

Dynamic factors affecting HPV-attributable fraction for head and neck cancers

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Head and neck squamous cell carcinoma (HNSCC) is attributable to carcinogen and oncogenic virus exposure and rates are driven by the prevalence, intensity, and duration of exposures. Recent dramatic shifts in human behavior have resulted in substantial heterogeneity in HNSCC incidence trends over calendar time. For example, changes in sexual behavior during the 1900s likely increased exposure to oral human papillomavirus (HPV) infection and, consequently, rates of HPV-positive HNSCC. Shifting rate-ratios for HPV-positive versus negative HNSCC determine the HPV attributable fraction (AF), best measured by direct tumor testing for HPV DNA and RNA. Potential high efficacy of HPV vaccines against oral HPV infections will affect future incidence trends, depending on calendar time of introduction, male and female coverage, and herd protection. Accurate estimates of HPV AF for all cancers, including HNSCC, may inform HPV immunization policy and surveillance of effectiveness.

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Introduction

According to the World Health Organization, approximately 660 000 people were diagnosed with head and neck squamous cell carcinoma (HNSCC) worldwide in 2018 [1]. A majority are oral cavity cancers in low and middle income countries in Asia attributable to smokeless tobacco, areca nut, and beetle-quit use [2–5]. In contrast, in high income countries, tobacco smoking and alcohol use remain the leading risk factors [6–8]. However, in several high income countries, a subset of oropharyngeal cancers increasing in incidence is attributable to human papillomavirus (HPV) infection [6,9–14]. HPV is one of

the most common cancer-causing pathogens in the world and is spread predominantly by sexual contact [15]. Observed global heterogeneity in incidence trends for HNSCC by anatomic site (e.g. oral cavity and oropharynx) therefore has its origins in the variability over time in behavioral risk factors (e.g. carcinogen use and sexual behavior) across cultures. The introduction of effective HPV prophylactic vaccines after 2006 and variability in population uptake in males and females across geographic regions will introduce yet another variable affecting incidence trends over the next several decades. Estimates of the HPV-attributable fraction of HNSCC will inform global and regional policymakers of the population-level potential for primary prevention of these cancers through HPV vaccination. Discussed here are the many dynamic factors that affect the HPV-attributable fraction and estimates of burden in populations.

Worldwide burden of HPV-attributable HNSCC

The HPV attributable fraction (AF) is the proportion of a specific cancer caused by HPV infection that could be eliminated in a population if HPV infection were prevented, for example, via vaccination. Best estimates for HPV AF are made with an accepted gold standard of detection of HPV DNA and viral E6/E7 mRNA expression in tumors [16]. For oropharyngeal cancers only, combined detection of p16 expression by immunohistochemistry and high-risk HPV DNA presence by in situ hybridization has high positive predictive value (98.6%) for HPV E6/E7 mRNA expression [16].

A study conducted by Castellsagué *et al.* [17] provides the best estimates for global HPV AF for HNSCC. Centralized testing for HPV E6/E7 mRNA expression was performed on 3680 archived HNSCC diagnosed in 29 countries during the period from 1990 to 2012. This study provided a worldwide HPV AF of 21.8% oropharyngeal, 3.9% oral cavity, and 3.1% laryngeal cancers [17] (Table 1). Estimates are slightly higher in a literature survey (30.8% for oropharynx, 4.3% oral cavity, 4.6% laryngeal cancer) that applied HPV AF obtained from case series with HPV E6/E7 mRNA expression testing to incidence data from 2003 to 2007 [15], and in a meta-analysis [18] (39.8% oropharyngeal, 16.3% oral cavity and 8.6% laryngeal cancer) of 148 studies from 1990 to 2012 in which tumor HPV status was determined by E6/E7 mRNA expression (Table 1). This heterogeneity in the global HPV AF across studies is best explained by variability in HPV detection assays, populations included, and calendar time.

Table 1

Human Papillomavirus (HPV) attributable fraction in head and neck cancer reported by three major studies

Authors and study year	Castellsagué <i>et al.</i> (2016) ^a	Plummer <i>et al.</i> (2016) ^b	Nadiye <i>et al.</i> (2014) ^c
Study description/data source	Centralized testing of 3680 archived head and neck cancers from 29 countries	Pooled published case series of head and neck cancers	Meta-analysis of 148 studies of head and neck cancers
Study period	1990–2012	2003–2007	1990–2012
HPV assay used	HPV DNA and E6/E7 mRNA expression	HPV DNA and E6/E7 mRNA expression	HPV DNA and E6/E7 mRNA expression
HPV attributable fraction			
Oropharynx	21.8%	30.8%	39.8%
Oral cavity	3.9%	4.3%	16.3%
Larynx	3.1%	4.6%	8.6%

^a Castellsagué X, Alemany L, Quer M, Halc G, Quirós B, Tous S, Clavero O, Alòs L, Biegner T, Szafarowski T: **HPV involvement in head and neck cancers: comprehensive assessment of biomarkers in 3680 patients.** *J Natl Cancer Inst* 2016, **108**:djv403.

^b Plummer M, de Martel C, Vignat J, Ferlay J, Bray F, Franceschi S: **Global burden of cancers attributable to infections in 2012: a synthetic analysis.** *Lancet Glob Health* 2016, **4**:e609–e616.

^c Ndiaye C, Mena M, Alemany L, Arbyn M, Castellsagué X, Laporte L, Bosch FX, de Sanjosé S, Trottier H: **HPV DNA, E6/E7 mRNA, and p16INK4a detection in head and neck cancers: a systematic review and meta-analysis.** *Lancet Oncol* 2014, **15**:1319–1331.

Indeed, Castellsagué and colleagues reported that the global HPV AF for oropharyngeal cancer increased sharply from 7.4% in 1990 to 32.1% in 2012 [17]. Data from the US provide substantial insight into an even more marked increase in HPV AF for oropharyngeal cancers from 16.3% in 1984 to 71.7% in 2004 [13]. This change was attributable to a 50% decrease in incidence rates for HPV-negative, coincident with a 225% increase in incidence for HPV-positive, oropharyngeal cancers [13]. This dramatic shift was due to rising rates for HPV-positive oropharyngeal cancer exclusively among men born after 1935–1940, a strong birth cohort effect [14,19]. Notably, as this birth cohort ages, the burden of HPV-positive oropharyngeal cancer in the US is shifting from younger to older (age ≥ 65 years) men [20*].

Castellsagué [17] also noted substantial geographic variability in HPV AF for oropharyngeal cancer during the period from 1990 to 2012. Estimates were 19.6% for Europe, 39.2% for Central-South America and 17.5% for Asia (Table 2). Of note, the global HPV AF for oropharyngeal cancer reported by Castellsagué [17] may be a slight underestimate because of low representation from North America, which as noted above had one of the highest HPV AF for oropharyngeal cancers in the world ($\sim 70\%$) after 2004 [13,15,16,21*]. Similar geographic heterogeneity in HPV AF was noted by Plummer and colleagues [15] (24% for South Europe, 51% for US, 22% of India and 41% for Australia) (Table 2) as well as by Anantharaman and colleagues [22], who conducted centralized testing for HPV DNA and p16INK4a expression in a large series ($N = 533$) of oropharyngeal cancers.

Thus, the HPV AF will depend on changes in the rate ratio for HPV-positive and HPV-negative HNSCC over time. In the US, Australia, Canada, Japan, and Slovakia, a significant upward trend was observed only in incidence of HPV-related

oropharyngeal cancer, predominantly among men [9]. An alternative pattern of parallel increases in both HPV-related and unrelated HNSCC observed in several European countries (Denmark, Estonia, France, Germany, Netherland, United Kingdom) in men and/or women is consistent with ongoing regional increases in tobacco smoking and alcohol use [9,23,24]. These data underscore the dynamic nature of the HPV AF across populations.

Shown in Figure 1a and b, respectively, are the estimated age-standardized incidence rates and burden (total no. of cases) of oropharyngeal cancer in 2018, stratified by gender and geographic region. Of note, these estimates do not account for HPV AF, as these data are not available for 2018. Nevertheless, the figures demonstrate the consistently higher incidence and burden among men versus women in all regions and the marked heterogeneity in incidence by region. Oceania has the highest and Africa has the lowest incidence of oropharyngeal cancer in the world (Figure 1a). In contrast, Asia has the highest whereas Oceania has the lowest burden of oropharyngeal cancer (Figure 1b). Although the HPV AF is highest for oropharyngeal cancer, the absolute regional cancer burden (e.g. annual number of HPV-positive cases) is also a function of cancer incidence. For example, a region with a very high incidence rate for oral cavity cancer may nevertheless have a higher burden of HPV-positive oral cavity than oropharyngeal cancers, despite the lower HPV AF for the former.

Risk factors for head and neck squamous cell carcinoma (HNSCC) and geographic heterogeneity

The International Head and Neck Cancer Epidemiology Consortium (INHANCE) [25] has pooled individual data from over 26 000 HNSCC cases and 34 000 controls to investigate associations between demographic and

Table 2

Human Papillomavirus attributable fraction in oropharyngeal cancer by region, based on HPV DNA positivity and E6/E7 mRNA expression

Regions/Countries	Castellsagué <i>et al.</i> ^{a,b} (2016) Study period: 1990–2012	Plummer <i>et al.</i> ^{c,d} (2016) Study period: 2003–2007
Europe	19.6%	–
East Europe	–	50%
Central-Eastern Europe	49.3%	–
Southern Europe	9.2%	24%
Western Europe	18.1%	–
Northern Europe	50.0%	–
Northwest Europe	–	42%
America	39.2%	–
South America	53.7%	–
Central America	15.5%	–
North America	–	51%
Asia	17.5%	–
Eastern Asia	21.2%	–
China	–	23%
India	–	22%
Japan	–	46%
South Korea	–	60%
Oceania	–	–
Australia	–	41%

^a Castellsagué X, Alemany L, Quer M, Halc G, Quirós B, Tous S, Clavero O, Alòs L, Biegner T, Szafarowski T: **HPV involvement in head and neck cancers: comprehensive assessment of biomarkers in 3680 patients.** *J Natl Cancer Inst* 2016, **108**:djv403.

^b Centralized testing of 3680 archived head and neck cancers from 29 countries from 1990 to 2012.

^c Plummer M, de Martel C, Vignat J, Ferlay J, Bray F, Franceschi S: **Global burden of cancers attributable to infections in 2012: a synthetic analysis.** *Lancet Glob Health* 2016, **4**:e609–e616.

^d Pooled published case series of head and neck cancers from 2003 to 2007.

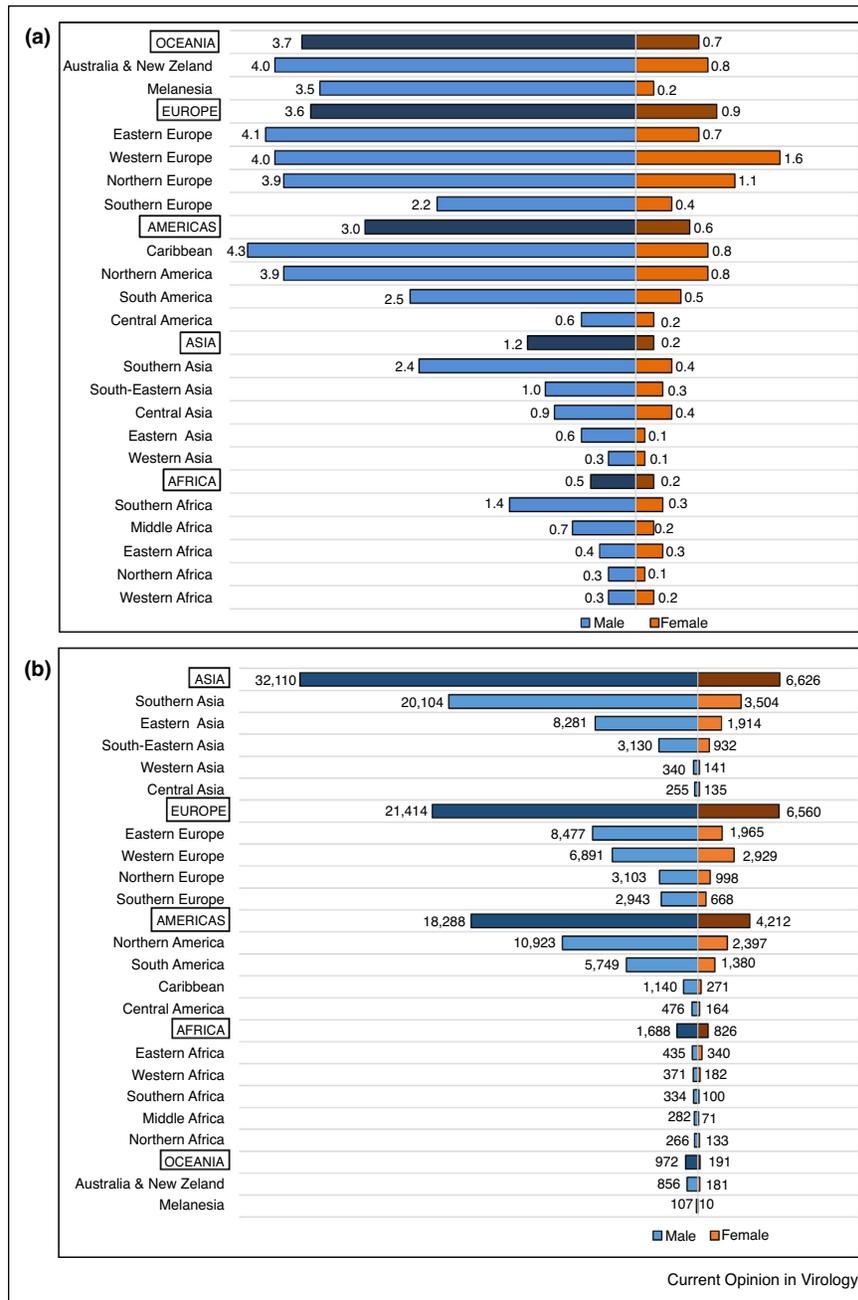
behavioral factors and odds of HNSCC. INHANCE case-control studies have demonstrated tobacco and alcohol use to be independent risk factors for HNSCC. Among never users of alcohol, a significant dose-response relationship was observed with increasing intensity, duration and pack-years of cigarette smoking and odds of HNSCC [8]. Among never users of tobacco, only high frequency alcohol consumption (three or more drinks per day) increased odds of HNSCC [8]. A greater than multiplicative joint effect of ever use of tobacco and alcohol was observed [7]. Heterogeneity by anatomic site was observed, with the joint effect of tobacco and alcohol significant for oral cavity and pharyngeal cancer, but not for laryngeal cancer. Moreover, heterogeneity by geographic region was observed, with the estimates of joint effect higher in Europe and Latin America than in North America. Effect of carcinogen exposure may also differ by race. In two US studies, modest racial heterogeneity was observed for the association of tobacco and alcohol use with HNSCC [26,27*]. Odd ratios for heavy alcohol and tobacco use were higher in Blacks compared to Whites, potentially explained by differences in tobacco and alcohol carcinogen metabolism or higher baseline risk of HNSCC (e.g. in the absence of tobacco and alcohol use) in Blacks versus Whites.

Use of areca/beetle nut with or without smokeless tobacco is prevalent in East and South Asia [3–5]. A multicenter

case-control study (2010–2015) in East Asia attributed 33% of oral cavity and 42.5% of oropharyngeal cancers to areca nut use [2]. In India, a meta-analysis (1933–2013) reported population AF of 4.5% for areca nut use alone and 49.5% for joint use with smokeless tobacco [28]. An INHANCE consortium study based on pooled data from European and American studies (1984–2007) reported that 72% of HNSCC overall and 64% of oral cavity, 71.5% of pharyngeal and 88.5% of laryngeal cancers are attributed to the combined use of tobacco and alcohol [7].

Case-control studies have associated sexual behavior with risk of HNSCC, predominantly of the oropharynx [6,12]. Dose response relationships between lifetime number of partners for oral or vaginal sex and odds of oropharyngeal cancer have been repeatedly demonstrated [6,12,29]. Lifetime number of sexual partners is, however, a surrogate for oral HPV infection. Temporal evidence linking oral HPV infection to risk of oropharyngeal cancer is provided by a case-control study nested in two US population-based cohorts. Oral HPV16 infection, detected an average of 4 years before the cancer diagnosis, increased risk (OR = 22.4) of oropharyngeal cancer [30]. HPV16 E6 seropositivity markedly increased risk (OR = 274) of oropharyngeal cancer in a case-control study nested within a European cohort [31]. Thus, both sexual behavior and oral HPV infection are now appreciated as risk factors for oropharyngeal cancers.

Figure 1



(a) and (b), respectively, illustrates estimates of age-standardized incidence rate and burden of oropharyngeal cancer for regions of the World in 2018, stratified by gender.

These figures show consistently higher incidence and burden of oropharyngeal cancer among men versus women in all regions as well as marked heterogeneity in incidence and burden by region.

This is redundant with information provided for each figure below.

(a) Age-standardized incidence of oropharyngeal cancer by gender and region of the World, 2018 estimates.

Estimates presented are age-standardized incidence rates per 100 000 people per year.

Includes ICD-10 codes C09-10: malignant neoplasm of tonsil and oropharynx.

Adapted from Bruni L, Albero G, Serrano B, Mena M, Gómez D, Muñoz J, Bosch FX, de Sanjosé S. ICO/IARC Information Centre on HPV and Cancer (HPV Information Centre). Human Papillomavirus and Related Diseases in the World. Summary Report 22 January 2019. Accessed [06 June 2019].

Original data source: Ferlay J, Ervik M, Lam F, Colombet M, Mery L, Piñeros M, Znaor A, Soerjomataram I, Bray F (2018). Global Cancer Observatory: Cancer Today. Lyon, France: International Agency for Research on Cancer.

(b) Number of cases of oropharyngeal cancer by sex and regions of the World, 2018 estimates.

Estimates presented are total number of cases for each region.

Heterogeneity and trends in risk factor behaviors over time

Given tobacco, areca nut, alcohol, and oral HPV infection are the principal risk factors for HNSCC, incidence rates for HNSCC will depend upon the prevalence, duration, and intensity of exposures in a population and their trends over calendar time. Overall, there has been a decrease in the worldwide prevalence of tobacco and alcohol use, but there is geographic variability in trends of these risk factors over calendar time. According to the latest WHO report [32], owing to public health efforts the global prevalence of tobacco smoking decreased from 26.9% in 2000 to 22.1% in 2010 and 20.2% in 2015. However, smoking rates are increasing in some regions (e.g. among men in the Middle East and several low-income countries). The tobacco smoking prevalence remains highest in Europe (37.3% in 2000, 32% in 2010, and 32% in 2015) and lowest in Africa (12.6% in 2000, 10.6% in 2010, and 10% in 2015). In contrast, smokeless tobacco prevalence remains highest in South-East Asia (22.1% in 2007–2017) and lowest in Europe (0.9% in 2007–2017).

With regard to heavy episodic alcohol drinking (defined as ≥ 60 g of pure alcohol \geq once per month), the global prevalence has decreased from 22.6% in 2000 to 20.5% in 2010 and 18.2% in 2016 [33]. This can be ascribed to considerable decrease in the prevalence of heavy episodic alcohol drinking in Africa, the Americas and Europe. These drinking rates remain highest in Europe (37.9% in 2000, 31.6 in 2010, and 26.4% in 2016) and lowest in the Middle East (0.8% in 2000, 0.6% in 2010 and 0.5% in 2016). These geographic differences in the trends of tobacco and alcohol use will affect the rate ratio of HPV-positive versus negative HNSCC, and consequently affect the geographic heterogeneity in estimates of HPV AF.

Somewhat dramatic changes in sexual norms occurred as a result of the 'sexual revolution' dating to the mid 1900's in North America and Europe [34,35]. Consequently, the prevalence of premarital sex and oral sex as well as median number of lifetime sexual partners increased in the US and England [36,37]. Nevertheless, there remain significant geographic differences in reported sexual behaviors, affected by cultural and religious norms and/or comfort in reporting sexual behaviors [29]. For example, in the control group within the INHANCE consortium from case-control studies conducted during the period 1984–2006, report of ever performance of oral sex varied dramatically across the studies, from 51 to 78% in the US to 6–9% in men in India and China [29].

This marked heterogeneity in sexual behavior likely contributes to differences in HPV AF by geographic region. HPV is spread in populations primarily by sexual contact. Risk of oral HPV infection increases with lifetime and recent number of oral sexual partners and differs by gender [38]. In the US during 2009–2010, the prevalence of oral HPV16 infection was five-fold higher in men versus women [39]. This higher prevalence in men arises from a higher number of lifetime sexual partners and a stronger increase in odds of infection per sexual partner in comparison to women [40]. Meta-analyses of the literature, although not population-based, also observed higher oral HPV prevalence in men [41], as well as geographic heterogeneity in prevalence [42,43]. This gender difference explains in part the higher risk of HPV-positive oropharyngeal cancer in men.

Thus, the underlying risk factors for HNSCC are influenced by gender and race and are considerably different across geographic regions. Moreover, these behaviors are undergoing dramatic shifts over calendar time.

Efficacy of HPV vaccines

HPV vaccines have demonstrated high efficacy ($\sim 100\%$ in women and 90% in men) in prevention of vaccine-type anogenital infections and associated lesions in both males and females in several randomized control trials [44–50]. The quadrivalent HPV vaccine (HPV 6, 11, 16 and 18) was first licensed by the US FDA in females ages 9–26 years in 2006, followed by bivalent vaccine (HPV 16 and 18) in 2007 and nonvalent vaccine (HPV 6, 11, 16, 18, 31, 33, 45, 52, and 58) in 2014 [51,52]. All three vaccines offer protection against HPV16 and 18, which account for 71.4% of HPV-positive cancers in women (cervix, vulva, vagina, and anal) and 82.3% of HPV-positive cancers in men (oropharynx, anus, and penis) [53]. In 2009, the WHO recommended routine HPV vaccination for females age 9–13 years before sexual debut [54], and in 2011 this recommendation was extended to females age 26 years. By the end of 2016, 82 countries (42%) introduced national HPV immunization program for girls, but only 13 high income countries introduced national HPV immunization programs for boys [55].

No clinical trials have evaluated the efficacy of HPV vaccines for the prevention of oral HPV infections that increase risk of HNSCC (e.g. HPV16). However, an estimate of 93.3% vaccine efficacy against oral HPV 16/18 infection was obtained in an anogenital prevention trial conducted among women aged 18–25 years in Costa Rica [56]. In this study, oral HPV 16/18 prevalence was

Includes ICD-10 codes C09-10: malignant neoplasm of tonsil and oropharynx.

Adapted from Bruni L, Albero G, Serrano B, Mena M, Gómez D, Muñoz J, Bosch FX, de Sanjosé S. ICO/IARC Information Centre on HPV and Cancer (HPV Information Centre). Human Papillomavirus and Related Diseases in the World. Summary Report 22 January 2019. Accessed [06 June 2019].

Original data source: Ferlay J, Ervik M, Lam F, Colombet M, Mery L, Piñeros M, Znaor A, Soerjomataram I, Bray F (2018). Global Cancer Observatory: Cancer Today. Lyon, France: International Agency for Research on Cancer.

compared in HPV-vaccinated versus unvaccinated women at a single time point 4 years after study entry [56]. In a US population-based study, oral HPV 16/18/6/11 infection prevalence was ~88% lower among young men and women (and 100% in men) who did versus did not report receipt of ≥ 1 HPV vaccine dose [57**]. These data support an approximate 90% efficacy of HPV vaccines in the prevention of HPV16/18 infections. However, these data are insufficient for regulatory approval or public health recommendations for routine vaccination of males or females for prevention of HNSCC.

As noted above, the burden of HPV-caused HNSCC is markedly higher in men than women. It is possible, however, that vaccination of women could result in reduced oral HPV infection prevalence in men. For example, the introduction of quadrivalent HPV vaccine into the national immunization program for females in Australia reduced the prevalence of penile vaccine-type HPV infection by 78% in unvaccinated males aged ≤ 25 years as compared to those aged > 25 years [58*]. Increasing vaccine coverage for young females is considered more cost effective in providing herd protection in both sexes in countries that already have moderate to high coverage rates ($> 75\%$) for females [59–62]. In contrast, in countries with low vaccine coverage rates ($< 50\%$) in females and with substantial burden of HPV-associated cancers in men, such as the US, increasing vaccine coverage for young males could prove cost-effective in providing herd protection in both sexes [60,62–65].

Conclusions

The HPV AF for HNSCC in any population is best estimated by direct testing of HPV E6/E7 mRNA expression at a given point in calendar time in a representative sampling of that population. Exposures to the predominant risk factor for both HPV-positive and negative HNSCC vary considerably across populations and are dramatically shifting over calendar time. As a consequence, rate ratios for HPV-positive versus negative cancers are also rapidly changing. Thus, an estimate of HPV AF measured at one point in calendar time may be inappropriate to apply to that same geographic region at another point in calendar time. Moving forward, HPV vaccine introduction and uptake in males and females and level of herd protection will be an additional dynamic factor that influences the HPV AF. These will manifest as strong birth cohort and period effects. Accurate estimates of HPV AF may inform policy decisions to scale up HPV immunization in women to provide herd protection in men in regions with existing high vaccine coverage and to increase coverage for men in regions with a high burden of HPV-related HNC and an existing low coverage for women.

Conflict of interest statement

Nothing declared.

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References and recommended reading

Papers of particular interest, published within the period of review, have been highlighted as:

- of special interest
 - of outstanding interest
1. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A: **Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries.** *CA Cancer J Clin* 2018, **68**:394-424.
 2. Lee YCA, Li S, Chen Y, Li Q, Chen CJ, Hsu WL, Lou PJ, Zhu C, Pan J, Shen H: **Tobacco smoking, alcohol drinking, betel quid chewing, and the risk of head and neck cancer in an East Asian population.** *Head Neck* 2019, **41**:92-102.
 3. World Health Organization, IARC Working Group on the Evaluation of Carcinogenic Risks to Humans, International Agency for Research on Cancer: **Betel-quid and areca-nut chewing and some areca-nut-derived nitrosamines.** *IARC* 2004, **85**.
 4. Merchant A, Husain SS, Hosain M, Fikree FF, Pitiphat W, Siddiqui AR, Hayder SJ, Haider SM, Ikram M, Chuang SK: **Paan without tobacco: an independent risk factor for oral cancer.** *Int J Cancer* 2000, **86**:128-131.
 5. Merchant AT, Pitiphat W: **Total, direct, and indirect effects of paan on oral cancer.** *Cancer Causes Control* 2015, **26**:487-491.
 6. Gillison ML, D'souza G, Westra W, Sugar E, Xiao W, Begum S, Viscidi R: **Distinct risk factor profiles for human papillomavirus type 16-positive and human papillomavirus type 16-negative head and neck cancers.** *J Natl Cancer Inst* 2008, **100**:407-420.
 7. Hashibe M, Brennan P, Chuang S-C, Boccia S, Castellsague X, Chen C, Curado MP, Dal Maso L, Daudt AW, Fabianova E: **Interaction between tobacco and alcohol use and the risk of head and neck cancer: pooled analysis in the International Head and Neck Cancer Epidemiology Consortium.** *Cancer Epidemiol Biomarkers Prev Biomark* 2009, **18**:541-550.
 8. Hashibe M, Brennan P, Benhamou S, Castellsague X, Chen C, Curado MP, Maso LD, Daudt AW, Fabianova E, Wunsch-Filho V: **Alcohol drinking in never users of tobacco, cigarette smoking in never drinkers, and the risk of head and neck cancer: pooled analysis in the International Head and Neck Cancer Epidemiology Consortium.** *J Natl Cancer Inst* 2007, **99**:777-789.
 9. Chaturvedi AK, Anderson WF, Lortet-Tieulent J, Curado MP, Ferlay J, Franceschi S, Rosenberg PS, Bray F, Gillison ML: **Worldwide trends in incidence rates for oral cavity and oropharyngeal cancers.** *J Clin Oncol* 2013, **31**:4550.
 10. IARC Working Group on the Evaluation of Carcinogenic Risks to Humans Meeting, World Health Organization, International Agency for Research on Cancer: **Human Papillomaviruses.** World Health Organization; 2007.
 11. Gillison ML, Koch WM, Capone RB, Spafford M, Westra WH, Wu L, Zahurak ML, Daniel RW, Viglione M, Symer DE: **Evidence for a causal association between human papillomavirus and a subset of head and neck cancers.** *J Natl Cancer Inst* 2000, **92**:709-720.
 12. D'souza G, Kreimer AR, Viscidi R, Pawlita M, Fakhry C, Koch WM, Westra WH, Gillison ML: **Case-control study of human papillomavirus and oropharyngeal cancer.** *N Engl J Med* 2007, **356**:1944-1956.
 13. Chaturvedi AK, Engels EA, Pfeiffer RM, Hernandez BY, Xiao W, Kim E, Jiang B, Goodman MT, Sibug-Saber M, Cozen W: **Human papillomavirus and rising oropharyngeal cancer incidence in the United States.** *J Clin Oncol* 2011, **29**:4294.
 14. Chaturvedi AK, Engels EA, Anderson WF, Gillison ML: **Incidence trends for human papillomavirus-related and -unrelated oral squamous cell carcinomas in the United States.** *J Clin Oncol* 2008, **26**:612-619.

15. Plummer M, de Martel C, Vignat J, Ferlay J, Bray F, Franceschi S: **Global burden of cancers attributable to infections in 2012: a synthetic analysis.** *Lancet Glob Health* 2016, **4**:e609–e616.
16. Jordan RC, Lingen MW, Perez-Ordóñez B, He X, Pickard R, Koluder M, Jiang B, Wakely P, Xiao W, Gillison ML: **Validation of methods for oropharyngeal cancer HPV status determination in United States cooperative group trials.** *Am J Surg Pathol* 2012, **36**:945.
17. Castellsagué X, Alemany L, Quer M, Halc G, Quirós B, Tous S, Clavero O, Alòs L, Biegner T, Szafarowski T: **HPV involvement in head and neck cancers: comprehensive assessment of biomarkers in 3680 patients.** *J Natl Cancer Inst* 2016, **108**:djv403.
18. Ndiaye C, Mena M, Alemany L, Arbyn M, Castellsagué X, Laporte L, Bosch FX, de Sanjosé S, Trottier H: **HPV DNA, E6/E7 mRNA, and p16INK4a detection in head and neck cancers: a systematic review and meta-analysis.** *Lancet Oncol* 2014, **15**:1319–1331.
19. Gillison ML, Chaturvedi AK, Anderson WF, Fakhry C: **Epidemiology of human papillomavirus-positive head and neck squamous cell carcinoma.** *J Clin Oncol* 2015, **33**:3235.
20. Tota JE, Best AF, Zumsteg ZS, Gillison ML, Rosenberg PS, Chaturvedi AK: **Evolution of the oropharynx cancer epidemic in the united states: moderation of increasing incidence in younger individuals and shift in the burden to older individuals.** *J Clin Oncol* 2019, **37**:1530–1546 JCO. 19.00370
- By use of a US population-based registry, rising rates for HPV-positive oropharyngeal cancer were observed predominantly among men born after 1935–1940: a strong birth cohort effect. Importantly, as this birth cohort ages, the burden of HPV-positive oropharyngeal cancer in the US is shifting from younger to older men (age ≥ 65 years).
21. Forman D, de Martel C, Lacey CJ, Soerjomataram I, Lortet-Tieulent J, Bruni L, Vignat J, Ferlay J, Bray F, Plummer M: **Global burden of human papillomavirus and related diseases.** *Vaccine* 2012, **30**:F12–F23
- This study estimated HPV AF from case series that tested for HPV in anogenital and head and neck cancer, and from incidence data obtained from GLOBOCAN 2012 and Cancer in Five Continents database 2003–2007. They reported that HPV16 and 18 account for 71.4% of HPV-positive cancers in women (cervix, vulva, vagina, and anal) and 82.3% of HPV-positive cancers in men (oropharynx, anus, and penis).
22. Anantharaman D, Abedi-Ardekani B, Beachler DC, Gheit T, Olshan AF, Wisniewski K, Wunsch-Filho V, Toporcov TN, Tajara EH, Levi JE: **Geographic heterogeneity in the prevalence of human papillomavirus in head and neck cancer.** *Int J Cancer* 2017, **140**:1968–1975.
23. Jansen L, Buttman-Schweiger N, Listl S, Rensing M, Hollecsek B, Katalinic A, Luttmann S, Kraywinkel K, Brenner H, Group GCSW: **Differences in incidence and survival of oral cavity and pharyngeal cancers between Germany and the United States depend on the HPV-association of the cancer site.** *Oral Oncol* 2018, **76**:8–15.
24. Schache AG, Powell NG, Cuschieri KS, Robinson M, Leary S, Mehanna H, Rapozo D, Long A, Cubie H, Junor E: **HPV-related oropharynx cancer in the United Kingdom: an evolution in the understanding of disease etiology.** *Cancer Res* 2016, **76**:6598–6606.
25. Conway DI, Hashibe M, Boffetta P, Wunsch-Filho V, Muscat J, La Vecchia C, Winn DM: **Enhancing epidemiologic research on head and neck cancer: INHANCE-The international head and neck cancer epidemiology consortium.** *Oral Oncol* 2009, **45**:743–746.
26. Stingone JA, Funkhouser WK, Weissler MC, Bell ME, Olshan AF: **Racial differences in the relationship between tobacco, alcohol, and squamous cell carcinoma of the head and neck.** *Cancer Causes Control* 2013, **24**:649–664.
27. Voltzke KJ, Lee Y-CA, Zhang Z-F, Zevallos JP, Yu G-P, Winn DM, Vaughan TL, Sturgis EM, Smith E, Schwartz SM: **Racial differences in the relationship between tobacco, alcohol, and the risk of head and neck cancer: pooled analysis of US studies in the INHANCE Consortium.** *Cancer Causes Control* 2018, **29**:619–630
- In this INHANCE consortium study based on pooled data from US studies, modest racial heterogeneity was observed for the association of tobacco and alcohol use with HNSCC. Odd ratios for heavy alcohol and tobacco use were higher in Blacks compared to Whites, potentially explained by racial differences in tobacco and alcohol carcinogen metabolism.
28. Guha N, Warnakulasuriya S, Vlaanderen J, Straif K: **Betel quid chewing and the risk of oral and oropharyngeal cancers: a meta-analysis with implications for cancer control.** *Int J Cancer* 2014, **135**:1433–1443.
29. Heck JE, Berthiller J, Vaccarella S, Winn DM, Smith EM, Shan'gina O, Schwartz SM, Purdue MP, Pilarska A, Eluf-Neto J: **Sexual behaviours and the risk of head and neck cancers: a pooled analysis in the International Head and Neck Cancer Epidemiology (INHANCE) consortium.** *Int J Epidemiol* 2009, **39**:166–181.
30. Agalliu I, Gapstur S, Chen Z, Wang T, Anderson RL, Teras L, Kreimer AR, Hayes RB, Freedman ND, Burk RD: **Associations of oral α -, β -, and γ -human papillomavirus types with risk of incident head and neck cancer.** *JAMA Oncol* 2016, **2**:599–606.
31. Kreimer AR, Johansson M, Waterboer T, Kaaks R, Chang-Claude J, Drogen D, Tjønneland A, Overvad K, Quirós JR, González CA: **Evaluation of human papillomavirus antibodies and risk of subsequent head and neck cancer.** *J Clin Oncol* 2013, **31**:2708.
32. *WHO global report on trends in prevalence of tobacco smoking 2000–2025.* end 2. Geneva: World Health Organization; 2018.
33. *Global status report on alcohol and health 2018.* Geneva: World Health Organization; 2018. Licence: CC BY-NC-SA 3.0 IGO.
34. Smith TW: **The polls—a report the sexual-revolution.** *Public Opin Q* 1990, **54**:415–435.
35. Singh BK: **Trends in attitudes toward premarital sexual relations.** *J Marriage Fam* 1980:387–393.
36. Liu G, Hariri S, Bradley H, Gottlieb SL, Leichter JS, Markowitz LE: **Trends and patterns of sexual behaviors among adolescents and adults aged 14 to 59 years, United States.** *Sex Transm Dis* 2015, **42**:20–26.
37. Lewis R, Tanton C, Mercer CH, Mitchell KR, Palmer M, Maccowall W, Wellings K: **Heterosexual practices among young people in Britain: evidence from three national surveys of sexual attitudes and lifestyles.** *J Adolesc Health* 2017, **61**:694–702.
38. Beachler DC, Sugar EA, Margolick JB, Weber KM, Strickler HD, Wiley DJ, Cranston RD, Burk RD, Minkoff H, Reddy S: **Risk factors for acquisition and clearance of oral human papillomavirus infection among HIV-infected and HIV-uninfected adults.** *Am J Epidemiol* 2014, **181**:40–53.
39. Gillison ML, Broutian T, Pickard RK, Tong Z-Y, Xiao W, Kahle L, Graubard BI, Chaturvedi AK: **Prevalence of oral HPV infection in the United States, 2009–2010.** *JAMA* 2012, **307**:693–703.
40. Chaturvedi AK, Graubard BI, Broutian T, Pickard RK, Tong Z-Y, Xiao W, Kahle L, Gillison ML: **NHANES 2009–2012 findings: association of sexual behaviors with higher prevalence of oral oncogenic human papillomavirus infections in US men.** *Cancer Res* 2015, **75**:2468–2477.
41. Tam S, Fu S, Xu L, Krause KJ, Lairson DR, Miao H, Sturgis EM, Dahlstrom KR: **The epidemiology of oral human papillomavirus infection in healthy populations: a systematic review and meta-analysis.** *Oral Oncol* 2018, **82**:91–99.
42. Smith JS, Melendy A, Rana RK, Pimenta JM: **Age-specific prevalence of infection with human papillomavirus in females: a global review.** *J Adolesc Health* 2008, **43**:S5.e1–S5.e62.
43. Smith JS, Gilbert PA, Melendy A, Rana RK, Pimenta JM: **Age-specific prevalence of human papillomavirus infection in males: a global review.** *J Adolesc Health* 2011, **48**:540–552.
44. Goldstone SE, Jessen H, Palefsky JM, Giuliano AR, Moreira ED Jr, Vardas E, Aranda C, Hillman RJ, Ferris DG, Coutlee F: **Quadrivalent HPV vaccine efficacy against disease related to vaccine and non-vaccine HPV types in males.** *Vaccine* 2013, **31**:3849–3855.
45. Joura EA, Giuliano AR, Iversen O-E, Bouchard C, Mao C, Mehlsen J, Moreira ED Jr, Ngan Y, Petersen LK, Lazcano-Ponce E: **A 9-valent HPV vaccine against infection and intraepithelial neoplasia in women.** *N Engl J Med* 2015, **372**:711–723.

46. Giuliano AR, Palefsky JM, Goldstone S, Moreira Jr ED, Penny ME, Aranda C, Vardas E, Moi H, Jessen H, Hillman R: **Efficacy of quadrivalent HPV vaccine against HPV infection and disease in males.** *N Engl J Med* 2011, **364**:401-411.
47. Paavonen J, Jenkins D, Bosch FX, Naud P, Salmerón J, Wheeler CM, Chow S-N, Apter DL, Kitchener HC, Castellsague X: **Efficacy of a prophylactic adjuvanted bivalent L1 virus-like-particle vaccine against infection with human papillomavirus types 16 and 18 in young women: an interim analysis of a phase III double-blind, randomised controlled trial.** *Lancet* 2007, **369**:2161-2170.
48. Palefsky JM, Giuliano AR, Goldstone S, Moreira ED Jr, Aranda C, Jessen H, Hillman R, Ferris D, Coutlee F, Stoler MH: **HPV vaccine against anal HPV infection and anal intraepithelial neoplasia.** *N Engl J Med* 2011, **365**:1576-1585.
49. Garland SM, Hernandez-Avila M, Wheeler CM, Perez G, Harper DM, Leodolter S, Tang GW, Ferris DG, Steben M, Bryan J: **Quadrivalent vaccine against human papillomavirus to prevent anogenital diseases.** *N Engl J Med* 2007, **356**:1928-1943.
50. Future II Study Group: **Quadrivalent vaccine against human papillomavirus to prevent high-grade cervical lesions.** *N Engl J Med* 2007, **356**:1915-1927.
51. Centers for Disease Control and Prevention: **Recommendations on the use of quadrivalent human papillomavirus vaccine in males—Advisory Committee on Immunization Practices (ACIP).** *MMWR Morb Mortal Wkly Rep* 2011, **60**:1705.
52. Petrosky E, Bocchini JA Jr, Hariri S, Chesson H, Curtis CR, Saraiya M, Unger ER, Markowitz LE: **Use of 9-valent human papillomavirus (HPV) vaccine: updated HPV vaccination recommendations of the advisory committee on immunization practices.** *MMWR Morb Mortal Wkly Rep* 2015, **64**:300.
53. de Martel C, Plummer M, Vignat J, Franceschi S: **Worldwide burden of cancer attributable to HPV by site, country and HPV type.** *Int J Cancer* 2017, **141**:664-670.
54. World Health Organization: **WHO position on HPV vaccines.** *Vaccine* 2009, **27**:7236-7237.
55. Bruni L, Diaz M, Barrionuevo-Rosas L, Herrero R, Bray F, Bosch FX, de Sanjosé S, Castellsagué X: **Global estimates of human papillomavirus vaccination coverage by region and income level: a pooled analysis.** *Lancet Glob Health* 2016, **4**:e453-e463.
56. Herrero R, Quint W, Hildesheim A, Gonzalez P, Struijk L, Katki HA, Porras C, Schiffman M, Rodriguez AC, Solomon D: **Reduced prevalence of oral human papillomavirus (HPV) 4 years after bivalent HPV vaccination in a randomized clinical trial in Costa Rica.** *PLoS One* 2013, **8**:e68329.
57. Chaturvedi AK, Graubard BI, Broutian T, Pickard RK, Tong Z-Y, Xiao W, Kahle L, Gillison ML: **Effect of prophylactic human papillomavirus (HPV) vaccination on oral HPV infections among young adults in the United States.** *J Clin Oncol* 2018, **36**:262
- This is the first population-based study to assess the effect of HPV vaccination on the prevalence of oral HPV infection. Oral HPV 16/18/6/11 infection prevalence was ~88% lower among young men and women (and 100% in men) who did versus did not report receipt of ≥ 1 HPV vaccine dose.
58. Machalek DA, Chow EP, Garland SM, Wigan R, Cornall AM, Fairley CK, Kaldor JM, Hocking JS, Williams H, McNulty A: **Human papillomavirus prevalence in unvaccinated heterosexual men after a national female vaccination program.** *J Infect Dis* 2017, **215**:202-208
- This was the first study to show population-level herd immunity in unvaccinated heterosexual men due to female HPV vaccination program. The introduction of quadrivalent HPV vaccine into the national immunization program for females in Australia reduced the prevalence of penile vaccine-type HPV infection by 78% in unvaccinated males aged ≤ 25 years (3%) as compared to those aged ≥ 25 years (14%).
59. Donovan B, Franklin N, Guy R, Grulich AE, Regan DG, Ali H, Wand H, Fairley CK: **Quadrivalent human papillomavirus vaccination and trends in genital warts in Australia: analysis of national sentinel surveillance data.** *Lancet Infect Dis* 2011, **11**:39-44.
60. Ng SS, Hutubessy R, Chaiyakunapruk N: **Systematic review of cost-effectiveness studies of human papillomavirus (HPV) vaccination: 9-valent vaccine, gender-neutral and multiple age cohort vaccination.** *Vaccine* 2018, **36**:2529-2544.
61. Smith MA, Lew J-B, Walker RJ, Brotherton JM, Nickson C, Canfell K: **The predicted impact of HPV vaccination on male infections and male HPV-related cancers in Australia.** *Vaccine* 2011, **29**:9112-9122.
62. Burger EA, Sy S, Nygård M, Kristiansen IS, Kim JJ: **Prevention of HPV-related cancers in Norway: cost-effectiveness of expanding the HPV vaccination program to include pre-adolescent boys.** *PLoS One* 2014, **9**:e89974.
63. Crosignani P, De Stefani A, Fara GM, Isidori AM, Lenzi A, Liverani CA, Lombardi A, Mennini FS, Pecorelli S, Peracino AP: **Towards the eradication of HPV infection through universal specific vaccination.** *BMC Public Health* 2013, **13**:642.
64. Giuliano AR, Salmon D: **The case for a gender-neutral (universal) human papillomavirus vaccination policy in the United States: point.** *Cancer Epidemiol Prev Biomark* 2008, **17**:805-808.
65. Marty R, Roze S, Bresse X, Largeron N, Smith-Palmer J: **Estimating the clinical benefits of vaccinating boys and girls against HPV-related diseases in Europe.** *BMC Cancer* 2013, **13**:10.