Ciências Odontológicas (Conceito CAPES 5).
Universidade de São Paulo, USP, Brasil.
com **período sanduíche** em Fundación para la Investigación Sanitária en Castilla-la Mancha (Orientador: José Luis rodriguez Martin).
Título: Hábitos Alimentares e Câncer de Boca e Orofaringe, Ano de obtenção: 2010.
Orientador: José Leopoldo Ferreira Antunes.
Bolsista do(a): Fundação de Amparo à Pesquisa do Estado de São Paulo, FAPESP, Brasil.
Palavras-chave: câncer bucal; caso controle; epidemiologia; hábitos alimentares; fatores de risco; Revisão Sistemática.
Grande área: Ciências da Saúde
Grande Área: Ciências da Saúde / Área: Odontologia / Subárea: Odontologia Social e Preventiva.
Grande Área: Ciências da Saúde / Área: Saúde Coletiva / Subárea: Saúde Pública.

2000 - 2005 Graduação em Odontologia.
Universidade de São Paulo, USP, Brasil.

Pós-doutorado e Livre-docência

2018 Livre-docência.
Faculdade de Saúde Pública da Universidade de São Paulo, FSP-USP, Brasil.
Título: Contribuições da epidemiologia para o controle do câncer de cabeça e pescoço: estudos realizados no Estado de São Paulo, Ano de obtenção: 2018.

2010 - 2013 Pós-Doutorado.
Faculdade de Saúde Pública- Universidade de São Paulo, FSP-USP, Brasil.
Bolsista do(a): Fundação de Amparo à Pesquisa do Estado de São Paulo, FAPESP, Brasil.
Grande área: Ciências da Saúde
Grande Área: Ciências da Saúde / Área: Saúde Coletiva / Subárea: Saúde Pública.
Grande Área: Ciências da Saúde / Área: Saúde Coletiva / Subárea: Medicina Preventiva.

Fonte: Plataforma Lattes.[176]