

# Ubiquitous Distribution of Epstein–Barr Virus and the Highly Uneven Distribution of Nasopharyngeal Carcinoma

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To the Editor: Nasopharyngeal carcinoma (NPC) is a type of cancer that is rare in western countries, but common in the Middle East, Southeast Asia, and Africa. Epstein–Barr virus (EBV) infection of nasopharyngeal epithelial cells, including interactions involving its putative cofactors, is commonly considered critical in NPC development.<sup>[1,2]</sup> We propose that if this hypothesis is true, either the geographic distribution of EBV infections, or the associated cofactors, should mirror that of NPC. That is, for at least one of these factors, their prevalence should be significantly higher in the Middle East, Southeast Asia, and Africa than in western countries. However, this is not the case. Rather, EBV is a ubiquitous human herpes virus; more than 90% of adults, worldwide, have evidence of infection. Furthermore, EBV's cofactors have not been shown to parallel the geographic distribution of NPC.

A virus is usually regarded as being oncogenic if it is able to induce the malignant transformation of cells. An EBV infection of healthy human nasopharyngeal epithelial cells is rare. Although such infections do occur, infection of these healthy cells primarily results in the lysis of the infected cells.<sup>[3,4]</sup> In contrast, EBV is commonly found in the nasopharyngeal epithelial tissue of patients with NPC. These observations indicate that nasopharyngeal epithelial cells may be more prone to EBV infection after the onset of malignancies. Thus, EBV infections may play a role in late NPC events.

Studies have shown that blood from NPC patients contains high densities of EBV or high titers of EBV antibodies; blood from healthy individuals shows low levels.<sup>[5]</sup> However, these studies were unable to determine whether the high EBV levels or EBV antibody titers occur before or after the onset of carcinogenesis. Thus, these data are amenable to two possible interpretations. First, EBV infection may be a risk factor for the transformation of healthy cells into NPC-positive cells. Second, the immune system may have been impaired, leading to the development of NPC and allowing an increase in the number of EBV. In the latter case, EBV infection is unlikely to be a risk factor for the development of NPC but occurs concurrently with NPC.

EBV can infect B-cells and is associated with immune disorders that impair the body's immune system function. In this regard, EBV infection may present a general risk for the development of

various diseases, including NPC. Indeed, research has shown that EBV infection is associated with a number of diseases, including infectious mononucleosis, lymphomatoid granulomatosis, Hodgkin's lymphoma, Burkitt's lymphoma, gastric cancer, NPC, and multiple sclerosis. This mechanism is different from the common hypothesis that EBV infects nasopharyngeal epithelial cells leading to the development of NPC.

Studies have suggested that genetic components may play a role in NPC development.<sup>[6]</sup> For example, familial aggregation of NPC has been widely observed in both low and high incidence populations.<sup>[7]</sup> Furthermore, Asian and African immigrants to western countries have a higher incidence of NPC, compared with local populations.<sup>[8]</sup> However, research has also shown that environmental factors play a role in the development of the disease. For example, Chinese immigrants to the United States have a lower NPC incidence than individuals continuing to live in China.<sup>[9]</sup> In addition, the prevalence of NPC in Hong Kong (China), Taiwan (China), and Singapore has steadily declined in recent decades.<sup>[10]</sup> Such observations suggest that environmental factors play a role in NPC development. Environmental factors may also explain familial aggregation of NPC due to the easy transmission of infectious pathogen, or other factor, between family members sharing a common living space. To advance our understanding of genetic factors or environmental factors which may involve in the development of NPC, studies that pool across multiple, well-designed, and coordinated efforts are required.

Since the prevalence of NPC is geographically distributed, there should be factors that impact the development of NPC. These factors should parallel the geographic distribution of the disease, e.g., the prevalence of these factors should be much higher in Southeast Asia, Africa, and the Middle East than in North America,

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**Received:** 07-06-2016 **Edited by:** Ning-Ning Wang  
**How to cite this article:** Wang CQ, He J. Ubiquitous Distribution of Epstein-Barr Virus and the Highly Uneven Distribution of Nasopharyngeal Carcinoma. *Chin Med J* 2016;129:2506-7.

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**DOI:**  
10.4103/0366-6999.191827

Western Europe, and Australia. Future studies dedicated specifically on this issue are required. These factors may or may not be cofactors of EBV. If they are cofactors of EBV, studies are further needed to examine whether or not these factors promote EBV infection of healthy nasopharyngeal epithelial cells, and whether the infected cells lyse.

### Financial support and sponsorship

This study was supported by the grant from the National Science Foundation of China (No. 81170743).

### Conflicts of interest

There are no conflicts of interest.

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