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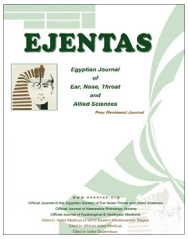

REVIEW

Human papillomavirus positive oropharyngeal cancer: The general information

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KEYWORDS

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Abstract Oropharyngeal squamous cell cancer (OPSCC) and especially Human papilloma virus positive (HPV+) OPSCC incidence is increasing worldwide over the last decades while the incidence of overall head and neck squamous cancers has declined in developed countries. HPV + OPSCC has favorable prognosis and is seen in younger patients with lower exposure to tobacco and alcohol. This review will summarize our current understanding about HPV + OPSCC and clinical differences comparing with HPV − OPSCC including current therapy approaches and describe the clinical importance of determining the HPV status.

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1. Introduction

Human Papilloma Virus (HPV) are a heterogeneous group of small epitheliotropic double stranded DNA viruses with more than 200 types identified.[1] HPV are arranged into classes depending on their tissue tropism with mucosal HPV called alpha and cutaneous types classified as beta, gamma, nu and mu.[2] There are 15 types that are thought to have a high- risk oncogenic potential. High-risk types are linked with cervical cancers, rarer anogenital cancers as well as oropharyngeal squamous cell carcinoma (OPSCC). Oncogenic types 16, 18, 31, 33 and 35 are associated with OPSCC and more than 90% of HPV + OPSCC and 52–58% of cervical cancers are induced by high-risk HPV16.[3]

Epidemiological studies show that OPSCC and especially HPV + OPSCC incidence is increasing worldwide over the last decades while the incidence of overall head and neck squamous cancer (HNSCC) has declined in developed countries.[4] Presently, the incidence of OSCC in the United States (U.S.) is 6.2/100.000 for men and 1.4/100.000 for women.[5] HPV is thought to be the primary cause for this increasing incidence of OPSCC and especially develops from the epithelium lining the crypts of the palatine tonsils and base of tongue.[6]

In England the patients with diagnosis of tonsillar cancer were 281 in 1997 and it increased to 703 in 2007; and in Sweden the cases of tonsillar cancers are twice in number between 1970 and 2006 with HPV positivity increased from 23% to 79%.[7,8] In 2005, Begum et al.[9] detected HPV in 82% of patients with tonsillar carcinoma. In recent studies prevalence of HPV in OSCC is at least 60–70% and it is rising.[10] Tural et al. demonstrated the same increase of HPV positivity in 81 Turkish patients with OPSCC. In this study HPV+ cases were 33% in 1996–1999, 43% in 2000–2003, 55% in 2004–2007 and 70% in 2008–2011. They detected 86% HPV16, 12% HPV18 and 2% HPV33 from the samples.[11]

Cervical cancer is the third most common gynecological cancer type in the world and approximately 500.000 women are diagnosed as cervical cancer, yearly.[12] HPV-DNA presence was shown in 95% of the cervical cancer cases. HPV16 was first isolated from cervical carcinoma in 1983 and since then a significant effort has been dedicated to determine the oncogenesis of HPV in the etiology of cervix cancer.[13] With its increasing incidence of HPV + OPSCC it is predicted that in the year 2020 the number of HPV + OPSCC will be greater than HPV related cervical cancers.[10]

2. Patients profile

HPV + OPSCC has favorable outcomes and is seen in younger people with lower exposure to tobacco and alcohol comparing with HPV − OPSCC.[14] HPV + OPSCC are mostly seen in men with high socioeconomic status who are more likely to be married.[4,15] HPV positive cancers have a distinct biology with lower T stage and higher nodal status with high American Joint Committee on Cancer (AJCC) stage. However these patients have surprisingly better prognosis with 60–80% reduced risk of death comparing with HPV − OPSCC.[16] This prognostic advantage of HPV + OPSCC persists in multivariate analyses with adjustment for age, tobacco exposure, performance status and comorbidities.[17]

3. Risk factors

Sexual transmission of HPV to oropharyngeal sites, requires mucosal orogenital skin to skin contact.[18] HPV + OPSCC patients have more exposure to sexual behaviors as compared with HPV − OPSCC. Likewise sexual behaviors have an important role as studies connected HPV + OPSCC with increased lifetime number of oral and genital sexual partners, younger age at the time of first sexual intercourse, infrequent use of condoms and history of previous sexually transmitted infection.[19] Women with HPV + cervical cancer or carcinoma insitu and their partners are at increased risk of HPV + OPSCC.[20]

Marijuana usage may also be another risk factor. Patients with HPV + OPSCC have more marijuana exposure with increasing intensity and duration comparing with HPV − OPSCC.[15] Beside this tobacco and alcohol exposure does not act synergistically with HPV to increase the development of HPV + OPSCC. Also some studies reported that French kiss (open mouth kissing) was found to be related with the development of oral HPV infection.[21] But on the other hand some other studies have not found any relationship.[22]

4. Radiologic and histopathologic findings

Cystic metastatic cervical nodes have been strongly associated with HPV + OPSCC that can cause erroneous diagnosis of branchial cleft cyst.[23] Finding HPV in a cervical metastasis with unknown primary site is a strong indicator of oropharyngeal site for squamous cell cancers. Studies revealed distinct radiological features of tumor and nodal characteristics between HPV statuses. For example, HPV + OPSCC are more likely to demonstrate exophytic well-defined borders, whereas HPV − OPSCC tumors are likely to demonstrate invasion of adjacent structures. In addition, well-defined cystic metastases are suggested to be associated with HPV positivity.[24]

At first studies HPV + OPSCC presented as poorly differentiated with basaloid morphology.[25] But recently with further histopathological analysis it is described as well differentiated because of the similarity in morphology to the reticulated epithelium of the tonsillar cypts.[26]

5. Prognosis

It is not clear what could be responsible for the differences in survival between HPV+ and HPV− patients. One difference

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