Epidemiology of HPV-Positive Tumors in Europe and in the World

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Abstract

Strong evidence has accumulated in the last 15 years showing that infection by certain human papillomaviruses (HPVs) is etiologically involved in a subset of head and neck cancers (HNCs). In this chapter, epidemiologic-related topics on HNCs are reviewed: (i) HPV-attributable fractions and HPV-type distributions by different anatomical HNC sites, using not only HPV DNA but other more specific markers of causality; (ii) an update of the HPV-related HNCs burden worldwide and by regions; and finally, (iii) the determinants for HPV positivity in HNCs, focussing on gender, age, smoking habits, sexual behavior, and other related factors such as tonsillectomy performance. This information is essential in order to understand the burden of the disease and its dynamics and changing patterns, as well as for planning and assessment of the potential impact of HPV-based preventive strategies for HNCs.

Keywords

Epidemiology · HPV · Head and neck cancer · Burden of disease

1 The Contribution of HPV in the Etiology of HNCs

Strong evidence has accumulated in the last 15 years showing that infection by certain human papillomaviruses (HPVs) is etiologically involved in a subset of head and neck cancers (HNCs) (A Review of Human Carcinogens 2009). While virtually

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all cervical cancers are considered HPV-driven (Walboomers et al. 1999), the quantitative assessment of the etiological involvement of HPVs in HNCs is challenged by their multifactorial etiology largely attributed to tobacco and alcohol use (IARC 1988, 2004; Gillison et al. 2012). Consequently, the unequivocal fraction of HPV-DNA-positive HNCs for which HPV infection is indeed the truly triggering carcinogenic event is unknown and its estimation remains a challenge (Herrero et al. 2003). Further, the mere presence of HPV DNA in HNCs is not sufficient to prove viral causation as it might just reflect a transient infection unrelated to the carcinogenic process (Holzinger et al. 2012; Ndiaye et al. 2014; Castellsagué et al. 2016).

Most previous studies and meta-analyses assessing the quantitative contribution of HPV in HNCs have used the presence and detection of HPV-DNA in the tumor as the sole criterion to classify the tumor as HPV-driven, probably resulting in an overestimation of the true impact of HPV in head and neck carcinogenesis. To accurately classify a tumor as HPV-driven, it is crucial to use in addition to HPV-DNA detection other markers related to HPV-induced carcinogenesis and thus assess the biological and oncogenic activity of the HPVs identified in HNCs.

1.1 The ICO Study on HPV in HNCs

The Catalan Institute of Oncology (ICO) conducted a large international study explicitly designed to generate robust estimates of HPV-attributable fractions (AFs) in HNCs by quantifying the expression of a selection of markers of HPV-induced carcinogenesis and using a strict single protocol that standardized the entire processing and testing of all tumor samples (Castellsagué et al. 2016).

The methods used in this study have been already published (de Sanjosé et al. 2010). In brief, formalin-fixed, paraffin-embedded cancer tissues of the oral cavity, pharynx and larynx were collected from pathology archives in 29 countries worldwide. All samples were subjected to central histopathological evaluation, DNA quality control, and HPV-DNA detection. Samples containing HPV-DNA were further tested for HPV E6*I mRNA detection and expression of $p16^{INK4a}$, pRb, p53, and Cyclin D1 by immunohistochemistry.

A total of 3,680 samples yielded valid results: 1,374 pharyngeal, 1,264 oral cavity, and 1,042 laryngeal cancers.

Figure 1 presents by major HNC site, estimated range of HPV-AFs using different combinations of markers of HPV carcinogenesis: HPV-DNA detection, HPV E6*I mRNA detection, and p16 over-expression. Ranges of AFs when considering HPV DNA plus E6*I mRNA and/or $p16^{INK4a}$ were: 18.5–22.4 % for the oropharynx, 3.0–4.4 % for the oral cavity, and 1.5–3.5 % for the larynx. Corresponding estimates for pharynx unspecified subsite, nasopharynx, and hypopharynx were, respectively, 7.5–16.1, 1.1–5.9 and 2.4 % (Castellsagué et al. 2016). We observed that within both the oral cavity and the larynx, those subsites that were more proximal to the oropharynx showed higher HPV-AFs than those that were more distal to the oropharynx. Thus, HPV-AFs in combined oral cavity subsites that were

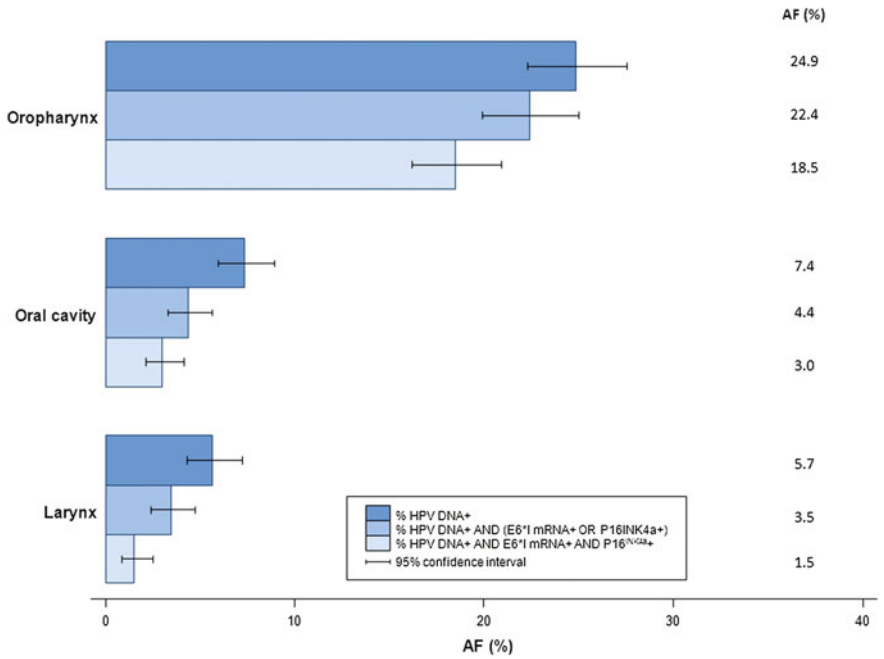

Fig. 1 HPV-attributable fractions for head and neck cancers according to positivity and/or over-expression of selected biomarkers of HPV-induced carcinogenesis

proximal to the oropharynx ranged (when considering HPV DNA plus E6*I mRNA and/or $p16^{INK4a}$) from 4.9 to 6.7 %, as opposed to 1.4–2.3 % in subsites that were distal to the oropharynx ($p < 0.001$ for both comparisons). Corresponding values in the larynx were 4.2 % versus 1.4–3.4 % in combined subsites that were proximal versus distal to the oropharynx, but these differences in the larynx were not statistically significant (Castellsagué et al. 2016).

Figure 2 shows oropharyngeal HPV-AFs by geography, gender, age group, and year of diagnosis. Estimates of HPV-AF in the oropharynx were highest in South America, Central and Eastern Europe and Northern Europe, and lowest in Southern Europe. Women showed higher HPV-AFs than men for cancers of the oropharynx. Globally, younger patients showed higher HPV-AFs than older patients and AFs tended to be higher in more recent decades with a statistically significant increasing trend in AFs with increasing recency.

1.2 HPV-Type Distribution in HNCs

Among HPV-DNA-positive cancer cases, the distribution of individual HPV types is different in HNCs when compared with cervical cancers, as HPV16 is systematically found in a much higher percentage of HNCs than of cervical cancer.

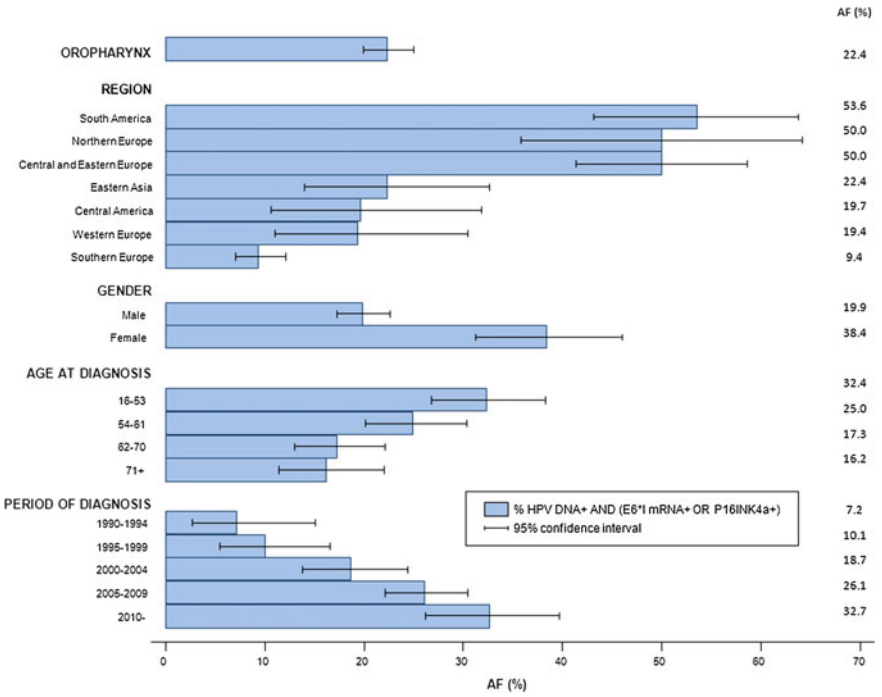

Fig. 2 HPV-attributable fractions for oropharyngeal cancer according to world region, gender, age, and period of diagnosis

Confirming results from several other studies, the ICO study found that HPV16 is the most frequently detected genotype among HPV-DNA-positive cases (75.2 %), but again with a wide range according to cancer site: 83 % in the oropharynx, 68.8 % in the oral cavity, and 50.8 % in the larynx (Castellsagué et al. 2016). The corresponding percentages for combined HPV types included in the nonavalent HPV vaccine (types 6, 11, 16, 18, 31, 33, 45, 52, and 58) were 89.7, 76.3, and 81.4 %, indicating that most HPV-positive HNCs could eventually be prevented through HPV immunization programs.

2 Burden of HPV-Related HNCs

HNC is the seventh cause of incident cancer cases worldwide, with an estimated 686,328 new cases and 375,622 deaths every year (Ferlay et al. 2013). These estimations include the oral cavity, larynx, and pharynx (nasopharynx, oropharynx, and hypopharynx). Among HNCs, oral cavity (including lips) is the most common,

representing more than 40 % of the cases. HNC shows a wide worldwide geographical heterogeneity in terms of incidence rates (Ferlay et al. 2013), likely reflecting a wide variability in the prevalence of established risk behaviors. Moreover, 75 % of the HNC burden occurs in men. As mentioned in the previous section, the association of HPV with HNC is also very heterogeneous with dramatic variations across anatomical sub-sites and geographical regions. The oropharynx is the sub-site with strongest associations with HPV. In some regions of the world such as USA or Northern Europe, more than 70 % of oropharyngeal cancer cases are estimated to be HPV-related (Chaturvedi et al. 2011), as compared with only 17 % in Southern Europe (De Martel et al. 2012).

However, as explained before, the mere use of HPV-DNA detection is not appropriate to classify a HNC as HPV-driven. Thus, the precise estimation of the burden of HPV-related HNCs requires the use of accurate HPV-AFs that include not only HPV-DNA detection but also at least one additional marker of HPV-induced carcinogenesis such as mRNA and/or p16 over-expression. The ICO survey is currently the largest and most robust study that used these markers in the definition of HPV-AFs in 3,680 HNC cases from Europe, Central and South America, Africa and Asia (Castellsagué et al. 2016). Based on sex- and region-specific HPV-AFs (as defined by HPV-DNA positivity and at least positivity by one additional marker, either mRNA or p16), we were able to estimate more accurately the burden of HPV-driven HNC in most world regions (Table 1). For regions not appropriately covered by the ICO study, global HPV-AFs from the ICO study or from other studies that tested for at least two HPV-related markers were used as indicated in the table footnotes. As shown in the table, we estimate that every year about 45,000 new HNC cases can be attributed to HPV infection worldwide. That table details the estimated burden by world region and sex for each major HNC site. It is important to mention that the HPV-AFs used in the ICO study might slightly underestimate the real number of HPV-driven HNCs because most HPV-DNA-negative samples were not tested for the additional markers and also because the assignment of HPV-driven cancers required positivity for at least two HPV-related markers.

In terms of trends, during the last years it has been evidenced that the annual number of new oropharyngeal cancer cases is increasing in some parts of the world (Chaturvedi et al. 2013), as well as the fraction of oropharyngeal cancer associated with HPV infection (Mehanna et al. 2013). The increased incidences have been observed particularly among young men (<60 years old) in several economically developed countries despite concomitant declines in incidence for oral cavity and lung squamous cell carcinomas. These contrasts suggest a role of HPV infection in increasing oropharyngeal cancer incidence rates among men. However, among women, incidence increased for all three HNCs, supporting a dominant effect of smoking on increasing incidence rates (Gillison et al. 2015).

Table 1 HPV-attributable fractions and estimated annual number of incident HNC cases attributable to HPV (requiring positivity for both HPV DNA and at least one additional HPV-related marker) by region, sex, and anatomical site

	Oral cavity[a]				Oropharynx[b]				Larynx[c]				ALL SITES		
	Male		Female		Male		Female		Male		Female		Male	Female	All
	AFs (%)	HPV-driven N	AFs (%)	HPV-driven N	AFs (%)	HPV-driven N	AFs (%)	HPV-driven N	AFs (%)	HPV-driven N	AFs (%)	HPV-driven N	HPV-driven N	HPV-driven N	HPV-driven N
Europe	4.4[d]	1,873	2.6[d]	490	16.9[d]	3,753	40.2[d]	1,792	2.2[d]	792	4.3[d]	169	6,418	2,451	8,869
Asia	4.7[e]	5,264	3.8[e]	2,161	18.8[d]	6,619	17.6[d]	1,429	2.8[e]	1,925	9.2[e]	805	13,808	4,395	18,203
North America	8.9[f]	1,683	1.7[f]	164	71.2 [g]	6,551	55.2 [g]	1,334	2.8[e]	300	9.2[e]	254	8,534	1,752	10,286
Central-South America	6.4[d]	831	6.8[d]	520	37.8[d]	1,919	51.6[d]	629	4.8[d]	686	15.6[d]	343	3,436	1,492	4,928
Africa	4.7[e]	281	3.8[e]	268	19.9[e]	511	38.4[e]	564	2.8[e]	213	9.2[e]	97	1,005	929	1,934
Oceania	4.7[e]	107	3.8[e]	51	19.9[e]	215	38.4[e]	93	2.8[e]	20	9.2[e]	9	342	153	495
World		10,039		3,654		19,568		5,841		3,936		1,677	33,543	11,172	44,715

AFs HPV-attributable fractions; *N* Number of incident cases attributable to HPV infection

[a]The total number of cases in 2012 has been obtained from GLOBOCAN 2012. Oral cavity includes lip, base of tongue, mobile tongue, gum, floor of the mouth, palate, other and unspecified parts of mouth, and salivary glands

[b]The total number of cases in 2012 has been extrapolated from initial estimates reported in Forman et al. (2012), which were only reported for both sexes combined using old GLOBOCAN 2008 and cancer registry data. To estimate corresponding updated 2012 figures, we assumed: (1) the same geographical distribution of oropharyngeal cases across European regions as the corresponding distribution of "other pharynx" cases available in GLOBOCAN 2012; (2) the same increment of oropharyngeal cases from GLOBOCAN 2008 to GLOBOCAN 2012 as that of "other pharynx" cases; and (3) the same gender distribution of oropharyngeal cases by region as that of "other pharynx" cases in GLOBOCAN 2012. Oropharynx includes oropharyngeal parts as well as tonsil and base of tongue

[c]The total number of cases in 2012 has been obtained from GLOBOCAN 2012. Larynx includes glottis, laryngeal cartilage, and unspecified and overlapping lesions of larynx

[d]AFs derived from the ICO study (Castellsagué et al. 2016) in which a case was classified as HPV-related if it was positive for both HPV DNA and either $p16^{INK4a}$ or E6*I mRNA

[e]Since this region was not appropriately represented in the ICO study, site-and sex-specific global HPV-AFs from the ICO study were used

[f]AFs derived from Lingen et al. (2013) in which a case was classified as HPV-related if it was positive for HPV E6/7

[g]AFs derived from Jordan et al. (2012) in which a case was classified as HPV-related if it was positive for HPV E6/7

3 Determinants for HPV-Positive Head and Neck Cancers

As mentioned before, HPV-AFs in HNCs are highly heterogeneous across geographical regions, particularly in oropharyngeal cancers (Castellsagué et al. 2016). Distinct trends in tobacco and alcohol consumption, sexual behavior, and sociodemographic variables may lead among others to these observed heterogeneous patterns.

Besides HPV infection, tobacco and alcohol are the classic and well-established risk factors for HNCs. Tobacco prevalence estimates exhibit substantial variation across age groups, sex, and countries (Ng et al. 2014). Prevalence estimates by country can vary from below 5 % for women in some African countries to more than 55 % for men in Timor-Leste and Indonesia. Gender differences are also important, with an estimated age-standardized prevalence of 31 % for men and 6 % for women, in 2012 (Ng et al. 2014). Differences in smoking prevalence trends are also observed with highest declining rates observed in Canada, USA, and European Nordic countries, and increased prevalence rates in other countries (Ng et al. 2014). Moreover, and beyond prevalence variations, it is still unclear whether tobacco and/or alcohol use can act as co-factors and/or effect modifiers in risk of developing HPV-positive HNCs. A review of case-control studies addressing this issue showed inconsistent results, with two studies reporting positive interactions between HPV infection and tobacco, two showing no interaction, and finally three reporting a negative joint effect (Gillison et al. 2012).

Some studies indicate that the most likely explanation for the origin of HPV-related HNCs is a sexually acquired oral HPV infection that is not cleared, persists, and evolves into a neoplastic lesion. Sexual behavior is a clear risk factor for oral HPV acquisition and HPV-related HNCs (Gillison et al. 2008). Like for tobacco and alcohol consumption, sexual behavior greatly varies across regions with proportions of ever having oral sex in USA higher than 65 % compared to lower than 20 % in countries from Southern Europe such as Spain (Heck et al. 2010).

Gender and age are also factors that can affect HNCs HPV positivity. HPV-positive HNCs patients show younger ages at diagnosis than HPV-negative ones (Castellsagué et al. 2016), probably linked to differential sexual behavior of younger versus older cohorts. Regarding gender, a recent systematic review on differences in the proportion of HPV-AF in oropharyngeal cancers between men and women revealed heterogeneous HPV-related HNCs patterns with the highest men-to-women ratio found in USA (1.5) and lowest found in Asia and some European countries (0.7) (Combes et al. 2014). This last observation is in agreement with our recently published results of higher oropharyngeal cancer HPV-AFs in women from some European countries (Castellsagué et al. 2016). Combes and colleagues also evaluated the sex-specific lung cancer rates in order to assess whether the observed gender differences in HNC could be explained by differences in tobacco consumption and found that HPV prevalence in oropharyngeal cancers differs by gender and country mainly as a consequence of the vast international

variation in male smoking habits (Combes et al. 2014). However, there are still unclear reasons for these gender findings besides gender differences in tobacco consumption. A recent work by D'Souza and colleagues showed differences in the natural history of oral HPV infections between men and women, such as a higher risk of acquiring an oral HPV infection with recent number of oral sexual partners among men and less HPV infection clearance in men (D'Souza et al. 2016)

Other factors may be contributing to this observed geographical heterogeneity in HPV-AFs in HNCs, for example trends in tonsillectomy rates. Tonsillectomy consists on the removal of the tonsils, the most susceptible head and neck site for HPV infection. Some countries have reported a decrease in tonsillectomies rates over time (Koshy et al. 2014; Fakhry et al. 2015), and a recent study reported both a decrease of this surgical procedure with a simultaneous increase in the risk of oropharyngeal cancer (Fakhry et al. 2015). Tonsillectomy likely reduces the palatine lymphoid tissue susceptible to carcinogenic factors and subsequent potential malignization.

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