Invited Commentary

Invited Commentary: Epstein-Barr Virus–Based Screening for the Early Detection of Nasopharyngeal Carcinoma—A New Frontier

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Approximately 2 million new cases of cancer are caused by infections each year. For many of these cancers, we have been successful at developing methods for prevention or effective treatment/control. Epstein-Barr virus (EBV), a ubiquitous infection that establishes lifelong latency, was the first infection to be linked to the development of cancers, including nasopharyngeal carcinoma, lymphomas, and gastric cancer. EBV infection is linked to the development of approximately 200,000 new cancers each year, yet there have been no successful efforts to implement EBV-based strategies for the reduction in the burden of EBV-associated cancers. In this issue of the Journal, Liu et al. (Am J Epidemiol. 2013;177(3):242–250) report results from the enrollment phase of an effort to demonstrate the efficacy of an EBV-based screening strategy to detect nasopharyngeal carcinoma at early stages and hopefully reduce the mortality associated with this disease. In this invited commentary, the design and initial findings from this demonstration project are reviewed, possible ways to enrich the effort are discussed, and populations that might benefit from EBV-based screening in the future are identified.

cancer; Epstein-Barr virus; infections; nasopharyngeal carcinoma; prevention; screening

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

The investment made in cancer research over the past few decades has led to important discoveries linking infection to the development of at least 1 in every 6 cancers worldwide (2 million new cancer cases each year) and an even larger proportion of cancers in developing countries (closer to 1 in 4) (1). Importantly, these scientific advances have led to practical applications that either have or promise to reduce cancer morbidity and mortality in significant ways. Prophylactic vaccines against the viruses that cause liver and anogenital cancers (hepatitis B virus and human papillomaviruses) are in use around the world, testing for human papillomaviruses is being used to optimize cervical cancer screening programs, and ever improving treatments for infections that cause liver and gastric cancers (hepatitis C virus and Helicobacter pylori) or that modulate cancer risk (human immunodeficiency virus) are increasingly available.

Epstein-Barr virus (EBV), a ubiquitous infection that establishes lifelong latency, was the first infection to be linked to the development of cancer (2). It is now known that EBV is linked to nearly all cases of nasopharyngeal carcinoma (NPC) and important subsets of Burkitt lymphomas, other non-Hodgkin lymphomas, Hodgkin lymphoma, and gastric cancer (Table 1) (3). In contrast to the successes alluded to above, there have been no successful efforts to implement EBV-based strategies for the reduction in the burden of EBV-associated cancers.

In this issue of the Journal, Liu et al. (4) report results from the enrollment phase of a large effort to demonstrate the efficacy of an EBV-based screening strategy to detect NPC at early stages and to reduce mortality associated with this disease. Historically, NPC has been diagnosed at very late stages because of the nonspecific nature of its symptoms, resulting in high mortality associated with this cancer despite treatment. Strategies aimed at detecting NPC cases at early stages, when treatments have proven highly effective, are therefore welcome.

The demonstration project reported by Liu et al. is being conducted in 2 regions in Guangdong province, southern
Table 1. Current Estimated Burden of Epstein-Barr Virus–Associated Cancersa

<table>
<thead>
<tr>
<th>Cancer</th>
<th>Total No. of Cases</th>
<th>No. of Cases Attributable to Epstein-Barr Virus</th>
</tr>
</thead>
<tbody>
<tr>
<td>Burkitt lymphoma³</td>
<td>8,200</td>
<td>6,700</td>
</tr>
<tr>
<td>Gastric carcinoma</td>
<td>933,900</td>
<td>84,050</td>
</tr>
<tr>
<td>Hodgkin lymphoma</td>
<td>62,400</td>
<td>28,600</td>
</tr>
<tr>
<td>Nasopharyngeal carcinoma</td>
<td>80,000</td>
<td>78,100</td>
</tr>
<tr>
<td>Total</td>
<td>1,023,500</td>
<td>197,450</td>
</tr>
</tbody>
</table>

⁴Adapted from Cohen et al., Sci Transl Med. 2011;3(107):107fs7 (3).
⁵A yet-to-be-quantified proportion of other non-Hodgkin lymphomas, particularly among immune-suppressed populations, are also linked to Epstein-Barr virus infection.

China, with one of the highest rates of NPC in the world (5). In brief, communities totaling 283,000 middle-aged adults were randomized into either active screening (n = 137,000) or control (n = 146,000) areas. Individuals aged 30–59 years in the communities selected for active screening were invited to attend a clinic visit where visual inspection of the nasopharynx and blood collection were performed. Serum obtained from blood was tested for the presence and levels of immunoglobulin A antibodies against 2 EBV antigens, viral capsid antigen (VCA) and Epstein-Barr virus nuclear antigen-1 (EBNA-1). A predefined algorithm that combined results from the 2 blood tests was used to select individuals requiring a follow-up visit (6). At the follow-up visit, fiberoptic examination of the nasopharynx was performed, and a biopsy was taken when indicated for the diagnosis of NPC. After exclusions, a total of 28,688 individuals (representing 21% of those eligible) participated in the enrollment phase of the demonstration project. Eight hundred and sixty-two individuals screened positive (3% of the population screened) on the basis of the predefined serology algorithm, of which 652 (76% compliance) attended the second visit. Thirty-eight NPC cases were identified in this subgroup, among which 68% were diagnosed at an early stage of disease. Linkage to existing cancer registries in the area identified an additional 3 NPC cases among screen-negative individuals from the communities selected for active follow-up, suggesting a sensitivity for detection of prevalent disease of 93%. An indirect mirror examination and lymphatic palpation method was also used to screen individuals who presented for the screening visit, but this method was found to be insensitive for NPC detection (17%) and will therefore not be considered further.

These initial results are very promising and suggest the possibility that EBV-based screening programs within NPC high-risk areas could ultimately lead to reduced mortality from this disease via early detection and treatment. Proof of this point, however, will require additional follow-up of individuals in both the active screening and control communities involved in the demonstration project. In fact, as described by Liu et al. in their article, several years of follow-up are planned as part of the ongoing demonstration project. The follow-up phase of the project, as currently envisioned, will consist of passive linkage of individuals from communities randomized to both the active and control arms to existing cancer and mortality registries in the region. In addition, among individuals from the active screening communities who have agreed to participate in the demonstration project, active EBV-based screening akin to that implemented during the enrollment phase is envisioned. More specifically, the authors indicate that rescreening is planned on an annual basis for individuals who screened positive at enrollment, every 2 years for individuals for whom elevations in anti-EBV antibodies were observed but whose screening score did not reach the predefined threshold used to trigger follow-up evaluation within the demonstration project, and every 3 years after the initial screen for the remaining participants from the active arm. During follow-up and at the end of the study, comparisons of NPC incidence, stage at diagnosis, and mortality are planned. Comparison of the rates observed in the active and control arms will provide critical information required for cost-effectiveness modeling used to determine whether implementation of broader screening programs is warranted.

The Guangdong demonstration project is an important and impressive effort. If successful, it could serve as a model for EBV-based NPC screening programs within high-risk areas in China and elsewhere. At this point in its implementation, with the enrollment phase completed, evaluation of the enrollment phase and reassessment of plans for follow-up could identify areas where the project might be strengthened and could help ensure the success of this important endeavor.

During the enrollment phase of the project, approximately 80% of eligible participants in the communities selected for active screening chose not to participate in the screening program. Furthermore, among participants who screened positive, 25% did not return for a second examination required for NPC diagnosis. These low rates of participation and compliance suggest that, even if screening proves to be effective at reducing NPC mortality among those who participate in the program, the overall impact at the population level is likely to be more modest. This, in turn, suggests the need to consider alternative approaches to maximize participation in screening programs. Evaluation of such alternative approaches could be considered in parallel with the follow-up phase of the demonstration project, so that better methods to structure population-wide screening programs in high-risk NPC regions can be successfully implemented without additional delays once results from the demonstration project are on hand.

Within the actively screened individuals during the initial phase of the demonstration project, over 90% of prevalent NPC cases were identified among the 3% of individuals who screened positive for the EBV markers considered. Furthermore, the cases identified were predominantly early stage cancers (68% Stages I/II) for which treatment has been shown to be highly effective. These are very
promising initial findings. Only 3 of 41 cases were identified among screen-negative individuals, but these cases were identified by using passive linkage to existing cancer and mortality registries in the region. The extent to which this passive ascertainment is complete is highly dependent on the quality of the existing registries. Careful evaluation of the quality and completeness of these registries is warranted in the early phases of the demonstration project, so that any deficiencies can be identified and corrected to ensure that the objectives of evaluating the impact of EBV-based screening in high-risk NPC regions can be achieved in the long term.

Another aspect of the demonstration project that might be strengthened is its ability to serve as the basis for the evaluation of novel screening and diagnostic approaches and for the study of the natural history of EBV and NPC. As currently designed, follow-up of participants within the communities selected for active screening is defined by the results of the screening test. Individuals who screen positively are evaluated annually, while those who do not are seen less frequently. Although this is warranted for the limited goal of comparing the single screening algorithm being implemented in the active screening communities against what is observed in the control communities, the lack of more active follow-up among individuals who screen negative by the current algorithm limits the ability of this cohort to serve as the basis for the evaluation of novel approaches in the future using stored biospecimens. At this early stage in the demonstration project, strategies might be considered to ameliorate this problem so that this valuable cohort can address its primary goal of evaluating the current screening program, while allowing for an unbiased assessment of novel strategies in the future.

Results from the Guangdong demonstration project are likely to be applicable to only a limited number of regions around the world where NPC rates are high. In most parts of the world, where NPC rates are lower, EBV-based population screening programs are unlikely to prove cost-effective. In lower incidence regions, however, approaches that target high-risk subgroups within the population might be considered. As one example, it has been shown that healthy individuals from families with multiple NPC cases are at considerably increased risk of NPC development themselves (7, 8). Although genetic predisposing factors are suspected within these families, no specific genes have been linked to these familial NPC cases to date, and identification of the subset of individuals within these families with the highest likelihood of developing disease themselves has not been possible. Because individuals from these families who subsequently develop NPC have been shown to have altered EBV marker profiles (9), it is possible that EBV-based screening might be considered to triage individuals within multiplex families into more and less aggressive monitoring and management algorithms. Indeed, efforts are currently underway to formally evaluate this possibility (9). These efforts will complement those underway in Guangdong to evaluate EBV-based screening in general population settings.

In summary, although prevention strategies for EBV-associated cancers do not currently exist, efforts such as those described by Dr. Liu et al. promise to deliver new ways to translate knowledge of the link between infections and cancer into public health programs that effectively reduce morbidity and mortality caused by EBV-associated cancers in the not too distant future.

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REFERENCES