Human Papillomavirus & WHO Type I Nasopharyngeal Carcinoma

Emily J. Lo, BA1,4; Diana Bell, MD3; Jason Woo, BS1,5; Guojun Li, MD, PhD1; Ehab Y. Hanna, MD1; Adel K. El-Naggar, MD, PhD1,3, Erich M. Sturgis, MD, MPH1,2

1Departments of Head and Neck Surgery, 2Epidemiology, and 3Pathology
2The University of Texas MD Anderson Cancer Center, Houston.
3Baylor College of Medicine, Houston.
4University of Texas Southwestern Medical School, Dallas.

ABSTRACT

Objectives: Nasopharyngeal carcinoma (NPC) is a rare cancer in the U.S. that has a well-established association with Epstein-Barr virus (EBV) for WHO types III/II but less so for WHO type I. Given the rise in oropharyngeal tumors positive for high-risk human papillomavirus (HPV) and the unique biology of WHO type I NPC, we chose to examine the relationship between HPV and WHO type I NPC.

Study Design: Retrospective case-control study.

Methods: A search of a large multidisciplinary cancer center tumor registry identified 183 patients seen from January 1999 to December 2008 with incident NPC and no history of prior cancer. Available paraffin-embedded tumor specimens (N=30) were analyzed for HPV status by in situ hybridization (ISH), polymerase chain reaction (PCR) for HPV 16 and 18, EBV status by ISH, and p16 expression by immunohistochemistry. Demographic parameters, including race, smoking, and alcohol exposure were obtained from the medical records.

Results: Patients with incident WHO-I NPC (N=18) tended to be smokers (66%) and only 17% were Asian, while for patients with incident WHO-III NPC (N=165), 44% were smokers and 24% were Asian. For WHO-I NPC patients with available paraffin blocks (N=8), 5 of 6 were HPV 16+ and 1 was HPV 18+. All of the HPV 16+ NPC were EBV+ by ISH, while only 2 of 8 were EBV+. Of patients with WHO-II/III NPC and available archival tissue (N=22), 60% were EBV+ and only one was HPV positive by ISH.

Conclusions: These results suggest that WHO type I NPC may be associated with oncogenic HPV, though larger studies are needed to verify these findings.

RESULTS

Table 2: Demographics for all patients with incident NPC (1999-2008)

| Variable          | Number | (%)
|-------------------|--------|-----
| Age               | 4 (18.2) | 9 (50.0) | 5 (27.8)
| Smoke             | 4 (18.2) | 9 (50.0) | 5 (27.8)
| Alcohol           | 4 (18.2) | 9 (50.0) | 5 (27.8)
| p16               | 4 (18.2) | 9 (50.0) | 5 (27.8)

Table 3: Demographics and characteristics of patients with incident NPC (1999-2008)1

| Characteristic     | Number | (%)
|-------------------|--------|-----
| Age               | 4 (18.2) | 9 (50.0) | 5 (27.8)
| Smoke             | 4 (18.2) | 9 (50.0) | 5 (27.8)
| Alcohol           | 4 (18.2) | 9 (50.0) | 5 (27.8)
| p16               | 4 (18.2) | 9 (50.0) | 5 (27.8)

DISCUSSION

Though endemic to Southern China, nasopharyngeal carcinoma remains a rare cancer in the United States. There is extensive literature investigating genetics, environmental exposures, diet, and the role of Epstein-Barr virus (EBV) in the pathogenesis of Nasopharyngeal Carcinoma (NPC). For WHO type III/II NPCs, the virus has been most commonly detected in WHO-I/II NPC; however, the fact that a significant subset of NPC patients are EBV negative suggests that other important risk factors play a role.1,2 High risk HPV may contribute to the development of NPC, as its role has been described in the etiology of head and neck squamous cell carcinomas, particularly the oropharynx.

Recent decades have seen a shift in the epidemiology of head and neck squamous cell carcinomas, likely in association with a decrease in EBV infection. Despite the decreasing prevalence of cigarette smoking and a subsequent decline in head and neck carcinoma incidence, the incidence of oropharyngeal and OSCC continues to rise, especially in non-smokers less than 60 years of age.3-6 HPV-positive tumors tend to originate in the oropharynx, have poorly differentiated histology, and are less likely to have the TP53 mutation. Compared to NPC, the virus has been detected in 50-70% of tumors and 90% of these are HPV-positive.

Epidemiologic studies have reported a geographic variation in the prevalence of HPV-positive NPC, with the highest reported among Japanese, second highest among North Americans, and the lowest among Orientals.7

In the United States, there is extensive literature investigating genetics, environmental exposures, and diet to explain the increased risk in certain populations.8

The role of cigarette smoking and alcohol consumption in the development of NPC has been extensively investigated. Patients with incident WHO-I NPC tended to be smokers with greater pack-years of use (mean 53.8, SD 37.6), while other studies have failed to demonstrate a statistically significant relationship between smoking and WHO-I NPC, but not in non-keratinizing NPC, and the link between smoking and WHO-I NPC may be more pronounced for patients presenting over 50 years of age.

Patients with incident NPC (N=165) compared with studies in China and Taiwan (7%).30

In NPC, we chose to examine the relationship between HPV and WHO type I NPC.

26-27 HPV positive tumors tend to be the most aggressive in terms of survival, with a statistically significant survival advantage for non-keratinizing over keratinizing NPC.

In NPC, we have shown to be an independent prognostic factor, chiefly this survival advantage is for non-keratinizing NPC, while others suggest that both viruses contribute to carcinogenesis in non-keratinizing NPC via coinfection.

The role of p16 in NPC has been questioned, with some suggesting that p16 may have no role in NPC, while others have shown that p16 expression is associated with better outcomes in NPC.

Asians may be due to an increased resistance of type I NPC to radiotherapy.

Additionally the WHO-I patients tended to be smokers with greater pack-years of use (mean 53.8, SD 37.6), while other studies have failed to demonstrate a statistically significant relationship between smoking and WHO-I NPC, but not in non-keratinizing NPC, and the link between smoking and WHO-I NPC may be more pronounced for patients presenting over 50 years of age.

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