Editorial

Focus on HPV-driven head and neck cancers

A brief search on Pubmed.org reveals a continuous increase in the number of publications regarding HPV (Human Papillomavirus) in Head and Neck Cancers (HNC): from less than 10 per year in the 1990's to over 100 in the present decade, with about 10 review articles solely in 2017! Many reasons account for such significant change, remarkably the recognition of high-risk HPVs (mainly HPV-16) as the etiological agent of a substantial proportion of HNC, although highly heterogeneous by cancer anatomical site, geographical region and gender. In fact, several features are being explored in diverse studies and trials around the World, which reflect on the large number of papers on the subject presented at the 31st International Papillomavirus Conference held in Cape Town (South Africa) last March. This Editorial highlight the reasons for the increased focus on HPV-related HNC.

HNC is a relatively common cancer that affects more males than females with an estimated incidence of about 700,000 cases per year and a high mortality rate worldwide. Although undoubtedly the main etiological factors for HNC are tobacco and alcohol consumption, a subset of oropharyngeal cancers (OPC) have been shown to be induced by high-risk HPVs, particularly HPV-16[1]. A steady raise in OPC is observed in the last decade in Northern Europe and in the US, which seems to reflect not only the reduction of smoking and drinking among these populations, but also an increase in HPV related OPCs (especially among men).

It is important to highlight that the fraction of HPV-driven OPCs clearly varies among geographical regions: whereas most OPC in the US (60%) are HPV-16 positive, in Europe this proportion is 31%, and solely 4% in Brazil[2]. Previous reports have pointed out for the low prevalence of HPV in HNC from Brazil, as compared to the HNC from other countries[3,4]. Significant differences in the prevalence of HPV in HNC have also being recorded in hospital series from the city of São Paulo[5]. Moreover, a wide variation is observed within European sub-regions, with globally higher detection in Northern Europe and lower in Southern Europe[1]. The clinical relevance of such divergence remains to be determined.

Geographical divergence in HPV-16 induced OPC rates could be attributed to differences in tobacco and alcohol use throughout different countries. Indeed, Anantharaman et al.[2] reported that ever smokers and ever drinkers were less likely to be HPV-16 positive. However, smoking prevalence reported in the general population of these regions does not clearly support this hypothesis. Alternatively, differences in oral sex behavior could contribute to the variability in the incidences observed, although this is a controversial issue.

Another intriguing aspect in the viral etiology of some HNC refers to the marked heterogeneity of HPV across anatomical sites. It has been estimated that the HPV attributable fraction in cancer of the hypopharynx, larynx and oral cavity is about five times lower than OPCs[1]. Interesting to note that even within the oral cavity, subsites more proximal to the oropharynx hold higher HPV attributable fractions as compared to those more distal from the oropharynx. Even so, geographical variation in HPV induced non-oropharyngeal HNC is maintained ranging from 7% in the US and 5% in Europe, to 0% in South America. Taken together, these data points towards a substantial contribution of HPV-16 for OPCs, which is however limited for oral cavity and laryngeal cancers.

Evidence is accumulating that links HPV-positivity to a better prognosis and response to treatment in comparison to alcohol and smoking related HNC[6]. Of note, the use of different HPV detection assays hampers the comparability of results stemming from different studies and, even more important, testing HPV in tumors is not routinely performed. In this direction, the search for additional biomarkers is crucial to early diagnosis and proper clinical management of patients.

Several studies in HNC have shown that the detection of HPV DNA alone is an insufficient proof for viral causality, thus requiring the evaluation of other individual or combined biological markers for the definition of truly HPV-driven tumors. A variety of algorithms have been proposed, including the detection of HPV RNA, antibodies against viral early and late oncoproteins, and $p16^{ink4a}$, pRb, p53 and Cyclin D1 protein expression as surrogate markers of HPV-induced transformation. Advantages and limitations for each of these markers have been described. Of note, Castellsagué et al.[1] reported that using either or both E6*I mRNA or $p16^{ink4a}$ together with viral DNA yielded comparable HPV attributable fractions for oropharyngeal, oral cavity or laryngeal cancers, and that differences between methods derived mostly from the lack of $p16^{ink4a}$ expression in a small fraction of HPV DNA and mRNA positive tumors. Nevertheless, others argue that the specificity of $p16^{ink4a}$ for non-oropharyngeal HNC is low. Moreover the pattern of HPV-16 status and $p16^{ink4a}$ expression in OPC has been shown to differ by race, being significantly higher in Whites as compared to Black and Asian individuals[7]. This trend was not observed in non-oropharyngeal HNCs.

HPV-16 serology has been assigned as a very sensitive and specific biomarker capable of predicting OPC onset. For instance, recently Kreimer et al.[8] analyzed the kinetics of HPV-16 E6 antibodies preceding OPC development and showed that stable antibody levels can be detected more than 10 years prior to cancer diagnosis. In addition, detection of viral HPV DNA in oral rinses and of HPV antibodies in the sera of patients with OPC could contribute to determining the potential risk of recurrence of HPV-positive HNC.

Further studies and clinical trials are warranted to better elucidate the diagnostic and therapeutic implications of HPV in HNC. The identification of additional biomarkers is in fact the subject of several ongoing studies, some of which were presented at the last International Papillomavirus Conference (www.hpv2017.org). Information on the different etiologies of HNC is seminal to develop more precise guidelines to benefit patients with HNC. Last but not least, the accumulated knowledge will contribute to understand the impact of HPV prophylactic vaccination in the reduction of HNC worldwide.

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