

## Short Communication

## Prevalence of Human Papillomavirus in Cancer of the Oropharynx by Gender

Jean-Damien Combes, Alyce A. Chen, and Silvia Franceschi

## Abstract

Oropharyngeal cancer (OPC) is more frequent in men than women mainly due to the heavier and longer duration of smoking in men. Human papillomavirus (HPV) has a role in the rising incidence of OPC in the United States and other high-income countries. To determine whether there is a difference in the proportion of HPV-attributable OPC between men and women, we systematically retrieved HPV prevalence data from 63 studies reporting separately on OPC by gender. The male/female (M/F) ratios of HPV prevalence in OPC across different countries and the corresponding M/F ratios of cumulative lung cancer risk (a proxy for smoking) were compared. The United States had the highest M/F ratios of HPV prevalence in OPC (1.5). The lowest M/F ratios ( $\leq 0.7$ ) were found in Asia and some European countries (e.g., France). The countries in which the M/F ratio of HPV prevalence in OPC was  $\geq 1.0$  had the most similar lung cancer risks for men and women. When HPV prevalence data were applied to age-standardized OPC incidence rates in the United States, Australia, the United Kingdom, and France, the M/F ratio for the HPV-positive OPC incidence rates was rather stable (around 4) in all countries. In contrast, the M/F ratio for the HPV-negative OPC incidence rates reached 10.2 in France versus  $< 3$  elsewhere. We showed that HPV prevalence in OPC differs by gender and country mainly as a consequence of the vast international variation in male smoking habits. Nevertheless, HPV-positive OPC may affect men more heavily than women in different populations for reasons that are unclear. *Cancer Epidemiol Biomarkers Prev*; 23(12); 2954–8. ©2014 AACR.

## Introduction

The fraction of cancer throughout the world that is attributed to human papillomavirus (HPV) is much larger in women (9.4%) than men (0.6%) due to the predominant influence of cervical cancer in developing countries (1). A still ill-defined fraction of oropharyngeal cancer (OPC) is included in these estimates, and this fraction is larger in North America, Northern Europe, Japan, and Australia than in the rest of the world (2). Globally, OPC is much more frequent in men (approximately 68,000 cases) than women (18,000; ref. 1), and the gender difference is mainly explained by the heavier and longer duration of tobacco smoking and the heavier alcohol drinking in men (3). The epidemiologic evidence strongly suggests a role for HPV in the rising incidence of OPC in the United States (4, 5) and other high-income countries (6).

Estimates of the fraction of OPC attributable to HPV infection have been so far assumed to be the same in men

and women (1). To elucidate whether there is a gender difference in HPV prevalence in OPC (a proxy for HPV-attributable fraction), we systematically explored the findings for HPV biomarkers in OPC specimens from men and women and compared the male/female (M/F) ratios of HPV prevalence across different countries and world regions. We also used gender differences in country-specific cumulative lung cancer risk to correlate the HPV findings with smoking habits. Finally, we attempted to evaluate the implications of the differences in HPV prevalence and smoking on incidence rates of estimated HPV-positive OPC and HPV-negative OPC in selected countries.

## Materials and Methods

The NIH's NCBI PubMed search engine was used to retrieve citations published between January 2000 and November 2013 using the MeSH terms "oropharyngeal neoplasms" or "head and neck neoplasms" in combination with "papillomaviridae" or "dna viruses." Additional suitable studies were identified in the reference lists of selected articles or in previous reviews. We defined OPC to include cancer in the base of the tongue (ICD-10 code C01), lingual tonsil (C02.4), soft palate (C05.1), uvula (C05.2), tonsil (C09.0-C09.9), oropharynx (C10.0-C10.9), and Waldeyer ring (C14.2). We selected OPC publications written in English that showed the prevalence of HPV markers separately for men and women and included information on at least one of three HPV biomarkers, that is, HPV DNA

International Agency for Research on Cancer, Lyon, France.

**Note:** Supplementary data for this article are available at Cancer Epidemiology, Biomarkers & Prevention Online (<http://cebp.aacrjournals.org/>).

**Corresponding Author:** Silvia Franceschi, International Agency for Research on Cancer, 150 cours Albert Thomas, 69372 Lyon cedex 08, France. Phone: 33-47-273-8402; Fax: 33-47-273-8345; E-mail: franceschi@iarc.fr

doi: 10.1158/1055-9965.EPI-14-0580

©2014 American Association for Cancer Research.

using PCR (hereafter referred to as PCR), HPV DNA using *in situ* hybridization (ISH), or HPV E6/E7 mRNA using either reverse transcription PCR or ISH. Because of limited data available, findings from mRNA and ISH were combined (hereafter referred together as mRNA/ISH). Countries were included if at least 100 individuals, of which at least 20 were women, were tested for HPV. A few studies that did not distinguish OPC from other head and neck cancer sites were included if OPC accounted for more than 80% of the total. PCR and mRNA/ISH detection methods were, in most instances, restricted to high-risk HPV types. However, some studies restricted detection to HPV16 or included low-risk HPV types. Key information on the 63 selected studies is given in Supplementary Table S1.

Countries were shown separately and, when possible grouped into regions: North America, Australia, Europe, and Asia. Prevalence of each HPV marker is given as the percentage of individuals with OPC who tested positive for the presence of HPV. The M/F ratios of HPV prevalence in OPC and the corresponding 95% confidence intervals (CI) were computed using a binomial regression model with a log link adjusted for study. M/F ratios from different regions were not combined because of the substantial heterogeneity.

As a proxy for the differences in tobacco smoking habits between men and women in the last decades, the country-

and sex-specific cumulative risk [1-exp (-cumulative incidence rate)] of lung cancer in the age range 0 to 69 years was obtained (7). Taiwan was not included because of the high prevalence of betel chewing that is associated with OPC but not lung cancer in this country (8). The correlation between the logarithmically transformed M/F ratios of cumulative lung cancer risk and M/F ratios of HPV prevalence in OPC (by PCR) was assessed using the Pearson correlation coefficient.

Finally, country- and sex-specific PCR-based HPV prevalence was applied to the corresponding world age-standardized incidence rates of OPC in four countries for which: (i) more than 200 OPC cases were tested for HPV by PCR (Table 1); and (ii) incidence rates using the same definition of OPC as described above have been published (6). The Netherlands was omitted from this analysis due to the initial screening of cases for overexpression of p16-protein before PCR testing.

## Results

Information on HPV PCR detection in OPC was available for North America (16 studies), Australia (one study), Europe (27 studies), and Asia (six studies). In men, HPV prevalence in OPC was highest in North America (65.8%) and lowest in Asia (28.9%, Table 1). In contrast, HPV prevalence in OPC in women was highest

**Table 1.** HPV prevalence in OPC by gender and corresponding M/F ratios by country, region, and the HPV detection method

| Country or region            | PCR          |                    |            |                    |                      | mRNA/ISH     |                    |            |                    |                      |
|------------------------------|--------------|--------------------|------------|--------------------|----------------------|--------------|--------------------|------------|--------------------|----------------------|
|                              | Male         |                    | Female     |                    |                      | Male         |                    | Female     |                    |                      |
|                              | OPC (N)      | HPV prevalence (%) | OPC (N)    | HPV prevalence (%) | M/F ratio (95% CI)   | OPC (N)      | HPV prevalence (%) | OPC (N)    | HPV prevalence (%) | M/F ratio (95% CI)   |
| Canada                       | 125          | 60.0               | 35         | 45.7               | 1.3 (0.9–1.9)        | 82           | 67.1               | 29         | 62.1               | 1.1 (0.8–1.5)        |
| United States                | 1,322        | 66.3               | 332        | 45.2               | 1.5 (1.3–1.7)        | 1,421        | 61.5               | 301        | 39.9               | 1.5 (1.3–1.8)        |
| <b>North America</b>         | <b>1,447</b> | <b>65.8</b>        | <b>367</b> | <b>45.2</b>        | <b>1.5 (1.3–1.6)</b> | <b>1,503</b> | <b>61.8</b>        | <b>330</b> | <b>41.8</b>        | <b>1.5 (1.3–1.7)</b> |
| Australia                    | 375          | 49.3               | 114        | 39.5               | 1.3 (1.0–1.6)        | —            | —                  | —          | —                  | — (—)                |
| The Netherlands <sup>a</sup> | 699          | 21.8               | 350        | 14.9               | 1.5 (1.1–1.9)        | —            | —                  | —          | —                  | — (—)                |
| Norway                       | 99           | 56.6               | 38         | 39.5               | 1.4 (0.9–2.2)        | —            | —                  | —          | —                  | — (—)                |
| United Kingdom               | 242          | 60.3               | 79         | 57.0               | 1.1 (0.9–1.3)        | 392          | 52.0               | 136        | 44.1               | 1.2 (1.0–1.5)        |
| Sweden                       | 426          | 59.4               | 161        | 57.8               | 1.0 (0.9–1.2)        | —            | —                  | —          | —                  | — (—)                |
| Czech Republic               | 141          | 56.0               | 29         | 65.6               | 0.9 (0.6–1.2)        | —            | —                  | —          | —                  | — (—)                |
| France                       | 508          | 40.6               | 135        | 61.5               | 0.7 (0.6–0.9)        | —            | —                  | —          | —                  | — (—)                |
| Germany                      | 550          | 36.0               | 174        | 54.0               | 0.7 (0.6–0.8)        | 330          | 20.0               | 109        | 32.1               | 0.6 (0.4–0.9)        |
| Italy                        | 89           | 21.4               | 30         | 30.0               | 0.8 (0.4–1.5)        | —            | —                  | —          | —                  | — (—)                |
| <b>Europe</b>                | <b>2,754</b> | <b>40.3</b>        | <b>996</b> | <b>41.2</b>        | <b>1.0 (0.9–1.1)</b> | <b>722</b>   | <b>37.4</b>        | <b>245</b> | <b>38.8</b>        | <b>1.0 (0.9–1.2)</b> |
| Korea                        | —            | —                  | —          | —                  | — (—)                | 134          | 51.5               | 21         | 38.1               | 1.1 (0.7–1.8)        |
| Japan                        | 159          | 33.3               | 33         | 51.5               | 0.7 (0.4–1.0)        | —            | —                  | —          | —                  | — (—)                |
| Taiwan                       | 340          | 26.8               | 32         | 71.9               | 0.4 (0.3–0.6)        | —            | —                  | —          | —                  | — (—)                |
| <b>Asia</b>                  | <b>499</b>   | <b>28.9</b>        | <b>65</b>  | <b>61.5</b>        | <b>0.5 (0.4–0.6)</b> | <b>134</b>   | <b>51.5</b>        | <b>21</b>  | <b>38.1</b>        | <b>1.1 (0.7–1.8)</b> |

<sup>a</sup>HPV testing was restricted to p16-positive OPC. HPV prevalence cannot be compared with other countries, although the M/F ratio should be consistent.

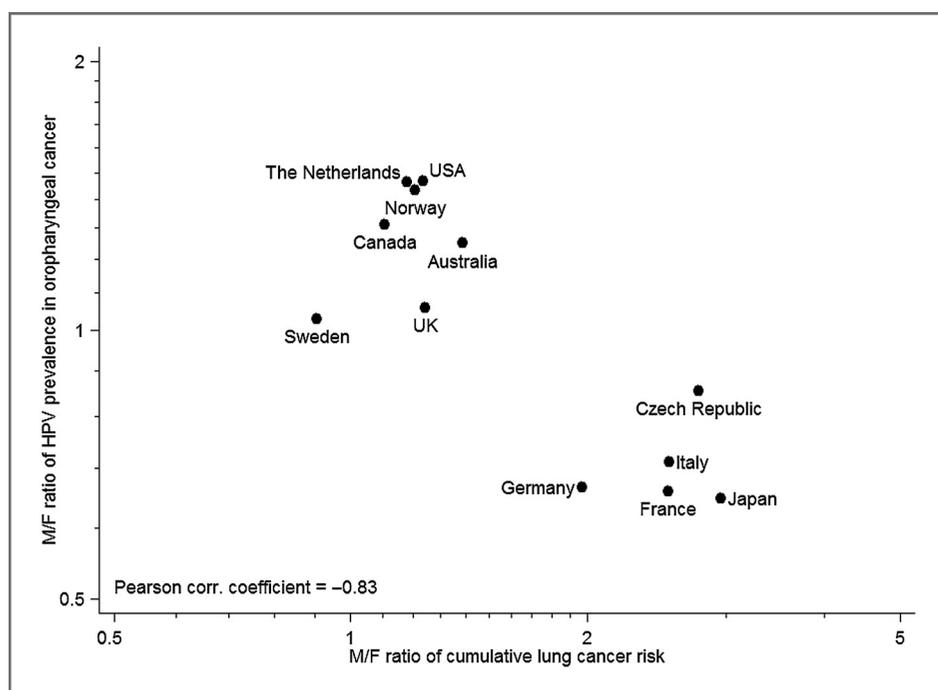


Figure 1. International correlation between male (M)/female (F) ratios of HPV prevalence in OPC and cumulative lung cancer risk for ages 0 to 69 years.

in Asia (61.5%). North America had the highest M/F ratio of HPV prevalence (1.5; 95% CI, 1.3–1.6), followed by Australia (1.3; 95% CI, 1.0–1.6), Europe (1.0; 95% CI, 0.9–1.1), and Asia (0.5; 95% CI, 0.4–0.6, Table 1). Among the countries for which HPV PCR data were available for more than 200 OPC cases, the highest M/F ratios were observed in the United States and the Netherlands (1.5 for both countries) and the lowest in France, Germany (0.7 for both countries), and Taiwan (0.4). Information on mRNA/ISH was available from North America (12 studies), Europe (9 studies), and Asia (2 studies). When available from the same country, the M/F ratios of HPV prevalence in OPC by mRNA/ISH were consistent with PCR findings (Table 1).

A moderate negative correlation was found between country-specific M/F ratios of cumulative lung cancer risk and the corresponding M/F ratios of HPV prevalence in OPC (Pearson correlation coefficient =  $-0.83$ , Fig. 1). Countries clustered in two groups: countries with M/F ratios for HPV prevalence in OPC  $\geq 1.0$  and relatively low ( $\leq 1.5$ ) M/F ratios for cumulative lung cancer risk and countries with M/F ratios for HPV prevalence  $< 1.0$  and M/F ratios for cumulative lung cancer risk  $\geq 2.0$ .

Figure 2 shows the estimated incidence rates of HPV-positive, HPV-negative, and all OPC in the United Kingdom, Australia, the United States, and France. The overall OPC incidence rate was consistently higher in men than in women and varied much more in men (from 4.7 to 17.8, or 3.8 times) than in women (from 1.5 to 2.7, or 1.8 times). The M/F ratio for incidence rates of HPV-positive OPC varied relatively little across the four countries (from 3.3 in the United Kingdom to 4.9 in the United States). In contrast, the M/F ratio of incidence rates for HPV-negative OPC

was much higher in France (10.2) than in the other three countries where the ratios ranged from 2.0 to 2.9. This ratio is consistent, although larger, with the high M/F ratio for cumulative lung cancer risk in France (3.4, Fig. 1).

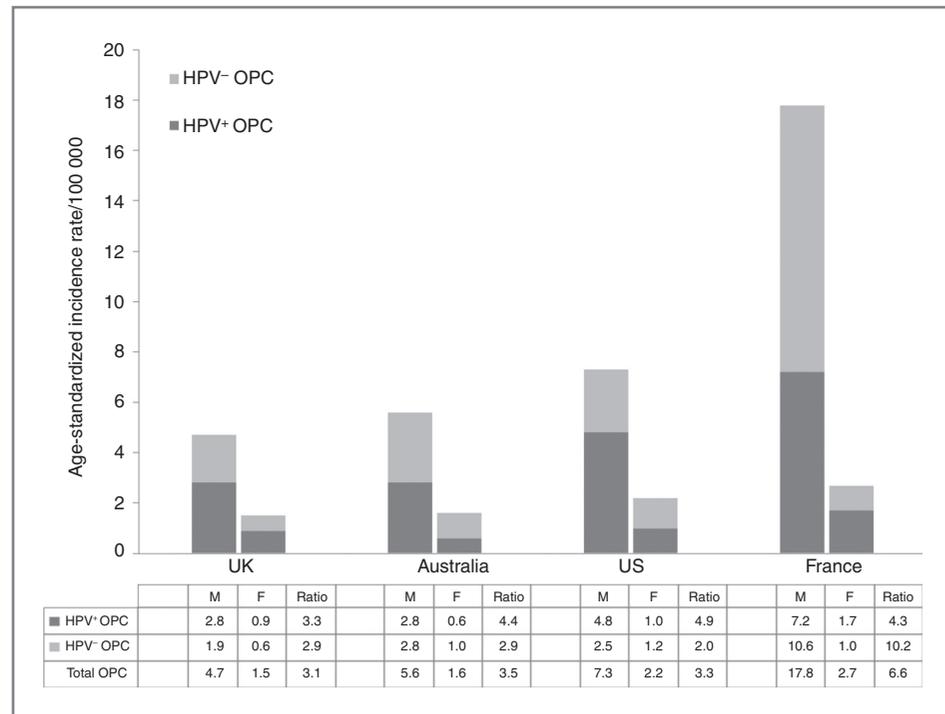
## Discussion

Our review shows that HPV prevalence in OPC was higher in men than in women in North America and Australia, but the opposite was true in Asia and some European countries, like France, in which the excess in the cumulative lung cancer risk (a proxy of smoking) in men versus women was among the highest. Conversely, the countries in which the M/F ratio of HPV prevalence in OPC was  $\geq 1.0$  had the most similar lung cancer risks for men and women.

When country-specific HPV prevalence from our meta-analysis was applied to previously reported OPC incidence rates, the M/F ratio for HPV-positive OPC was rather stable (around 4) in the United Kingdom, Australia, the United States, and France; whereas the M/F ratio for HPV-negative OPC was particularly elevated in France (10.2). Our review suggests, therefore, that HPV prevalence in OPC differs by gender and country but mainly as a consequence of the vast international variations in the prevalence of smoking in men. Nevertheless, HPV-positive OPC may affect men more heavily than women in different populations.

A gender difference in the prevalence of HPV in OPC is puzzling because HPV infection is predominantly transmitted through heterosexual transmission, and the infection should, therefore, involve both genders equally. However, it was hypothesized that men have a higher

**Figure 2.** Age-standardized (world) incidence rates of OPC per 100,000 persons stratified by country, gender, and HPV status and corresponding male (M)/female (F) ratios. HPV-positive (HPV<sup>+</sup>) and HPV-negative (HPV<sup>-</sup>) incidence rates are estimated from HPV prevalence in Table 1.



probability of acquisition of oral HPV infection during orogenital sex (9). Furthermore, a large population-based survey of oral HPV infection in the United States showed a significantly higher oral HPV prevalence in men (10.1%) than in women (3.6%) and in current smokers (5). In countries other than the United States, little is known about the prevalence of oral HPV infection (10).

The main weakness of our study lies in the fact that there is limited or no country-specific data on HPV prevalence in OPC and incidence rates for the OPC sub-sites (mainly tonsil and base of the tongue) of the head and neck in which HPV is a strong carcinogen. The national representativeness, especially for underrepresented women, of HPV prevalence in OPC for the selected studies is uncertain; and individual information on age, smoking history, and year of OPC diagnosis was not systematically provided in publications. Findings from mRNA/ISH, which are the gold-standard tests for HPV attribution (11), are consistent with PCR findings, but they are available from very few countries other than the United States. Obviously, cumulative lung cancer risk is an imperfect proxy of smoking habits and does not capture the additional impact of heavy alcohol consumption on OPC. In France, OPC incidence rates were derived from a few regional cancer registries that showed substantially different OPC burdens (7). Finally, the restriction to studies that reported on HPV prevalence in OPC separately for men and women reduced the information available in the present study but allowed the obtainment of M/F ratios that are not affected by the large cross-study variations in HPV assay sensitivity.

Notwithstanding the limitations of HPV data and ecologic correlations, our study sheds some new light on the

interaction between HPV infection and a strong lifestyle risk factor for OPC, namely smoking. Case-control studies suggest that the interaction between HPV and tobacco in OPC is sub-multiplicative; that is, the effect of HPV on OPC is stronger in non-smokers than smokers (11), but only robust data from prospective studies in which the presence of HPV infection can be evaluated before cancer onset would be able to provide an accurate answer. However, the sex-specific population-based incidence rates of OPC that we have estimated suggest that, in addition to having higher incidence rates of HPV-negative OPC, men in different countries are more prone than women to develop HPV-positive OPC, which is in agreement with data on incidence rates and incidence trends from the United States (4, 5). However, these findings are compatible with different explanations. Smoking and heavy drinking may either enhance the carcinogenic effect of HPV infection or hamper the accurate attribution of HPV-positive OPC to HPV in men who have both the infection and the two lifestyle risk factors. A specific vulnerability of men to either contracting an oral HPV infection or the progression of HPV infection to OPC is also a possibility that requires further research.

#### Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

#### Authors' Contributions

**Conception and design:** J.-D. Combes, S. Franceschi

**Development of methodology:** J.-D. Combes, A.A. Chen, S. Franceschi

**Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.):** J.-D. Combes

**Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis):** J.-D. Combes, A.A. Chen, S. Franceschi

**Writing, review, and/or revision of the manuscript:** J.-D. Combes, A.A. Chen, S. Franceschi

### Acknowledgments

The authors thank Drs. Martyn Plummer, Salvatore Vaccarella, and Gary Clifford for their useful comments and Mathieu Laversanne and Veronique Chabanis for technical assistance.

### Grant Support

This work was supported by the Institut National du Cancer (INCa), SPLIT project N°2011/196. J.-D. Combes was partly supported by a fellowship from the Association pour la Recherche sur le Cancer (ARC,

N°20111204169). The work of A.A. Chen was undertaken during the tenure of a Postdoctoral Fellowship from the International Agency for Research on Cancer, partially supported by the European Commission FP7 Marie Curie Actions—People—Co-funding of regional, national, and international programmes (COFUND).

The costs of publication of this article were defrayed in part by the payment of page charges. This article must therefore be hereby marked *advertisement* in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

Received May 22, 2014; revised July 31, 2014; accepted September 5, 2014; published OnlineFirst September 9, 2014.

### References

1. de Martel C, Ferlay J, Franceschi S, Vignat J, Bray F, Forman D, et al. Global burden of cancers attributable to infections in 2008: a review and synthetic analysis. *Lancet Oncol* 2012;13:607–15.
2. Mehanna H, Beech T, Nicholson T, El-Hariry I, McConkey C, Paleri V, et al. Prevalence of human papillomavirus in oropharyngeal and non-oropharyngeal head and neck cancer—systematic review and meta-analysis of trends by time and region. *Head Neck* 2013;35:747–55.
3. Franceschi S, Bidoli E, Herrero R, Muñoz N. Comparison of cancers of the oral cavity and pharynx worldwide: etiological clues. *Oral Oncol* 2000;36:106–15.
4. Chaturvedi AK, Engels EA, Pfeiffer RM, Hernandez BY, Xiao W, Kim E, et al. Human papillomavirus and rising oropharyngeal cancer incidence in the United States. *J Clin Oncol* 2011;29:4294–301.
5. Gillison ML, Broutian T, Pickard RK, Tong ZY, Xiao W, Kahle L, et al. Prevalence of oral HPV infection in the United States, 2009–2010. *JAMA* 2012;307:693–703.
6. Chaturvedi AK, Anderson WF, Lortet-Tieulent J, Curado MP, Ferlay J, Franceschi S, et al. Worldwide trends in incidence rates for oral cavity and oropharyngeal cancers. *J Clin Oncol* 2013;31:4550–9.
7. Ferlay J, Soerjomataram I, Ervik M, Dikshit R, Eser S, Mathers C, et al. GLOBOCAN 2012 v1.0, Cancer incidence and mortality worldwide: IARC CancerBase no. 11 [Internet]. Lyon, France: International Agency for Research on Cancer; 2013.
8. IARC. Monographs on the evaluation of carcinogenic risks to humans volume 85: betel-quid and areca-nut chewing and some areca-nut-derived nitrosamines. Lyon: International Agency for Research on Cancer; 2004.
9. Hernandez BY, Wilkens LR, Zhu X, Thompson P, McDuffie K, Shvetsov YB, et al. Transmission of human papillomavirus in heterosexual couples. *Emerg Infect Dis* 2008;14:888–94.
10. Kreimer AR, Bhatia RK, Messegue AL, Gonzalez P, Herrero R, Giuliano AR, et al. Oral human papillomavirus in healthy individuals: a systematic review of the literature. *Sex Transm Dis* 2010;37:386–91.
11. Combes JD, Franceschi S. Role of human papillomavirus in non-oropharyngeal head and neck cancers. *Oral Oncol* 2014;50:370–9.

# Cancer Epidemiology, Biomarkers & Prevention

## Prevalence of Human Papillomavirus in Cancer of the Oropharynx by Gender

Jean-Damien Combes, Alyce A. Chen and Silvia Franceschi

*Cancer Epidemiol Biomarkers Prev* 2014;23:2954-2958. Published OnlineFirst September 9, 2014.

**Updated version** Access the most recent version of this article at:  
doi:[10.1158/1055-9965.EPI-14-0580](https://doi.org/10.1158/1055-9965.EPI-14-0580)

**Supplementary  
Material** Access the most recent supplemental material at:  
<http://cebp.aacrjournals.org/content/suppl/2014/09/10/1055-9965.EPI-14-0580.DC1>

**Cited articles** This article cites 9 articles, 2 of which you can access for free at:  
<http://cebp.aacrjournals.org/content/23/12/2954.full#ref-list-1>

**Citing articles** This article has been cited by 1 HighWire-hosted articles. Access the articles at:  
<http://cebp.aacrjournals.org/content/23/12/2954.full#related-urls>

**E-mail alerts** [Sign up to receive free email-alerts](#) related to this article or journal.

**Reprints and  
Subscriptions** To order reprints of this article or to subscribe to the journal, contact the AACR Publications Department  
at [pubs@aacr.org](mailto:pubs@aacr.org).

**Permissions** To request permission to re-use all or part of this article, use this link  
<http://cebp.aacrjournals.org/content/23/12/2954>.  
Click on "Request Permissions" which will take you to the Copyright Clearance Center's (CCC)  
Rightslink site.