Response to Invited Commentary

Liu et al. Respond to “Epstein-Barr Virus Screening for Nasopharyngeal Carcinoma”

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Abbreviations: EBV, Epstein-Barr virus; NPC, nasopharyngeal carcinoma.

We thank Dr. Hildesheim (1) for his careful review and thoughtful addition to our report (2) of the initial results from a nasopharyngeal carcinoma (NPC) screening program using 2 Epstein-Barr virus (EBV)–related serologic antibody tests in southern China. We agree with the points raised by the author about the potential possibility for reducing this cancer burden by mass screening in high-risk populations, and we read with interest his suggestions for future research, which may amplify the achievements of EBV-based screening.

We are particularly intrigued by Dr. Hildesheim’s emphasis on additional follow-up of individuals in screening and control towns/communities (2). Currently, we are unable to actively follow up all individuals, and only individuals who were grouped as high risk are followed up annually with clinical workup because of financial constraints. As pointed out by the author (1), the initial round did not include clinical workup (e.g., fiberoptic endoscopy/biopsy) among subjects in the medium-risk or low-risk groups, making it difficult to directly compare incidence and staging of NPC cases among these 3 groups within the intervention communities. Therefore, in order to maximize the value of this unique screening cohort, we plan to incorporate active clinical workup of a stratified random sample of the medium-/low-risk groups within the second round of screening. This will allow for the adjustment of verification bias and lead time bias of the current screening strategy and, moreover, can provide more accurate baseline data for evaluating other screening biomarkers or strategies within this screening cohort in the future.

We agree with Dr. Hildesheim that our results are limited by generalization. In most parts of the world where the incidence of NPC is lower, obtaining satisfactory cost-effectiveness for NPC mass screening is difficult and, thus, our results might be applicable only in some high-incidence regions. An alternative screening strategy that aims at NPC high-risk subgroups might be more useful in nonendemic areas, and an example from Taiwan that screened individuals with a familial history of NPC has shown promising results (3, 4). A risk prediction model incorporating other risk factors might also be used to improve the efficiency of NPC screening in both endemic and nonendemic areas. Experiences from other cancer screening programs have provided good examples (5–7).

As mentioned by Dr. Hildesheim, the 21% participation rate among eligible residents in screening towns/communities is relatively low, although efforts have been made to increase the rate, such as distributing leaflets and promoting the study by television announcements. Even among those subjects in the high-risk group defined by our serology algorithm, only 652 individuals (76% of 862) participated in further diagnostic fiberoptic endoscopy. These relatively low compliance rates, partly due to the frequent movements of the target population and low awareness of the advantages of the screening program, may influence the generalizability of the screening results and limit the benefits to the target population. Other approaches, such as extending the screening duration, implementing a system of multiple reminders, and obtaining financial support for NPC treatment, should be considered to maximize the participation rate in future screening courses.

EBV is highly associated with the development of NPC in both high- and low-incidence areas, although the underlying mechanism of how EBV infects normal epithelial cells has not been fully understood, partly because samples of dysplasia or precancerous lesions are limited (8). To our knowledge, only a few studies with limited samples have demonstrated that EBV infection is an early event that
occurs prior to clonal expansion of a premalignant pool of cells (9, 10). Although the observed elevation of immunoglobulin A antibody titers to EBV expression protein during replication suggests a role of EBV reactivation in NPC development, risk factors influencing the process have not been well established (11). Additional research in this area is greatly needed. The value of this screening cohort could be strengthened by using the longitudinally collected biosamples to study the natural history of EBV infection and NPC development.

In summary, the initial round results, although with some limitations, have demonstrated the usefulness of the new population-based screening scheme in an NPC endemic area by using 2 anti-EBV antibodies. Data collected during future follow-up would, we hope, provide valuable resources for cost-effectiveness analyses regarding implementation of more widespread NPC screening programs in high-risk regions.

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REFERENCES