REVIEW

NASOPHARYNGEAL CARCINOMA: EPIDEMIOLOGICAL REVIEW IN RELATION TO ITS ETIOLOGY

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Introduction

Nasopharyngeal Carcinoma

Nasopharyngeal carcinoma is a malignant tumor arising from the epithelial cells(1) lining a recess along the lateral wall of the nasopharynx named "Fossa of Rosenmuller" (2,3). It is one of the most rapidly developing tumors of the head and neck and comprises more than two thirds of all tumors arising in the nasopharynx (4). Unlike other head and neck cancers, the natural history of nasopharyngeal carcinoma unfolds certain features, which make this cancer a special entity by itself. One of the most unique features is its geographic distribution. While its incidence among the people living in the Southeastern region of China and Hong Kong and their descendants living in other parts of the world is as high as 30 per 100,000 per year for males(5), its incidence among those living in the rest of the world is less than 1 per 100,000 per year. Besides ethnic Chinese, other local ethnic Mongoloid group of people living in the South-East Asian countries have a relatively higher risk as compared to Caucasians living in the same geographic regions (6). People at intermediate risk to the development of nasopharyngeal carcinoma are those from certain northern African countries (4) like Morocco, Tunisia and Algeria, and from Arctic regions like Alaska and Greenland (7). Another unique feature of nasopharyngeal carcinoma is its incidence at relatively early age. For most cancers, the incidence is low before the age of 55 years which steadily increases after this age with no tendency to decline. For nasopharyngeal carcinoma there is significant rise in incidence (10 per 100,000 per year) from the age of 30 and after reaching a plateau between 40 and 49 years (8) the incidence rate steadily decreases. For the Malaysian Chinese male in the age group 40-49 years, the age-adjusted incidence rate was noted to be as high as 40.1 per 100,000 per year (8). Almost 75% of patients belonged to the age group 30-60 years. This observation was more obvious among patients of Chinese and South-East Asian origin.

So far as sex incidence is concerned the average male to female ratio is 2.5 to 1. This sex incidence has been noted to be almost uniform among the patient population all over the world, without much variation.

It is generally considered that the etiology of nasopharyngeal carcinoma is multifactorial with at least three factors playing their respective roles. The factors are genetic, Epstein-Barr Virus (EBV), and other environmental agent/s which has/have EBV-activating and/or co-carcinogenic function. While considering these factors from the epidemiological point of view it is essential to have the background knowledge of the histogenesis of this cancer so as to interpret the relevance of epidemiological information in relation to its actual development.

The epithelial origin of nasopharyngeal carcinoma is now well established (1,4), and so is the fact that irrespective of the type of cell lining (whether stratified squamous or pseudostratified columnar), it is the squamous cells either original or metaplastic (pseudostratified columnar cells after having undergone metaplastic/dysplastic change) which undergo neoplastic transformation (9,10,11). It has been noted that the basal cells of the pharyngeal epithelia are endowed with receptors for EBV(12) which facilitate its entry. It is felt that the subsequent interaction of EBV DNA with the DNA of basal cells could be the crucial event in bringing about the neoplastic change (13). A question often raised is whether EBV infects normal epithelial cell in the nasopharynx or after dysplastic/metaplastic changes have occured (11). None the less, the presence of EBV DNA has been consistently noted in each and every viable nasopharyngeal carcinoma cell obtained from all parts of world (14). Besides, all the three histopathological types of nasopharyngeal carcinoma (WHO I or the keratinising squamous cell carcinoma, WHO II or the non-keratinising carcinoma and the WHO III or the undifferentialed carcinoma), as defined by the World Heath Organisation (15) have been noted to be associated with EBV (16).

In so far as pathogenesis is concerned there is a need to put together the role of genetics, EBV and other environmental factors which effect the ultimate change (17). EBV, which in normal circumstances remains dormant due to factors yet to be firmly established springs into activity and paves the way for changes in multiple step fashion towards malignancy. Genetic factors inherent in the cells play a role, most probably in all the steps involved.

Epidemiology

Epidemiology can be descriptive (or observational) or analytic. The former states the facts as observed which forms the basis for generating a hypothesis, while the latter attempts to test the hypothesis through laboratory assays using various techniques. These techniques could be used to study various factors like etiology, pathogenesis, diagnosis and control of a particular disease.

In this article an attempt is made to look into the etiological factors involved in the development of nasopharyngeal carcinoma using descriptive as well as analytic epidemiological methods.

Etiological factors

Genetics

With regards to the role of genetics in the etiology of nasopharyngeal carcinoma, the main support is from a descriptive studies which include unique geographic distribution, familial clustering in low-risk population (18) and the increased risk of developing this cancer in individuals with a family history of the disease (19). However the observation of a lower risk among second and third generation migrant Chinese as compared to native Chinese (20) favors a role of environmental factors over genetic factors.

Analytic studies have largely been centered around the examination of specific genetic markers of susceptibility like Human Leucocyte Antigen (HLA) studies (21,22), study of the immunoglobulin allotypes (23), red cell enzymes and serum proteins (24). Association of Chinese nasopharyngeal carcinoma with HLA-A2/BW46 has been observed in several studies (21,25,26) and association of HLA antigens other than A2/BW46 has been observed in non-Chinese population (22,27). In another study (28) involving 30 families with at least two siblings affected with nasopharyngeal carcinoma, a 21-fold increased risk was attributed to a gene closely linked to the HLA locus, still undetermined.

Results of studies to investigate the relation of immunoglobulin allotypes, red cell enzymes, serum protein and other potential genetic markers have so far remained conflicting and not much progress has been made in this direction.

Epstein-Barr Virus

It is generally believed that EBV is etiologically associated with the development of nasopharyngeal carcinoma. Evidences in support of this belief are both observational as well as analytic.

Since the time Old *et al* (29) noted unusually strong precipitating bands against EBV antigens in the sera samples from nasopharyngeal carcinoma patients and Henle *et al* (30) established that immunoglobulin A antibody titer against the viral capsid antigen of EBV was significantly elevated in 93% of nasopharyngeal carcinoma patients, there have been many similar reports in the literature. Furthermore, this titer was noted to have been raised even up to 41 months prior to the confirmation of nasopharyngeal carcinoma in a group of patients observed during a survey conducted in China (31). These sero-epidemiological findings suggest that the change in the state of EBV from dormant to active takes place long before the actual neoplastic change. This increased activity over a prolonged period of time might be a significant contributing factor in bringing about change in the epithelial cells harbouring this virus.

Laboratory evidences in support of an etiological role of EBV in nasopharyngeal carcinoma are increasing rather rapidly. It is established that EBV has carcinogenic potential (32) and that vaccination against EBV provides full protection against tumour development in animals (33). Several EBV antigens like EBV-nuclear antigen 1, EBERs, latent membrane proteins 1 and 2 and Bam HI-A fragment have been noted to be expressed in almost all nasopharyngeal carcinoma (16,24). It has been suggested (3,4) that expression of latent membrane proteins may have a role in preventing the process of apoptosis (programmed cell death), thus leading the cells to immortality. The full significance of all these expressions have remained unexplored so far.

Based on molecular studies (34) of the pre-invasive lesions (dysplasia and carcinoma in situ), related to nasopharyngeal carcinoma, it has been possible to ascertain that these lesions arose from a single EBV-infected cell, which is indeed an early event in the pathogenesis of nasopharyngeal carcinoma. This identification of premalignant clones of EBV-infected cells has been considered (35) to be a remarkable new evidence suggesting that EBV is a primary etiologic agent in the multistep process that leads to the development of nasopharyngeal carcinoma.

Other environmental factors.

Numerous epidemiological studies have been conducted in order to explore the possibility of participation of other environmental factor/s which could play an etiologic role in nasopharyngeal carcinoma. Factors which have been examined in depth include diet, smoke (cigarette, tobacco, incense, anti-mosquito coils), wood, wood dust, formaldehyde, chlorophenols, herbal medicines, nasal oils, alcohol and micronutrients. Results of most of the studies are rather conflicting but those concerning dietary factors seem to have some relevance. Among the studies including dietary factors, the one which has been most extensively studied

involved consumption of salted fish. Ho (37) was the first to propose its involvement in the etiology of nasopharyngeal carcinoma having observed in an epidemiological study that the seafaring Tanka Chinese, a subgroup of Cantonese, who consumed salted fish quite frequently had a two times higher risk to the development of nasopharyngeal carcinoma as compared to land-dwelling Cantonese. Subsequently there have been many studies which support the strong association between consumption of salted fish and the risk of development of nasopharyngeal carcinoma (38,39,40). The risk is more if the salted fish is consumed over several years, since childhood or quite frequently (e.g. daily or weekly).

Besides observational evidence, analytic findings through laboratory studies also support an etiological association of nasopharyngeal carcinoma with the consumption of salted fish. Rats fed salted fish tend to develop nasal cavity tumours (41) and urine collected from them has mutagenic capabilities (42).

Consumption by Chinese of preserved and processed food like salted shrimp paste (39), salted duck egg (43), salted mustard green (43), salted soy beans (44), salted Chinese tuber (44), canned pickled vegetable (44), "Sze chuan chye" and "Kiam chye" (44) have also been incriminated. Certain food taken by Tunisians like harissa, quaddid and stewing mixture have been found to impart an increased risk of nasopharyngeal carcinoma among consumers as compared to non-consumers (45). Laboratory evidence of nitrosamines or their precursors in salted fish and several other foods items have been found (46). Salted fish as well as several of these food have also the capability to induce EBV *in vitro* (44). Yet definitive evidence of a role of the dietary factor or factors in the etiology of nasopharyngeal carcinoma remains elusive.

Discussion

Descriptive as well as analytic epidemiological evidences strongly support a causative role of EBV in the development of nasopharyngeal carcinoma. EBV, a ubiquitous virus, which infects nasopharyngeal epithelial cells normally remains latent and needs to be induced to be active. Suggestions that salted fish and some of other food items have the capability of inducing EBV *in vitro* and that they are endowed with chemical carcinogenic potential, make them favourable candidates for consideration in the list of etiological factors. At this stage one can only speculate about the site and the mechanism of their actions, acting independently or in association with EBV.

That a genetic factor plays a significant role cannot be ruled out. While overwhelmingly large data on geographic and ethnic distributions strongly favor the genetic contribution, there is no substantive analytic support forthcoming so far. Even studies of the migrant status of vulnerable population (20,47,48) seem to dilute the genetic theory. Results of studies of the incidence of nasopharyngeal carcinoma among migrant populations as compared to native ones, have clearly shown that there is a consistent decrease in the incidence among the second generation population as compared to the first generation or the homeland population. These observations favor an environmental role more than genetic. However, in one such study (49) involving Chinese males in Los Angeles, it was noted that the annual incidence rate between 1972 and 1974 was lower (3.5/100,000) for US-born Chinese as compared to foreign-born Chinese (13.9/100,000), but it was pretty high as compared to Caucasians (0.6/100,000). This reflected a residual increased incidence among the second and third generation Chinese migrants who were in US as compared to Caucasians, thus providing support to the genetic theory.

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