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UPDATE

HPV and head and neck cancer

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Summary Head and neck cancer is frequent worldwide and oropharyngeal locations are presently sharply on the increase, in relation with an increasing incidence of oropharyngeal infection by oncogenic type-16 human papillomavirus (HPV). The clinical and biologic profile of these patients is distinct from that of other oropharyngeal carcinoma patients, with earlier onset, cystic cervical nodes and basaloid carcinoma histopathology. Detection of intratumoral viral DNA is essential to confirm the role of HPV, and *E6/E7* mRNA expression is the most relevant indicator for stratification. Several methods can reveal intratumoral oncogenic HPV DNA, but PCR with hybridization is the most sensitive and most widely used. According to several reports, prognosis in terms of survival and locoregional control is better in HPV-positive oropharyngeal carcinoma than in oropharyngeal carcinoma associated with smoking and alcohol consumption. The future lies in vaccination, but further studies will determine whether the rate of oropharyngeal carcinoma falls in women vaccinated against cervical cancer.

Introduction

Head and neck carcinoma is frequent, with the sixth highest incidence of all locations, worldwide. In France, incidence in 2007 was 14,697 (11,158 in males), ranking it in fourth place [http://globocan.iarc.fr], with 36,268 hospital admissions [1]. Ninety-five percent are squamous cell carcinomas. Alcohol consumption and smoking are usually associated. Prognosis is poor, with a risk of locoregional failure in advanced stages (III, IVa). In recent years, many studies have shown that some 25% of oropharyngeal carcinomas are associated with oncogenic or high-risk human papillomavirus (HPV), already widely implicated in cervical carcinoma [2—4]. HPV16 is the genotype implicated in some 90% of high-risk HPV oropharyngeal carcinomas, as compared to only 50% of cervical carcinomas [5]. The incidence of head and neck carcinoma associated with alcohol consumption and smoking is falling or stabilizing in western countries, but oropharyngeal carcinoma related to HPV is increasing so regularly that some speak of an ''epidemic'' [6—10]. Registry studies in the US and Scandinavia reported increases of 2.1% to 3.9% per year in the frequency of oropharyngeal cancer between 1973 and 2001, with hypopharyngeal and laryngeal cancer rates diminishing [8,10].

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Clinico-epidemiological profile of HPV-positive head and neck cancers

Notable features have been reported in head and neck cancer according to HPV status. Histopathologically, HPV-positive head and neck cancer tends to be less differentiated and of basaloid type. Oropharyngeal cancer, involving tonsils, tongue-base, soft palate or pharyngeal wall, is frequently HPV-associated, while laryngeal and hypopharyngeal locations are strongly associated with smoking and alcohol addiction [5,7]. This prime risk factor in HPV-negative oropharyngeal cancer is less frequently found in HPV-positive forms, this trend being significant in the case of alcohol. Possible synergy between HPV and alcohol consumption and smoking remains controversial [4,11,12]. According to Ang's team [13], survival in smokers with HPV-positive oropharyngeal cancer is lower than in HPV-positive non-smokers; likewise, HPV-negative patients' survival is better in case of non-smoking. Smoking seems to be an independent risk factor. HPV-positive oropharyngeal cancer patients are generally 5—10 years younger than HPV-negative patients. Several studies have demonstrated a relation between these cancers and certain forms of sexual behavior: early first sexual relations, history of genital warts, infrequent condom use, number of sexual partners and oral sexual practices [4,14]. Some authors consider that change in sexual behavioral patterns has contributed to the rise in HPV oropharyngeal cancer in the younger population [15]. Women with history of in situ carcinoma or cervical cancer and their partners also show elevated risk of HPV-positive oropharyngeal cancer, suggesting orogenital transmission, without necessarily excluding transmission by oral contact [16].

Unlike cervical cancer, exclusively implicating high-risk HPV, only some head and neck cancers are HPV-associated. A recent systematic review of 60 studies estimated a 25.9% overall prevalence of high-risk HPV DNA in head and neck cancer as a whole [3]. Prevalence was significantly higher (36%) in oropharyngeal cancer, and could exceed 50%, especially in tonsillar locations. Prevalence was 23.5% in oral cavity cancer and 24% in laryngeal cancer. A retrospective study (EDiTH VI) of 523 paraffin-embedded oropharyngeal and oral cavity cancer samples from 12 centers located all over France reported an HPV prevalence of 46.5% for the oropharynx and 10.5% for the oral cavity [17]; it reached 57% for tonsillar cancer [18], comparable to other reports for this location.

Genotype detection and identification is based on techniques that have evolved over time, which partly accounts for differences in literature reports, which also, however, reflect geographic variations in risk factors. The latter were demonstrated in a report of two case-control studies in Central European and Latin American populations, where the smoking/alcohol risk factor predominates [19]: HPV16 DNA prevalence was very low (4.4% in oropharyngeal cancer), despite the high-incidence of head and neck cancer in these regions.

HPV-positive oropharyngeal squamous cell carcinoma thus presents specific characteristics, and represents an original entity among head and neck cancers (Table 1).

Virology and pathogenesis

HPV is an environment-resistant species-specific epitheliotropic non-enveloped DNA virus [20]. It is implicated in a wide range of frequent and usually benign cutaneous and mucosal lesions. About 120 genotypes have been described, including some 40 liable to infect mucosa and at least 15 associated to precancerous and cancerous anogenital and upper aerodigestive tract mucosal lesions. HPV 16 accounts for 85—95% of HPVs detected in HPV-positive oropharyngeal tumors, other genotypes (notably, HPV 18 and 31) accounting for less than 10% [5]. In the French EDiTH VI study [17], HPV16 was reported in 89.7% of oropharyngeal cancers (89% for tonsillar locations), and 95.5% of oral cavity cancers.

Presently, the role of high-risk HPV is best proven in cervical carcinoma. Viral DNA is almost systematically detected, and persistent high-risk HPV infection of the cervix is the main risk factor for oncologic evolution, especially when the HPV16 genotype is implicated. Cervical cancer is now considered by the WHO as being virus-induced, although viral infection is not a sufficient condition. In vitro, high-risk

Table 1 Main characteristics of HPV-positive and negative patients.

	HPV-positive	HPV-negative
Biology	p53: increased catabolism (E6) pRb: increased catabolism (E7) Abnormal $p16^{INK4a}$ expression	p53 inactivation by mutation No pRb degradation $p16^{INK4a}$ -CyclineD1/CDK-pRb pathway deactivated: $p16^{INK4a}$ not expressed
Age	Younger patients (45—55 years)	Elderly (55—65 years)
Performance status	Good	Poor
Risk factors	Sexual: number of partners, early first sexual relations, oral sex	Alcohol/smoking
Adenopathy	Cystic	Tissular
Anatomopathology	Poorly differentiated or basaloid squamous cell carcinoma	Moderately or well differentiated squamous cell carcinoma
Prognosis	''Good''	Poor

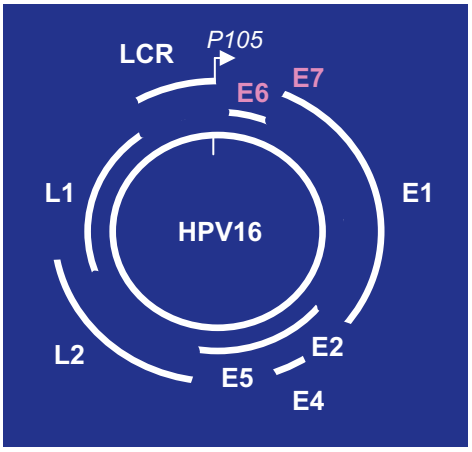

Figure 1 Schema of HPV16 genome. E: early region; L: late region; LCR: long control region.

HPV can immortalize primary keratinocytes, whether from the cervix, foreskin or tonsillar epithelium, but transformation occurs only after repeated passages or co-expression of another oncogene: i.e., additional events are necessary for a transformed phenotype to appear [21,22].

It is indispensable to detect viral DNA within the tumor to confirm the role of HPV in oncogenesis. *E6/E7* mRNA, however, is a more relevant indicator for stratification [23,24]. In cervical cancer, the *E6 and E7* genes are transcribed, and in vitro studies suggest that their expression is a prerequisite in maintaining the transformed phenotype. The same findings would seem to apply in HPV oropharyngeal carcinoma, although studies are as yet rare [23,25].

E6 and E7 proteins are coded by a particular, so-called ''early'', region of the viral genome (Fig. 1). They underlie the oncogenic properties of high-risk HPV. Their functions mainly depend on their interaction with numerous cellular regulatory and signalling pathways involved in cell proliferation, apoptosis, DNA repair and gene stability, transcription regulation, cell polarity, angiogenesis and immune response, thus mimicking most of the effects of gene alterations in other forms of cancer [21,22]. The cell cycle regulation pathways are a prime target of E6 and E7 viral proteins. pRb protein, an inhibitor of cell cycle progression in the S-phase of DNA replication, is targeted by E7 and degraded, inducing expression of $p16^{INK4a}$, another cell cycle inhibitor, commonly used as a marker for high-risk HPV, although actually reflecting a consequence of E7 expression. p53 protein, able to induce cell cycle arrest or apoptosis under various stimulations such as overexpression of an oncogene or cellular DNA abnormality, is degraded via E6, mimicking but not equivalent to the deactivating mutations of p53 frequently found in HPV-negative cancer, as E6 inhibition (under cisplatin treatment, for example) restores functional p53, whereas mutated p53 is definitively inactive. In summary, the properties of E6 and E7 in high-risk HPV promote cell survival and proliferation, avoidance of immune response and a genetic instability that contributes to the development of cancer.

In cervical cancer, viral genome integration into the cell genome is predominant and correlated with precancerous lesion progression, but is not a precondition for the development of cancer. HPV16 viral DNA is purely episomal in up to a quarter of cases. In oropharyngeal carcinoma, although there have been few studies and some of these were discordant, integrated forms would seem to be equally preponderant [22,26,27].

The mechanisms of viral oncogenesis in the oropharynx are probably similar to those of cervical cancer. The properties of E6 and E7 seemed similar in in vitro studies of genital and of oropharyngeal keratinocytes [22,23]. Differences related to the anatomic, cellular and immune environment and to contact with exogenic risk factors probably play a major role. Moreover, there is no region in the oropharynx equivalent to the uterine cervix's junction or transformation region, where the malpighian epithelium of the exocervix joins the unistratified glandular epithelium of the endocervix and which is where most cancers develop. In the tonsillar crypts, areas of malpighian epithelium alternate with areas of specialized reticulated epithelium associated with interruptions in basement continuity; some authors suggest that the crypts are preferentially targeted, enabling infection to endure and thus possibly accounting for the greater prevalence of HPV-positive cancer in the tonsils as compared to other head and neck sites [27,28].

Stratification of HPV head and neck cancers: detection of direct and indirect virologic markers

There are several methods for revealing high-risk HPV DNA in tumor tissue [29]. One of the earliest to be mentioned in the oropharyngeal cancer literature is in situ hybridization, using specific probes to determine the cellular location of the viral DNA. However, PCR (polymerase chain reaction) followed by hybridization with dedicated probes is the most sensitive and widely used technique, with numerous kits on the market. It is easy to perform on biopsy samples placed in transport medium or directly frozen. It can be performed retrospectively on paraffin-embedded tissue, but with lower sensitivity than in fresh or frozen tissue. E6/E7 mRNA induces expression of viral oncoproteins and is the most informative and relevant factor for stratifying high-risk HPV cancers. Samples should be placed in media enabling conservation of the labile RNA, which cannot be efficiently detected in paraffin-embedded sections. Immunohistochemical detection of $p16^{INK4a}$ protein (also known as p16) resulting from pRb degradation by E7 may further help detection of DNA, confirming the association with high-risk HPV, especially in patients with other risk factors in whom mRNA cannot be detected. Several studies have shown that most HPV tumors express p16 [7]; but it is to be borne in mind that some p16-positive tumors can be HPV-negative: p16 detection in itself does not reliably diagnose head and neck cancer associated with HPV, and needs supplementing by viral DNA detection.

The chromosomal alteration profile of HPV-positive oropharyngeal cancer seems generally similar to that of cervical cancer, but shows more differences with respect to HPV-negative oropharyngeal cancer [30,31]. Deletions and allele loss are more frequent in HPV-negative tumor. For example, deletion at 3p and 5q and amplification at 11q is frequent only in HPV-negative oropharyngeal cancer

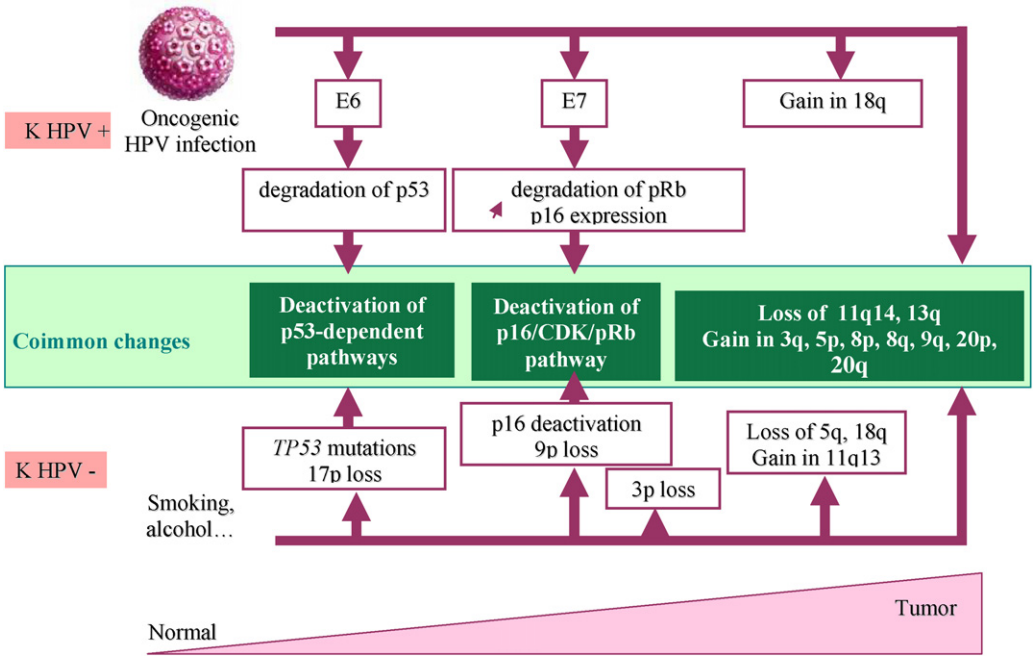

Figure 2 Model of head and neck oncogenesis.
Adapted from Smeets et al. [31].

(Fig. 2). Expression profiles correlate with these findings [32]. Affected regions often concern genes involved in cell cycle and growth [23]. Deactivation of p53-MDM2 and $p16^{INK4a}$-cyclin D1/CDK4/6-pRb pathways is common, resulting from mutations, deletions, methylation (9p21, CDKN2A coding $p16^{INK4a}$) or amplification (11q13, CCND1 coding cyclin D1) in HPV-negative cancer or from expression of high-risk E6 and E7 (degradation of p53 and pRb, activation of CDK) in HPV-positive cancer.

HPV status, prognosis and treatment response

Several studies showed HPV status to be a strong independent prognostic factor: prognosis in terms of survival and locoregional control is better in case of HPV-positive oropharyngeal carcinoma [13,33]. Treatment strategies in oropharyngeal carcinoma consist in various associations of local and lymph-node surgery, radiation therapy, concomitant radiochemotherapy, induction chemotherapy, biotherapy by targeted therapy and repair surgery [34,35]. Indications follow guidelines, but have yet to take account of HPV status. Comparative studies of oropharyngeal cancer treatment should henceforth include stratification according to HPV status.

Patients with HPV-positive oropharyngeal carcinoma show better treatment response to induction chemotherapy, concomitant radiochemotherapy and exclusive radiation therapy than HPV-negative patients. Fakhry et al. [36] reported significantly higher complete and partial response rates following induction chemotherapy (two cycles of carboplatin and paclitaxel) in HPV-positive than negative patients (82% versus 55%, $P = 0.01$). HPV-positive oropharyngeal carcinoma patients treated by conventional radiation therapy or surgery with or without postoperative radiation therapy also showed better local control and overall recurrence-free survival than HPV-negative patients [37—39]. On the other hand, adding a molecule promoting tissue hypoxia to radiation therapy improved local control and recurrence-free survival in HPV-negative but not HPV-positive patients [40].

Kumar et al. [41] reported better overall and specific survival in HPV-positive patients with low as compared to high EGFR expression. Smoking induces tissue hypoxia and may also increase EGFR expression. Metachronic tumor is also significantly less frequent in HPV-positive patients with low EGFR expression. HPV status may not, however, influence local control and recurrence-free survival under accelerated radiation therapy or EGFR inhibitors [42].

The search for biomarkers

The search for biomarkers to enable fine prognostic stratification and/or treatment optimization is an essential challenge. Some teams have suggested supplementary stratifications according to p53, $p16^{INK4A}$, EGFR, cyclin D1 or $p21^{WAF1}$, another cell cycle inhibitor [23,41,43,44]. Wild-form p53 and $p16^{INK4A}$ and $p21^{WAF1}$ expression are associated with improved prognosis. A Dutch team [45] crossed HPV status with a gene expression profile previously shown to be prognostic: the profile combined with HPV-negative status was associated with elevated risk of local recurrence after chemotherapy in advanced cancer. Further large-scale studies appear necessary.

Various viral markers may be prognostic at diagnosis and/or follow-up of oropharyngeal carcinoma, as demonstrated in precancerous and cancerous cervical lesions. The impact of HPV load and of mRNA coding for E6 and E7 detected at diagnosis and follow-up on recurrence and

survival remains to be determined. In cervical cancer, HPV16 DNA in pelvic nodes is predictive of recurrence. Viral DNA was detected in cervical nodes, invaded or not, in oropharyngeal carcinoma patients, but its prognostic value was not investigated [46]. Detecting viral DNA or *E6/E7* mRNA in invaded or non-invaded lymph-nodes would help determine the prognostic value. Likewise, in the uterine cervix, it has been clearly established that persistent high-risk HPV infection is predictive of progression toward high-grade dysplasia and cancer, especially when the viral load is elevated. Similarly, persistent infection after conization in dysplasia or radiation therapy in cervical cancer appears to be predictive of recurrence. The influence of recurrence or persistence of viral (viral DNA or mRNA) infection on relapse is not known; it may be hypothesized that recurrence or persistence of oncogenic HPV infection after treatment for oropharyngeal carcinoma is predictive of locoregional recurrence.

Perspectives

The number of HPV-related oropharyngeal carcinomas is constantly rising and the physiopathology of cervical cancer can be transposed to oropharyngeal cancer, with persistent viral infection inducing genetic changes then cell transformation. Persistent HPV infection of the head and neck, however, is at present poorly understood. Biological prognostic factors identifiable at diagnosis and follow-up of oropharyngeal carcinoma would be of great use. High-risk HPV is a prognostic factor that will very probably soon be used to optimize indications for radiochemotherapy or chemotherapy in these tumors. It is now indispensable to perform stratification according to HPV status and include these patients in randomized prospective studies so as to determine stratification-based treatment attitudes. Moreover, finer substratification (p53, p16, EGFR, etc.) should further refine indications. It is also essential to understand the mechanisms involved in variable response to radiation therapy and radiochemotherapy according to HPV status so as to determine adjuvant treatments to optimize response.

The relation of cervical cancer to HPV is now clearly established. A policy of vaccination for girls has been implemented for the last 5 years to prevent high-risk HPV-16 and 18 infection and the onset of associated precancerous and cancerous lesions of the cervix (Gardasil®, Sanofi-Pasteur-MSD, Cervarix®, GSK) and genital lesions related to HPV-6 and 11 (Gardasil®), the two low-risk genotypes implicated in 90% of cases of condyloma acuminatum and also in respiratory papillomatosis. The number of oropharyngeal cancers related to HPV infection is rising in most western countries, and the long-term aim should be to reduce incidence in vaccinated females; but this will require many years' observation. Then vaccination could be extended to males, as is already the case in certain countries to reduce the incidence of HPV-related male genital infection and cancer, with the further aim of reducing the incidence of HPV-related head and neck infection and cancer if the vaccines prove effective in preventing oropharyngeal infection.

Disclosure of interest

The authors took part in the EDITH VI study set up by Sanofi-Pasteur MSD to determine the genotypes found in oropharyngeal cancer in France [17,18].

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