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Etiological factors of nasopharyngeal carcinoma

Sai Wah Tsao [a,*], Yim Ling Yip [a], Chi Man Tsang [a], Pei Shin Pang [a], Victoria Ming Yi Lau [a], Guitao Zhang [a], Kwok Wai Lo [b,*]

[a] Department of Anatomy and Center for Cancer Research, LKS Faculty of Medicine, The University of Hong Kong, Hong Kong Special Administrative Region
[b] Department of Anatomical and Cellular Pathology and Li Ka Shing Institute of Health Science, The Chinese University of Hong Kong, Hong Kong Special Administrative Region

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SUMMARY

Nasopharyngeal carcinoma (NPC) is a common disease among southern Chinese. The major etiological factors proposed for NPC pathogenesis include genetic susceptibility, environment factors and EBV infection. In the high risk population, genetic susceptibility to NPC has been mapped to the HLA loci and adjacent genes in MHC region on chromosome 6p21. Consumption of preserved food including salted fish has been implicated in its etiology in earlier studies. Its contribution to pathogenesis of NPC remains to be determined. A decreasing trend of NPC incidence was observed in Hong Kong, Taiwan and Singapore in recent years which may be accounted by a change of dietary habits. A comprehensive epidemiological study will help to elucidate the relative importance of various risk factors in the pathogenesis of NPC. Despite the close association of EBV infection with NPC, the etiological role of EBV in NPC pathogenesis remains enigmatic. EBV infection in primary nasopharyngeal epithelial cells is uncommon and difficult to achieve. EBV does not transform primary nasopharyngeal epithelial cells into proliferative clones, which contrasts greatly with the well-documented ability of EBV to transform and immortalize primary B cells. Genetic alterations identified in premalignant nasopharyngeal epithelium may play crucial roles to support stable EBV infection. Subsequently, latent and lytic EBV gene products may drive clonal expansion and transformation of premalignant nasopharyngeal epithelial cells into cancer cells. Stromal inflammation in nasopharyngeal mucosa is believed to play an important role in modulating the growth and possibly drive the malignant transformation of EBV-infected nasopharyngeal epithelial cells. Furthermore, there are increasing evidences supporting a role of EBV infection to evade host immune surveillance. EBV-infected cells may have selective growth advantages in vivo by acquiring a stress–resistance phenotype. Understanding the etiological factors and pathogenesis of NPC will contribute effectively to the prevention and treatment of this disease.

Geographical distribution of nasopharyngeal carcinoma

Nasopharyngeal carcinoma (NPC) stands out from other epithelial cancers arising from the head and neck regions in its distinct geographical distribution and close association with EBV infection [1,2]. The anatomic site of NPC is also unique which may implicate a contributing role of microenvironment in its pathogenesis. The incidence rate of NPC is remarkably variable worldwide. In most parts of the world, NPC incidence is low (<1/100,000 per year). NPC incidence is high among ethnic southern Chinese and native Eskimos living in Greenland and Alaska. High incidence of NPC is also seen in regions in North Africa. Globally, approximately 65,000 new cases of NPC are reported each year and more than 80% are from southern China and Southeast Asia. The highest incidence rate of NPC is amongst Cantonese living in Hong Kong and Guang-dong province of Southern China (>20 per 100,000 per year in males) [3–5]. Relatively high incidence of NPC was also reported in other provinces of Southern China region including GuangXi, Fujian and Hunan. The incidence rate of NPC is low in Northern China (~1 to 5 per 100,000 persons per year). Notably, southern Chinese migrated to non-endemic regions still retains a much higher incidence rate compared to other ethnic groups living in the same geographical regions. Among the high-risk population, incidence of NPC peaks between 45 and 54 years old and declines thereafter. For unknown reason, men are roughly 2–3 folds more frequently affected than women [3–5]. The remarkable racial and geographic distribution of NPC suggests a strong association of NPC with genetic susceptibility and environmental factors.

* Corresponding authors. Address: Laboratory Block, Department of Anatomy, LKS Faculty of Medicine, The University of Hong Kong, Hong Kong Special Administrative Region. Tel.: +852 28199227; fax: +852 28170857 (S.W. Tsao).
E-mail addresses: gswtsao@hku.hk (S.W. Tsao), kwlo@cuhk.edu.hk (K.W. Lo).

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Interestingly, the incidence rate of NPC has been decreasing continuously in Hong Kong from 1980 (28.5/100,000 in males and 11.2/100,000 in females) to 2009 (14.0/100,000 in males and 4.6/100,000 in females), a mark decrease of over 50% in the past 30 years [6,7]. The decreasing trend in this high-risk region may reflect the change of certain risk factors related to dietary habits and lifestyle. The continuous immigration of Chinese from non-endemic region to Hong Kong may also contribute partly to the decreasing incidence rate of NPC [8]. Similar decreasing trend was also reported in Taiwan [9] and Singapore [10]. The decreasing trend of incidence of NPC in the past 20–25 years was however not observed in other regions of Guangdong province, including Sihui and Cangwu counties, where traditional dietary habits were still maintained until early 1990's [11].

Histopathology of NPC

The nasopharynx is a tubular space situated at the base of the skull. It represents a transitional area between the nasal cavities and the oropharynx, forming part of the Waldeyer ring of lymphoid tissues. The nasopharyngeal mucosa shows numerous folds and crypts. It consists of a special type of stratified squamous epithelium referred as intermediate or transitional epithelium [12]. Variable amount of mixed stratified squamous epithelium and ciliated epithelium are present at the lateral and posterior wall of the nasopharynx. Aside from sero-mucous glands, abundant infiltration of lymphocytes are found in the underlying stroma of the nasopharyngeal epithelium. NPC is commonly developed from the lateral wall of nasopharynx, especially at the fossa of Rosenmüller and superior posterior wall [13]. The WHO classification in 1978 recognized three histological subtypes of nasopharyngeal carcinoma: squamous cell carcinoma (WHO type 1), nonkeratinizing carcinoma (WHO type 2), and undifferentiated carcinoma (WHO type 3) which was modified in 1991. The WHO type 1 NPC was retained, while the WHO type 2 and type 3 are combined into a single category of "nonkeratinizing carcinoma", which was further subdivided as "differentiated" or "undifferentiated" [14]. The histological features of keratinizing squamous cell carcinoma of NPC are similar to squamous cell carcinoma arising from other sites of the head and neck regions with well-differentiated histological features including presence of intercellular bridges, keratin production and epithelial pearl formation. NPC in the endemic areas of Southern China is mainly of the nonkeratinizing carcinoma which occupies up to 99% of all cases. The nonkeratinizing carcinoma lacks keratinization features and is ubiquitously associated with EBV infection [4,15].

Etiological factors of NPC

The epidemiological studies reveal distinctive ethnic and geographic distribution of NPC strongly indicating that genetic susceptibility plays a major contributing role. The aforementioned decreasing trends of NPC incidence reported in Hong Kong, Taiwan and Singapore population indicate that alteration of dietary habits and change in environment factors may also alter incidence rate of NPC. The clonal origin of EBV infection and its ubiquitous presence in NPC strongly indicates its involvement in NPC pathogenesis [2]. EBV infection, together with genetic susceptibility and environmental factors are considered as the three major etiological factors of NPC among southern Chinese in endemic areas of NPC.

Genetic susceptibility

The distinct ethnicity of NPC indicates the important contribution of genetic susceptibility to the pathogenesis of NPC. As stated earlier, the incidence of NPC is 20–50 folds higher in southern Chinese compared to populations in Western countries. Notably, the secondary and third generations of the southern Chinese who emigrated to low incidence area in the USA still retains a higher risk of NPC than the resident population despite of cultural assimilation [16]. Familial clustering of the disease was observed at a frequency around 10% among Chinese patients [17]. Sharing common environmental risk factors may also account for familial aggregation of NPC and may be difficult to distinguish from inherited genetic susceptibility. Nonetheless, genetic susceptibility loci to NPC in high-risk population have been reported notably the association with the HLA class I genes in the MHC locus at chromosome 6p21 [18]. The HLA class I genes encode proteins to identify and present foreign antigens, including EBV-encoded peptides, to the cytotoxic T cells to trigger the host immune response against virally infected cells. The variable degree of susceptibility to NPC among different ethnic populations may reflect the differential ability of HLA haplotypes in controlling EBV infection in infected populations. Individuals with specific HLA alleles may be less efficient in mounting a cytotoxic immune response against EBV-infected cells and may contribute to increased susceptibility to NPC. An early study in affected sib pairs from southern China identified a NPC susceptible locus closely linked to the HLA region [19]. A large scale genome-wide association studies (GWAS) reported recently also revealed that genes within the HLA region on chromosome 6p21 are strongly associated with NPC [20]. Independent and strong association signals in the HLA-A and HLA-B/C loci were observed. Other studies have also confirmed the consistent association of NPC risk with HLA regions [21]. However, several non-HLA genes including GABBR1 and MICA in the HLA region also show strong association on NPC susceptibility [22,23]. Apart from the genes in HLA region, significant association with MDS1-EVI1 at 3q26.2, CDKN2A/2B at 9p21.3, and TNFRSF19 at 13q12.12 was also reported [20]. Identification of the causal variants in these loci and elucidation of their functions should enhance our understanding on the contribution of genetic factors in NPC pathogenesis.

In addition to GWAS, three pedigree-based linkage studies performed in high-risk NPC Chinese families have also identified NPC associated genes with high penetrance. Using microsatellite polymorphic markers, three disease susceptibility loci on chromosomes 3p21.3, 4p15.1-q12 and 5p13 were identified from high-risk NPC Chinese pedigrees [24–26]. However, the susceptibility locus identified in each of these familial studies is diverse. These non-concordant findings may be due to genetic heterogeneity and limited number of the Chinese familial NPC cases in these studies. Fine-mapping and functional characterization of these susceptibility genes are warranted.

Case-control studies have demonstrated a link between genetic polymorphism and NPC risk by influencing the individual susceptibility to EBV infection and/or chemical carcinogen-induced cell transformation. By candidate gene-based approach, increased risks of NPC were shown to be associated with genetic polymorphisms involved in nitrosamine metabolism (CYP2E1, CYP2A6), detoxifying carcinogenic electrophiles (GSTM1), DNA repair (XRCC1, hOGG1, NBS1), EBV entry into nasopharyngeal epithelium (PIGR), interleukins (IL1A, IL1B, IL2, IL8 and IL10) and toll-like receptors (TLR3, TLR4, TLR10) [27–36]. Significant correlation of variants of cancer-associated genes, including TP53, MDM2, CCND1 and NEDD4, was also reported to be associated with increased NPC risk among southern Chinese [37–41].

Environmental factors

A number of agents in the environment have been postulated to be associated with NPC risk. It has been reported in earlier studies that the ingestion of Cantonese-style salted fish, especially during