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Eurogin Roadmap: Comparative epidemiology of HPV infection and associated cancers of the head and neck and cervix

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Mini Review

The EUROGIN 2012 roadmap is focused on the comparative epidemiology of human papillomavirus (HPV) associated head and neck squamous cell cancers (HNSCC) and cervical cancers. Discussed are the similarities and differences between the two cancers with regard to global disease burden, HPV prevalence and type distribution, disease cofactors, molecular pathogenesis, treatment approaches, prognostic factors and primary and secondary prevention. The global incidence of HNSCC and cervical cancer is similar; however, a minority of HNSCC in comparison to virtually all cervical cancers is caused by HPV. HPV infection prevalence is considerably lower in the oral than genital regions for reasons that are as yet unclear. Infection at both sites is strongly associated with sexual behavior, but this association does not appear to explain the male predominance of oral HPV infection. Studies of the molecular pathogenesis of HPV-associated HNSCC (predominantly oropharyngeal cancers) are hampered by the lack of a readily detectable intermediate clinical endpoint analogous to cervix intraepithelial neoplasia. Nevertheless, similarities in chromosomal aberrations, gene expression, methylation and microRNA profiles between HPV-positive HNSCC and cervical cancer argue for shared carcinogenic pathways. Treatment approaches to oropharyngeal and cervical cancers are remarkably similar, with the development of HPV-targeted therapies as the ultimate treatment goal. Key research challenges include understanding oral HPV transmission and male predominance, clarifying the role of cofactors, and developing new screening and treatment methods for HPV-associated HNSCC.

Introduction

Human papillomavirus (HPV) 16 was first isolated from a cervical cancer in 1983[1] and within 12 years was declared a human carcinogen[2] necessary for the development of cervical cancer.[3] A pre-existing clinical infrastructure for cervical cytology screening facilitated natural history studies of cervical HPV infection that ultimately resulted in several important public health interventions, including screening to detect and vaccination to prevent HPV infection. Cervical cancer is thus the paradigm for an HPV-caused cancer and demonstrates how elucidation of a causal association can culminate in effective interventions into the natural history of disease.

Formal reviews on the carcinogenicity of HPV in humans conducted by the International Agency for Research on Cancer (IARC) in 2007[4] and 2012[5] concluded that there was sufficient evidence for the carcinogenicity of HPV16 in the oropharynx and possibly the oral cavity. In contrast to cervical cancer, neither an established clinical infrastructure for screening nor a clear understanding of precancerous lesions exists for head and neck cancer. Thus, the field is still in its relative infancy. Nevertheless, data are beginning to emerge that indicate both significant homology to and divergence from the epidemiological association between HPV and cervical cancer.

While much could be learned from comparisons among all tumors caused by HPV at multiple anatomic sites, this article will compare and contrast the relationship between HPV and oropharyngeal cancer to that of cervical cancer. For clarity, the term oropharynx refers to the anatomic region that includes the soft palate and uvula, tonsils, posterior pharyngeal wall and the base of tongue. This region is distinct

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from the oral cavity, which includes the lips, floor of mouth, buccal mucosa, gingiva, hard palate and the mobile part of the tongue. Oral cancer refers to the combination of oropharyngeal and oral cavity cancers.

Similarities and Differences in the Epidemiology of Oral vs. Cervical HPV Infection

Longitudinal studies have elucidated the natural history of cervical HPV infection and the association of persistent viral infection with cervical neoplasia.[6] Data are emerging that indicate several key differences in the epidemiology (prevalence, incidence and clearance) and demographic correlates of oral as compared to cervical HPV infection (Table 1).

Prevalence of HPV infection

A clear difference between oral and cervical HPV epidemiology is prevalence of infection: oral HPV prevalence is 5–10-fold lower than cervical–vaginal HPV prevalence. Results from a nationally representative survey of the U.S. population (NHANES) aged 14–59 years observed an oral HPV prevalence of ~7%, an estimate that was sixfold lower than the 42% prevalence of cervical HPV.[7–9] Despite lower prevalence, the type distribution of oral HPV infections appears similar to cervical HPV infections, with HPV16 infection being among the most prevalent types.[7,9]

The lower prevalence of oral *versus* cervical HPV infection may arise from lower incidence of oral HPV infection. Large, population-based cohort studies have observed incidence of cervical HPV infections to exceed 100 per 1,000 person-years, but ~90–95% of infections cleared within 2 years.[10,11] Data from a few short-term (6-month) prospective studies of oral HPV infection observed significantly lower incidence of oral HPV infections when compared with cervical HPV infections, but similar persistence for prevalently detected infections.[12–14] However, large natural history studies of oral HPV infection have yet to be conducted.

Both oral and cervical HPV infections are strongly associated with sexual behaviors, with prevalence increasing with number of partners for oral–genital contact for oral HPV and genital–genital contact for cervical HPV.[6,7,10,15] Differences in number of lifetime partners for oral *versus* genital sex may in part explain the lower prevalence of oral HPV infections. In the United States, men and women report a twofold lower average number of lifetime oral sex partners when compared with vaginal sex partners.[7] Recent studies of oral HPV infection also support nonsexual contact, including salivary transmission through behaviors such as deep kissing.[12,15]

Demographic differences

Oral HPV infection differs from genital infection with regard to associations with gender and age. The largest population-based study of oral HPV infection conducted in the United States observed a two to threefold higher prevalence among

Table 1. Similarities and differences in the epidemiology of cervical and oral HPV infection

	Cervical HPV	Oral HPV
Transmission	Predominantly sexual	Predominantly sexual
Associations with sexual behaviors	Strong	Strong
Transmissibility	High	Unknown
Prevalence in adult general population	High	Low
Any HPV	~40%	~7%
High-risk HPV	~30%	~3%
Low-risk HPV	<1% to 7%	<1%
Type distribution	HPV16 among most common	HPV16 among most common
Common HR types	HPV16, HPV53, HPV51	HPV16, HPV66, HPV51
Common LR types	HPV62, HPV84, HPV89	HPV62, HPV55, HPV84
Age-specific prevalence	Decreases with age. Peak prevalence at 20–24 years. Second, lower peak at older age (>=50) observed in some populations.	No decrease with age. Stable prevalence with age. Bimodal prevalence in some populations, with 2 peaks (30–34 years and 60–64 years).
Natural history studies	Numerous large, population-based studies conducted around the world	Few and often targeting high-risk groups
Incidence	High (>100 per 1,000 person-years)	Unknown (likely low)
Clearance	Median clearance time of 9–12 months. 90–95% of infections clear within 24 months.	Unknown (likely similar to cervical infections)

References: Trottier et al., 2006[6]; Gillison et al., 2012[7]; Dunne et al., 2007[8]; Harari et al., 2011[9]; Burchell et al., 2006[10]; Moscicki et al., 2012[11]; D'souza et al., 2007[15]; Gravitt, 2011[16]; Bruni et al., 2012[17]; Kreimer et al., 2011[18]; Kreimer et al., 2010.[19]

men compared to women.[7] This male predominance of oral HPV infection does not appear to be readily explained by differences in sexual behaviors, suggesting gender differences in natural history or exposure to cofactors.

With respect to age-specific prevalence patterns, most studies, but not all, have shown that prevalence of cervical HPV infections peaks soon after the societal average at sexual debut and significantly declines thereafter.[16,17] A second, relatively lower peak at around menopause is also observed in some geographic regions. In contrast, oral HPV prevalence remains relatively stable or increases significantly with increasing age.[7,18,19] The recent NHANES study of oral HPV infection found no decline in HPV prevalence with age, with peak prevalence at 30–34 years and 60–64 years. Of note, age-specific prevalence of anal and penile HPV infections is believed to be stable across ages.[20] This makes the decline in cervical HPV prevalence with age an exception rather than the rule.

In summary, emerging evidence points to several key differences in the epidemiology of oral and cervical HPV infections. The current paucity of data on transmissibility, incidence, clearance, persistence and predictors thereof for oral HPV infections underscores the need for natural history studies of oral HPV infections.

Similarities and Differences in the Epidemiology of Head and Neck Versus Cervical Cancers

Oncogenic HPV types are necessary for the development of virtually all cervical cancers[3] and for a subset of HNSCC (in particular, oropharyngeal cancer) and other anogenital cancers.[21,22] In this section, selected indicators of the burden and epidemiology of these cancers will be compared and contrasted (summarized in Table 2).

Cancer burden

Data compiled from cancer registries clearly indicate that both HNSCC and cervical cancers contribute substantially to the burden of cancer worldwide. Even though only a small fraction of HNSCC are HPV-related, overall an approximately equal number of new cases of HNSCC and cervical

Table 2. Similarities and differences in the epidemiology of cervical *versus* oropharyngeal cancers

Epidemiologic trait	Cervical cancer (CC)	Oropharyngeal cancer (OC)
Etiology	Oncogenic HPV infection only with or without intervening cofactors	Multifactorial: tobacco, alcohol, HPV, among others
Number of cases worldwide (2008)	530,000	85,000
Quality and amount of accumulated evidence for HPV role	Large, robust, diverse in study designs and consistent across geography and study populations	Less strong and consistent across geography and limited in study designs and study populations
Etiological HPV fraction	100%	26%
Number of cases attributed to HPV worldwide (2008)	530,000	21,400 (17,000 men, 4,400 women)
Developing/developed burden of HPV-related cases	453,000/77,000	6,400/15,000
Burden of HPV-related cancer cases relative to all cancers attributable to infectious agents	48.2% (530,000/1,100,000 female cases)	Male: 1.7% (17,000/990,000) Female: 0.4% (4,400/1,100,100)
Trends	Decreasing in most but not all developed and developing countries	Sharp increase (in the US and some North-European countries), in contrast to other HNC
Geographical variability in HPV DNA detection	None	Substantial (fourfold) (North America: 56%; Japan: 52%; Australia: 45%; Northern & Western Europe: 39%; Eastern Europe: 38%; Southern Europe: 17%; rest of world: 13%)
HPV 16 relative contribution	61% (smaller than in OC)	90% (larger than in CC)
HPV 18 relative contribution	10% (larger than in OC)	2% (smaller than in CC)
Relative contribution of HPV 16 and 18	71%	92%
Relative contribution of other types	Between 2 and 6% each (31, 33, 35, 39, 45, 52, & 58 among many others)	<2% each (Anecdotic and fewer types: 35, 45, 59; in addition to 6/11 and 33)
Evidence for type-specific carcinogenicity	For all high-risk types: 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59	Only for HPV 16

References: IARC Monograph 100b 2012[5]; de Martel et al., 2012[21]; Arbyn et al: 2012[22]; Li et al., 2010[28]; Kreimer et al., 2005[26]; de Sanjosé et al., 2010[27]; Globocan 2008 (globocan.iarc.fr/).

cancers are diagnosed on an annual basis: 550,300 (85,000 for oropharyngeal cancer), *versus* 530,000, respectively (Fig. 1, Table 2).[23] In terms of mortality, annual estimates are 305,100 deaths from HNSCC as compared to 275,000 deaths from cervical cancer.

Notably, 75% of the HNSCC burden occurs in men. Both cancers are much more frequent in developing than in developed countries, although a substantially higher proportion of cervical cancers occur in less developed regions (85% *vs.* 64% of HNSCC). Worldwide, HNSCC ranks as the 7th most common cancer in men and the 13th most common in women, whereas cervical cancer ranks as the 3rd most common female cancer.

Analogous to cervical cancer, HNSCC shows a wide worldwide geographical heterogeneity in terms of incidence rates (Fig. 2). This likely reflects wide variability in the prevalence of established risk behaviors and modifiers, whereas in the case of cervical cancer access to early detection and treatment of precancerous lesions is a more significant contributing factor. For example, HIV infection is known to increase the risk of several HPV-associated malignancies, but the relative risk appears lower for HNSCC as compared to cervical cancer.[24]

Etiologic fraction for HPV

In contrast to cervical cancer where HPV is a necessary cause, the study of HPV in HNSCC is complicated by etiological heterogeneity. Consequently, the precise fraction of HPV DNA-positive HNSCC where HPV is responsible for carcinogenesis is unknown.

To date, most reviews assume that 100% of high-risk HPV DNA present in tumor tissue is causally related to disease. For example, a recent IARC review estimated that 25.6% of oropharyngeal cancers worldwide are associated with HPV infection.[21] This would correspond to ~22,000 oropharyngeal cancer cases (17,000 in men and 4,400 in women) attributed to HPV (Table 2). Estimates varied by geographical region. For example, the proportion of HPV-positive oropharyngeal cancers was 56% in North America; 52% in Japan; 45% in Australia; 39% in Northern and Western Europe; 38% in Eastern Europe; 17% in Southern Europe; and 13% in the rest of the world (Table 2). In another recent review of this topic, HPV prevalence in HNSCC was substantially higher in oropharyngeal cancer than in non-oropharyngeal cancer and HPV prevalence differed by region and by calendar period.[25]

HPV type distribution

Among HPV DNA-positive cancer cases, the distribution of individual HPV types is different in oropharyngeal when compared with cervical cancers. HPV16 is found in 80–100% of HPV DNA-positive oropharyngeal cancers based on data from studies that included at least 30 cases.[26] In contrast, the relative contribution of HPV16 in cervical cancers is ~61% according to the recent Catalan Institute of Oncology (ICO) survey[27] (Table 2). The ICO study confirms results from a large meta-analysis[28] indicating the contribution of the eight most common oncogenic HPV types to ~91% of invasive cervical cancer, *i.e.,* HPV 16, 18, 31, 33, 35, 45, 52 and 58 (Table 2). Only a small proportion of oropharyngeal cancers may be caused by additional HPV types such as 18, 31, 33, 35, 52 and 58.[29,30]

Other additional similarities and differences between the two cancers are presented in Table 1, including: quality and amount of accumulated evidence for an HPV role, burden of HPV-related cancer cases relative to all cancers attributable to infectious agents, time trends in incidence, geographical variability in HPV DNA detection, developing *versus* developed country burden of HPV-related cases and evidence for type-specific carcinogenicity, among others.

Risk Factors for Head and Neck and Cervical Cancers Other than HPV

Tobacco smoking is positively associated with both HNSCC[31] and cervical cancers.[32] Tobacco smoking or chewing and alcohol drinking have been known for decades to represent strong risk factors for HNSCC cancer. The strong excess of HNSCC cancer in men compared to women is consistent with corresponding difference in the use of tobacco and alcohol.[31] However, the association is rather weak for cervical cancer after adjustment for sexual and reproductive factors (pooled OR for current *versus* never smokers in a large collaborative reanalysis: 1.60; 95% CI: 1.48–1.73).[32]

It has been hypothesized that HNSCC includes distinct entities, *e.g.,* one mainly caused by tobacco and alcohol use and another caused by persistent HPV infection.[33] HPV-positive oropharynx cancers exhibit a distinct risk profile compared to HPV-negative HNSCC, *i.e.,* an association with white race, number of sexual partners, and marijuana use in HPV-positive malignancies *versus* tobacco and alcohol use in HPV-negative malignancies.[33,34] Additionally, existing literature[33–36] suggests a departure from a multiplicative model for interactions between tobacco and HPV, *i.e.,* the relative risk for tobacco use is lower among HPV-positive individuals or the relative risk for HPV infection is lower among smokers. While these data certainly support a hypothesis of alternative pathways, further confirmatory studies are warranted.

In contrast to HNSCC, separate assessment of HPV-positive and HPV-negative tumors was not an issue in case-control studies of cervical cancer. To identify possible HPV risk modifiers, attempts to restrict comparison to HPV-positive cases and HPV-infected control women were made. This approach was eventually dismissed because HPV-positivity has a different meaning in cervical cancer cases (almost certainly a long-term persistent infection) and in control women (possibly a recently acquired transient infection). For this reason, prospective cohort studies of factors associated with HPV infection persistence or development of high-grade dysplasia have been more informative.

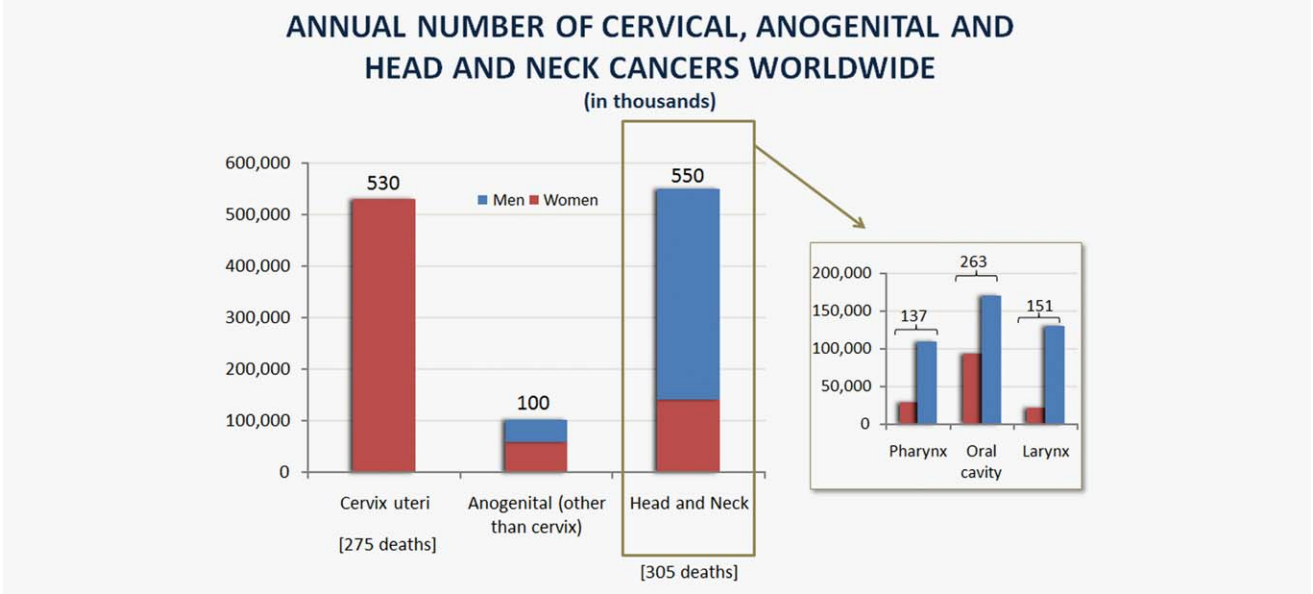

Figure 1. Annual number of cervical, anogenital and head and neck cancers worldwide. Data source is International Association for Research on Cancer (IARC) Globocan 2008 (4.5-2011). Annual number for men is represented in blue and for women in red. Inset panel represents head and neck cancer cases stratified by anatomic site and gender. Numbers do not reflect HPV-attributable fraction for head and neck cancers. Annual numbers of deaths due to each cancer type are indicated (in thousands).

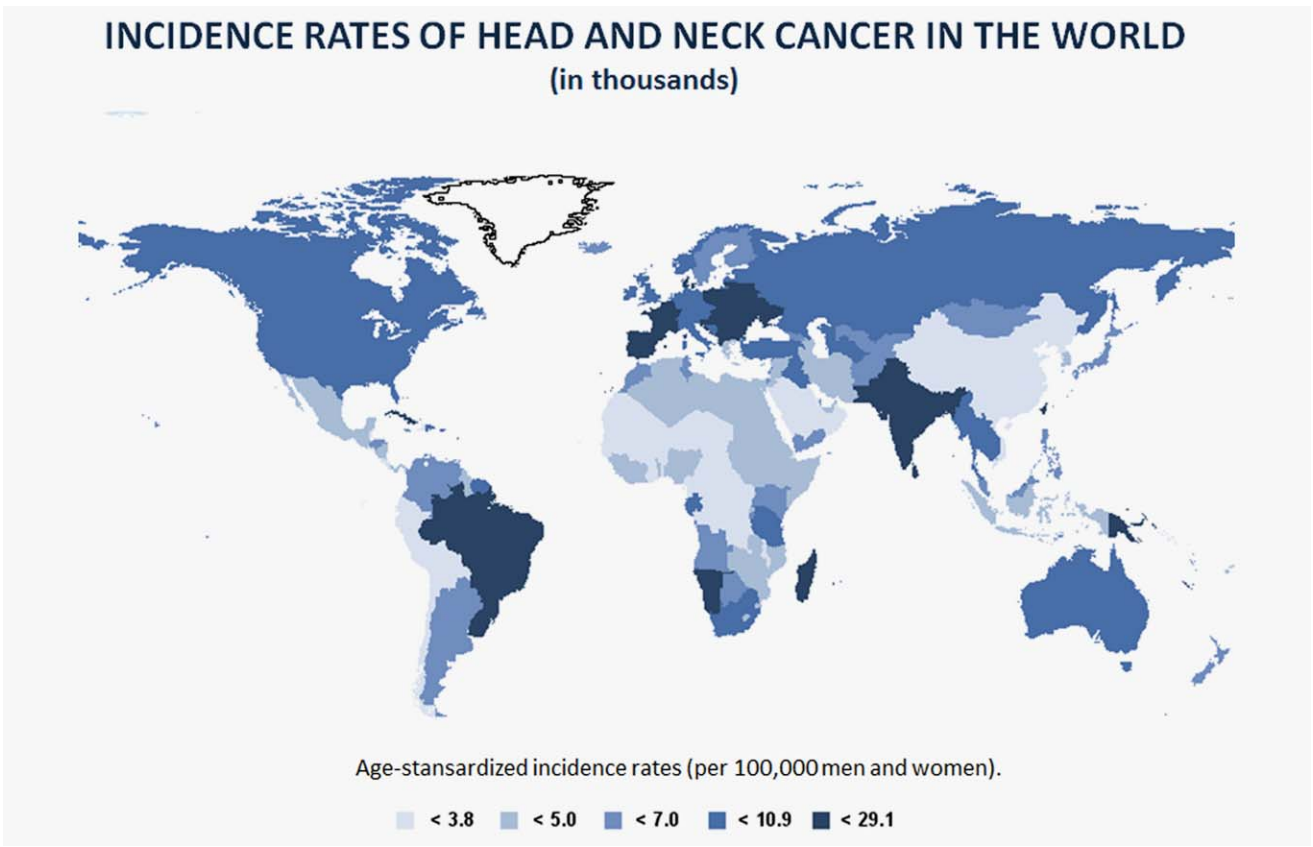

Figure 2. Age-standardized incidence rates (per 100,000 men and women) of head and neck cancer in the world, 2008. Data source is International Association for Research on Cancer (IARC) Globocan 2008 (4.5-2011). Incidence rates per geographic region are represented in various shades of blue per index.

Markers of poor diet and poor hygiene have been repeatedly found to be associated with HNSCC risk[37,38] and also with cervical cancer risk.[39] However, confounding by other correlates of low socioeconomic status (and tobacco and alcohol consumption) is difficult to rule out completely, as both HNSCC and cervical cancer occur with greater frequency among the poor and disadvantaged with limited access to medical care.[40,41]

Measures of poor oral hygiene could be a surrogate for either chronic inflammation or infection by specific microorganisms, and thus the role of bacterial and viral infectious cofactors in the pathogenesis of HNSCC and cervical cancer is of interest. The relationship between infections other than HPV and HNSCC cancer has been studied very little (with the exception of Epstein Barr Virus and nasopharyngeal cancer), but a role for chronic oral inflammation has been hypothesized.[37,42] Periodontitis, a chronic inflammatory disease of the structure around the teeth, has been associated with HNSCC.[43–45] Further studies of the characteristics of oral flora are necessary to better understand the role of chronic inflammation and specific infections in HNSCC.

In the case of cervical cancer, the study of the role of sexually transmitted infections (STIs) other than HPV as potential cofactors for the development of cervical cancer among HPV infected women is hampered by a common transmission mode. A role of HIV-associated immunosuppression in enhancing the probability of acquisition, persistence of HPV infection and, in the lack of adequate screening, progression to cervical cancer has been well-established.[5] Large meta-analyses of cross-sectional studies observe positive associations with various STIs other than HIV, including bacterial vaginosis[46]; herpes simplex virus[47]; and Chlamydia Trachomatis.[48] The possibility that Chlamydia Trachomatis may enhance HPV-driven carcinogenicity was supported by a cohort study from Sweden[49] but not from Costa Rica.[50] From a pathophysiological perspective, co-infections and associated chronic inflammation may increase cancer risk independently or facilitate the acquisition or persistence of HPV infection.

In most regions of the world, the incidence of HNSCC is higher in men than women. This has been attributed to more frequent and higher use of tobacco and alcohol among men. In the United States, the gender differences in risk are observed, however, for both HPV-negative and HPV-positive HNSCC.[33] As noted above, differences in risk by gender for HPV-positive HNSCC may be explained in part by sexual behaviors and the higher prevalence of oral high-risk HPV infections among men.[7] At this time, an independent role for sex hormones in oral HPV natural history cannot be excluded. For example, gender may be associated with oral HPV infection persistence. Androgens are involved in the development of the larynx in adolescent boys, but the relationship between sex steroid hormones and HNSCC has never been directly studied.

In the case of cervical cancer, risk factors other than HPV infection are generally weak in magnitude (relative risk, RR, ≤ 2) and are correlates of the probability of acquisition (number of sexual partners) or modifiers of HPV-related cancer risk. For example, HPV infection occurs soon after first sexual intercourse, and therefore early age at first intercourse is a reasonable proxy for early age at first exposure to HPV.[51]

Heavy exposure to sex steroid hormones (either oestrogens and/or progesterone) probably explains the association between cervical cancer risk and high parity[52] and prolonged oral contraceptive use.[53] However, the increase of cervical cancer risk with the square of time since first intercourse stops around the peri-menopausal period, consistent with an independent role for sex hormones. Overall, epidemiological findings[54,55] and mouse models[56,57] suggest that sex hormones are necessary to the development of HPV infection into cancer in the cervix uteri, a site that undergoes profound changes during a woman's reproductive life.[58] However, a better understanding of risk factors (including hormonal factors) that affect the risk of persistence and progression of HPV infection in the cervix is needed.

In conclusion, use of tobacco and alcohol remain the predominant source for the variation in the incidence of HNSCC between sexes and across different world regions. However, HPV infection is likely to account for an increasing proportion of cancer of the oropharynx in high-resource settings.

Molecular Pathogenesis of Head and Neck Cancers Versus Cervical Cancer

A key event in cervical carcinogenesis involves deregulated activity of the viral E6 and E7 genes, which target, amongst others, p53 and pRB, respectively. Deregulated E7 activity in proliferating cells results in increased expression of $p16^{INK4a}$,[59] which is a hallmark of cervical carcinomas and their true precursor lesions.[60] HNSCC with viral E6/E7 expression almost invariably display $p16^{INK4A}$ overexpression, as well.[61,62] Moreover, inactivating p53 mutations that are common in HPV-negative HNSCC are rare amongst HPV-positive HNSCC,[63–66] suggesting that E6 activity obviates the need for somatic mutations to inactivate the p53 pathway. These findings are consistent with active roles of E6 and E7 in the pathogenesis of a subset of HNSCC, which is supported by mouse models revealing that HPV 16 E6/E7 strongly increases the susceptibility of mice not only to cervical cancer but also to oral and oropharyngeal carcinomas.[67,68]

Despite the lack of information from precursor stages, a tumor initiating role of HPV in HNSCC is substantiated by molecular genetics and chromosomal profiling studies showing that chromosomal losses of regions representing the first genetic hits in the HPV-negative process of HNSCC carcinogenesis (*i.e.,* 9p, 3p and 17p) are far less common in HPV-positive compared to HPV-negative HNSCC.[64,69]

Evidence for a role of HPV in the maintenance of the transformed phenotype in HNSCC comes from both observational and *in vitro* studies. When detected by *in situ* hybridization, HPV DNA in HNSCC is diffusely present throughout the tumor[61,70,71] and the viral genome is often integrated into that of the host,[61,72] indicating clonality. Moreover, HPV16 containing oral and oropharyngeal cancer cell lines appear dependent on E6/E7 activity because, similar to cervical cancer cells,[73,74] induced knockdown of E6/E7 expression ultimately leads to apoptosis.[75]

Similarities in chromosomal aberrations, gene expression, methylation and micro-RNA (miRNA) profiles between cervical and HPV-positive HNSCC further support the notion of shared mechanisms of carcinogenesis. Unsupervised hierarchical clustering of array comparative genomic hybridization (a method that allows for identification of regions of chromosomal loss or gain) profiles of cervical and HNSCC has revealed two clusters of which one contained mainly HPV-positive tumors.[76] Loss of 13q and gain of 20p were more common in HPV-positive cancer, whereas loss at 3p and 5q and gain /amplification at 11q were more frequent in HPV-negative HNSCC. Moreover, expression profiling revealed that compared with HPV-negative HNSCC, HPV-positive HNSCC and cervical cancer showed differential expression of various gene sets, including cell cycle regulatory genes, a phenomenon that was suggested to be due to E7 activity.[77] In addition, HPV-positive HNSCC and cervical cells have greater levels of CpG methylation than HPV-negative HNSCC cells.[78] Amongst the genes that were more highly methylated in HPV-positive cells were polycomb repressive two target genes. Finally, HPV-positive HNSCC had a distinct miRNA profile compared with HPV–negative HNSCCs and the similarity in miRNA profile was higher between HPV-positive HNSCC and cervical SCC than HPV-negative HNSCC and cervical cancer.[79] Taken together, these findings argue for similar molecular pathways in the pathogenesis of HPV-positive HNSCC and cervical cancer.

Treatment and Prognosis of Head and Neck Versus Cervical Cancers

Despite distinctions in anatomy, there is considerable homology between treatment approaches for oropharyngeal and cervical cancers. Primary therapy is largely determined by the clinical stage at diagnosis.

Treatment of early stage cancers clinically confined to the oropharynx or cervix is usually surgical resection, which frequently includes regional lymphadenectomy (*e.g.,* neck dissection and pelvic lymphadenectomy, respectively). For both cancer types, defined histopathological features in the resected specimen are used to determine risk of local-regional recurrence and need for adjuvant postoperative radiotherapy[80,81] or chemoradiotherapy.[82–84] Disease control with primary radiotherapy alone is generally considered equivalent to surgery for early stage, organ confined oropharyngeal cancers, but has been shown to be inferior for cervical cancers.[85]

For individuals with large primary tumors or regional nodal metastases, primary chemoradiotherapy is frequently the treatment of choice for both oropharyngeal and cervical cancers. For oropharyngeal cancers, surgical resection followed by adjuvant (chemo)radiation is a treatment option as is induction chemotherapy followed by chemoradiation.[86] Meta-analyses have demonstrated that concomitant administration of cisplatin chemotherapy and radiotherapy reduces the risk of local-regional recurrence and death for both HNSCC[87] (inclusive of oropharyngeal cancer) and cervical cancer.[88] The standard of care for recurrent or metastatic disease for both cancers is palliative platinum-based combination chemotherapy (*e.g.,* cisplatin and paclitaxel). In the case of HNSCC, a monoclonal antibody to the epidermal growth factor receptor (EGFR), cetuximab, is as alternative to cisplatin for chemoradiotherapy[89] and has also improved survival when administered with palliative chemotherapy.[90]

The ultimate therapeutic goal for all HPV-associated malignancies would be development of HPV-specific therapeutics, including small molecules targeted to viral oncoproteins and therapeutic HPV vaccines designed to augment cellular immune responses to viral oncoproteins. An HPV16 E7 long-peptide vaccine demonstrated initial promise among women with vulvar dysplasia.[91]

The 5-year survival rates for localized and regionally advanced cervical cancers (90.7% and 56.7%, respectively) were quite similar to those for oral cavity and pharyngeal cancers overall (82% and 57%, respectively) in the United States from 2002 to 2008 per SEER.[92] However, survival rates for oropharyngeal cancer are significantly influenced by tumor HPV status.[93] The median survival for HPV-positive oropharyngeal cancers in the United States per SEER was significantly better than for HPV-negative oropharyngeal cancers (131 *vs.* 20 months, $p < 0.001$).[33] In randomized clinical trials, patients with HPV-positive oropharyngeal cancer have a consistent 70% relative reduction in risk of death when compared to HPV-negative patients.[93]

Tumor HPV status is now routinely used as a stratification factor or eligibility criterion for clinical trials that include patients with oropharyngeal cancer. The performance of clinical assays for determination of tumor HPV status is therefore of increasing importance, whereas in the cervix it has no clinical relevance (and all would be positive). It is important to note, however, that HPV testing results do not currently affect the standard of care for oropharyngeal cancers outside of the context of a clinical trial. In research settings, there is growing consensus that HPV-PCR based assays alone have high sensitivity but inadequate specificity.[94] P16 immunohistochemistry alone is frequently used as a surrogate test, and has high sensitivity, but moderate (75–85%) specificity,[95] whereas commercially available *in situ* hybridization assays have high specificity but moderate sensitivity.[96] The use of PCR detection in combination with p16-immunohistochemistry has improved specificity in comparison to a gold standard of high-risk HPV oncogene expression.[97]

Primary and Secondary Prevention of Oropharyngeal and Cervical Cancers

The development of methods for the primary and secondary prevention of cervical cancer with HPV virus-like particles (VLP) vaccines and cytology-based or HPV-based screening, respectively, serves as a model for the prevention of HPV-associated noncervical cancers. There are, however, current barriers to the development of analogous prevention strategies for HPV-positive HNSCC.

Death rates from cervical cancer have dramatically fallen in populations that have access to cervical cytology screening.[98,99] By contrast, there are no widely utilized and validated screening methods for HNSCC. A single cluster-randomized trial conducted in India demonstrated a reduction in oral cavity cancer mortality rates by use of screening with oral visual inspection for mucosal abnormalities (*e.g.,* leukoplakia, erythroleukoplakia, ulcers and masses),[100] but did not evaluate the utility of screening oropharyngeal cancer, a cancer that is considerably more difficult to detect with visual inspection.

The cervical transformation zone, where most cervical cancers arise, is relatively easily amenable to visual or colposcopic inspection and direct cell and tissue sampling. In contrast, the majority of HPV-positive cancers arise from the invaginating tonsillar crypt epithelium and are not visible on the surface epithelium. A recent study of a tonsillar papsmear equivalent observed strong associations between HPV16 and cancer in visible lesions, but no association between HPV16 and cytopathology in the absence of visible lesions.[101] Premalignant lesions for HPV-positive oropharyngeal cancer have been identified, albeit rarely, in tonsillectomy specimens.[71,102] Thus, the infeasibility of performing natural history studies of the histopathological progression of HPV-positive oropharynx in healthy subjects limits studies for secondary prevention of oropharyngeal cancer.

The persistent presence of high-risk HPV is necessary for the development of cervical cancer, and thus HPV detection is an excellent biomarker for risk of high-grade cervical dysplasia.[103] Natural history studies have identified persistent infection by HPV16 or 18 to be associated with greatest risk.[104] Indeed, a single round of HPV testing has been shown to reduce cervical cancer mortality in a large cluster-randomized trial in India.[105] Furthermore, randomized trials conducted in Europe have demonstrated a consistent reduction in CIN3 and invasive cancer among women who were HPV-negative *versus* cytology-negative in the first screening round.[106] Whether targeted detection of oral HPV16 infection could be used to identify individuals at risk for HPV-positive oropharyngeal cancer is unknown. This presupposes that the limitations regarding detection of precursor lesions noted above are resolved.

Prospective, randomized controlled trials have shown HPV virus-like particle (VLP) vaccines to have very high efficacy for the prevention of high-grade cervical dysplasia caused by HPV16 and 18 infection in HPV-negative subjects.[107,108] Whether the HPV vaccines prevent oral HPV16 infections is unknown. The design of clinical trials to evaluate the efficacy of HPV VLP vaccines for prevention of oral HPV infection has been impeded, in part, by lack of data regarding rates of incidence and clearance of oral HPV infection and lack of well-defined precancerous lesions (*i.e.,* the disease endpoint recommended by U.S. Food and Drug Administration, FDA). It is unclear as yet whether the FDA and other regulatory agencies will accept virological endpoints of efficacy (*i.e.,* incident and persistent HPV infection). Such acceptance would greatly facilitate and accelerate the evaluation of current and future HPV vaccines in different anatomical sites.

Assuming efficacy against oral HPV infections equivalent to that for cervical infection, a higher proportion of HPV-caused oropharyngeal cancers might be prevented with current generation vaccines, because the attributable fraction for HPV16 and 18 is 90-95%. An additional consideration for the potential of HPV vaccines to reduce the incidence of oropharyngeal cancer is rates of vaccine uptake in girls and boys. In most regions of the world, HPV-positive oropharyngeal cancer occurs at a 3:1 ratio of men to women. Vaccine uptake among girls must be sufficiently high (>80%) so as to prevent transmission of oral HPV16 infection to boys through herd immunity, or, vaccine must be directly administered to boys. Additionally, populations with vaccination rates sufficient for herd immunity might observe reductions in oropharyngeal cancer incidence as a consequence of reduced rates of genital-to-oral HPV transmission.

Conclusions and Avenues for Future Research

To increase our understanding of the etiology of HNSCC and the role of HPV infection and other risk factors, specific areas for future research are recommended.

First, the best established markers of malignant transformation in the presence of HPV DNA (*e.g.,* HPV16 *in situ* hybridization[26] and E6/7 mRNA[33,94]) should be used in large epidemiological studies. Second, these methods should be used in combination with accurate classification of the anatomic site of origin of the cancer. Last, we recommend analysis of the combined effect of HPV infection and tobacco and alcohol exposure in case control and cohort studies. Future studies need to better define the interaction between HPV infection and gender, tobacco, alcohol, and chronic inflammation in the causation of HNSCC from both statistical and biological perspectives. Natural history studies of oral HPV infection would be necessary for the development of primary and secondary prevention strategies analogous to those for cervical cancer. We acknowledge such studies are hampered by the low prevalence of infection in healthy populations and the current infeasibility of detection of premalignant lesions that are likely deep within tonsillar crypts.

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