



# The etiology of nasopharyngeal carcinoma and challenges for its diagnosis and treatment monitoring

Nasopharyngeal carcinoma (NPC) is an undifferentiated nonkeratinizing epithelial tumor arising from the recesses of the Fossa of Rosenmüller of the nasopharynx (1). Its distinctive worldwide distribution shows that certain regions of the world have higher frequencies of endemic NPC in comparison to other regions of the world, where this cancer is rare (2,3).

Interestingly the development of this cancer appears to be associated with infection with a ubiquitous Epstein-Barr virus (EBV) early in life, as well as other host factors, and exposure to environmental factors such as diet (3,4). It is believed that host factors affecting EBV infection and carriage in a restricted latent state are involved in inherent genetic risk for NPC.

Early-age onset of NPC has been reported in NPC patients with a family history of the cancer (5). The major histocompatibility leukocyte antigen (HLA) complex was implicated as contributing to NPC risk, with certain HLA subtypes showing higher frequencies in NPC patients compared to other healthy individuals in endemic regions for NPC (6,7). A genetic linkage of the chromosome 6p21 *HLA* region to NPC was reported (8). In addition to the *HLA* genes, other genes of interest mapping to this region of chromosome 6 were identified in more recent years using genome-wide association studies and next-generation sequencing (NGS) approaches and were shown to be associated with increased genetic risk for NPC (9-11).

There is an intimate association of EBV with NPC development in high-risk endemic regions of NPC. Early serological studies identified a close correlation of EBV infections in NPC patients (12). EBV genomes were also detected in NPC patients (13,14). An important role of EBV in NPC pathogenesis was established (15,16). In addition to viral proteins and DNAs in NPC patients, the presence of EBV-encoded microRNAs, such as the BART miRNAs, were found in abundance in NPC (17).

The incidence of NPC has a peak in individuals in their upper forties and lower fifties, which is much younger than occurs with most other cancer types (2). It also displays a predominance in males vs. females. Early symptoms are innocuous and, therefore, individuals, who develop NPC, are usually not diagnosed until late in the progression of this deadly cancer. NPC is an aggressive but radiosensitive tumor, so the outcomes of treatment of localized tumors is favorable. However, if diagnosis is not made until late in its progression, when it has already metastasized to distant sites, then survival is compromised and treatment challenging. Overall, 5-year survival rates for this cancer are quite good and are over 75%, but the later the stage at diagnosis, the worse the survival outcomes (18). Because of the location of the tumor in the center of the head, close to many important organs at risk, despite improved treatment modalities such as intensity-modulated radiotherapy, some patients develop serious sequelae after treatment (19). Therefore, identifying NPC early will help to minimize side effects of its treatment and improve the quality of life of these patients.

To improve clinical care of NPC patients and their ultimate quality of life after treatment is the goal. The challenge is to identify useful biomarkers for screening populations with endemic NPC, early diagnosis, and for monitoring disease progression to decrease patient relapse in order to treat the patient with more precision medicine. NPC biomarkers include both host and viral-related genes (20). Early studies of NPC showed that EBV serology was a useful predictor of NPC. The Henles detected IgA serum antibodies against EBV viral capsid antigen in NPC patients (21). Large-scale mass serological surveys of asymptomatic individuals in endemic high-risk NPC regions have identified early cases of NPC (22,23). Detection of circulating cell-free tumor DNA in blood of NPC patients showed that detection of EBV plasma DNA was useful for early diagnosis, as well as monitoring for relapse after treatment (24-26). Methylated host genes and viral miRNAs were also used for NPC detection (20). More sensitive and specific markers for predictive patient stratification to optimize treatment outcomes are needed.

With the advent of powerful NGS and bioinformatics tools, detection, quantitation and detailed analysis of circulating tumor DNA (ctDNA) and circulating tumor cells (CTCs) provide the means to identify powerful predictive biomarkers for precision medicine by detection of EBV and altered host gene signaling pathways and identification of new druggable targets for treatment. The current immense interest in non-invasive liquid biopsies is based on exciting and robust values of plasma EBV ctDNAs, as a marker for early screening, prognosis and detection of recurrence of NPC. Pre-treatment and post-treatment levels of EBV DNA in plasma specimens of NPC patients are highly predictive of clinical recurrence or distant metastasis (27). Furthermore, the minimally-invasive liquid biopsies may be used to monitor treatment efficacy in a patient real-time and to contribute to our understanding of evolving treatment resistance and tumor recurrence (28). Current

emphasis using targeted gene sequencing are focused on actionable alterations that can be used for clinical intervention (29). Cancer NGS profiling has given rise to identifying alterations that are useful guides for patient treatment and the evaluation of the tumor mutational burden is useful for predicting recurrent disease. Detection of CTCs, miRNAs, and DNA hypermethylation of host genes involved in NPC tumorigenesis have potential to contribute to the NPC detection and patient management (30).

The purpose of this special series on NPC biomarkers is to present an overview of conventional biomarkers used in NPC detection and monitoring, as well as include several more recent “novel” approaches for study of NPC and EBV for biomarker discovery, which are expected to identify informative biomarkers for its early detection or new biomarkers having prognostic implications. Experts in the field have been invited to provide several papers in this special series of *Annals of Nasopharynx Cancer* on EBV markers, as well as host biomarkers, for NPC screening, diagnosis, and prognosis and to present new avenues for NPC biomarker discovery. We expect these ongoing concerted efforts for advances in NPC diagnostics will herald in an era for improved early diagnosis and identification of targeted drugs for precision treatment of NPC.

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