Cost-effectiveness of Screening for Nasopharyngeal Carcinoma among Asian American Men in the United States

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Abstract

Objective. Most patients with nasopharyngeal carcinoma (NPC) in the United States are diagnosed with stage III-IV disease. Screening for NPC in endemic areas results in earlier detection and improved outcomes. We examined the cost-effectiveness of screening for NPC with plasma Epstein-Barr virus DNA among Asian American men in the United States.

Study Design. We used a Markov cohort model to estimate discounted life-years, quality-adjusted life-years (QALYs), costs, and incremental cost-effectiveness ratios for screening as compared with usual care without screening.

Setting. The base case analysis considered one-time screening for 50-year-old Asian American men.

Subjects and Methods. Confirmatory testing was magnetic resonance imaging and nasopharyngoscopy. Cancer-specific outcomes, health utility values, and costs were determined from cancer registries and the published literature.

Results. For Asian American men, usual care without screening resulted in the detection of NPC at stages I, II, III-IVB, and IVC among 6%, 29%, 54%, and 11% of those with cancer, respectively, whereas screening resulted in earlier detection with a stage distribution of 43%, 24%, 32%, and 1%. This corresponded to an additional 0.00055 QALYs gained at a cost of $63 per person: an incremental cost of $113,341 per QALY gained. In probabilistic sensitivity analysis, screening Asian American men was cost-effective at $100,000 per QALY gained in 35% of samples.

Conclusion. Although screening for NPC with plasma Epstein-Barr virus DNA for 50-year-old Asian American men may result in earlier detection, in this study it was unlikely to be cost-effective. Screening may be reasonable for certain subpopulations at higher risk for NPC, but clinical studies are necessary before implementation.

Keywords

nasopharyngeal carcinoma, Epstein-Barr virus, screening, cost-effectiveness

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Nasopharyngeal carcinoma (NPC) is the most common cancer of the nasopharynx but is rare in the United States. The mean annual incidence of new diagnoses for men in the United States is 0.7 per 100,000.1 Asian American men are at higher risk, with a mean annual incidence of 3.0 per 100,000, although this increases to 7.6 per 100,000 at 50 to 54 years of age, and estimates are even higher in endemic areas, such as southern China.1-3 Most patients in the United States are diagnosed with stage III-IV disease, and despite improvements in treatment, 5-year survival remains lower in the United States than in endemic regions.

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radiation technique and chemotherapy, outcomes for most of these patients remain modest, with 5-year progression-free survival estimates of approximately 62% after treatment with concurrent chemoradiation and adjuvant chemotherapy. However, if the disease is diagnosed at an earlier stage, patients can avoid chemotherapy and still achieve 5-year progression-free survival >90%.5,6

Screening for asymptomatic cases of NPC has become possible through the recognition that latent Epstein-Barr virus (EBV) infection may contribute to the development of NPC.7 In fact, screening studies dating back to the 1970s have been conducted in southern China.8,9 A clinical study of a screening target for plasma EBV DNA in an endemic population in Hong Kong recently showed not only a more favorable stage distribution but also improved cancer outcomes.2 The test targets viral DNA fragments and so is relatively inexpensive as compared with conventional cell-free tumor DNA tests, offering the possibility for use in populations with lower NPC rates. Thus, we sought to determine whether screening for NPC with plasma EBV DNA would be cost-effective among 50-year-old Asian American men, who are at higher risk than the general US population.

Methods
We developed a Markov cohort model to determine the cost-effectiveness of screening for NPC as compared with usual care without screening. This study did not involve human participants and was exempt from formal review by the Stanford University Institutional Review Board.

Participants and Intervention
The screening program was modeled after a study reported by Chan et al of 20,174 men in Hong Kong who were screened with plasma EBV DNA.2 The base case considered one-time screening for Asian American men entering the model at age 50 years. The screened arm was composed of a test for plasma EBV DNA, which was repeated 1 month later to rule out transient positivity due to infection. The BamHI-W region of EBV DNA was used for the polymerase chain reaction assay.10 A positive screen (2 tests for plasma EBV DNA) was then confirmed via gold standard testing with magnetic resonance imaging (MRI) of the head and a nasopharyngoscopy. Sensitivity and specificity were directly measured at 97.1% and 98.6%, respectively.2 NPC was treated according to the burden of disease at the time of diagnosis: stage I NPC was treated with radiation, stage II-IVB with chemoradiation, and stage IVC with chemotherapy.

Model Characteristics
We assessed outcomes using a decision-analytic Markov cohort model.11 The model reflected 10 health states: healthy, undetected stage I-IVC NPC, detected stage I-IVC NPC, and dead (Supplemental Figure S1, available in the online version of the article). A true positive from the screening test resulted in immediate detection of cancer at the patient’s current stage. A false negative or the decision not to screen allowed cancer progression until detection. A false positive resulted in gold standard testing. Incidental findings from MRI could result in additional imaging and physician visits.12 The most common incidental finding requiring additional intervention was a brain aneurysm, which was modeled according to treatment with clipping or endovascular repair.13 Incidental findings from nasopharyngoscopy were assumed to be negligible.14,15 We accounted for toxicities from treatment and the risk of cancer recurrence in assigned stage-specific utilities and costs. Patients were followed over their remaining lifetimes.

We estimated life-years, quality-adjusted life-years (QALYs), and health care costs—all discounted at 3% annually—as well as incremental cost-effectiveness ratios comparing screening with no screening.16 We employed a willingness-to-pay threshold of $100,000 spent per QALY gained.17

Disease State Transition Probabilities
In the United States, the annual incidence of newly diagnosed NPC cases is known from epidemiologic studies, but the number of men who unknowingly harbor NPC and who could be diagnosed through screening is unknown. In Hong Kong, the annual incidence of newly diagnosed NPC cases for 50- to 54-year-old men is 40 per 100,000, but the prevalence of NPC that was determined through screening in the area was 173 per 100,000.2,18 The difference likely has to do with the natural progression of the disease and that most people are not diagnosed until the cancer becomes more advanced. We assumed that the biological progression and clinical diagnostic patterns of nonkeratinizing squamous cell carcinoma were similar to those in Hong Kong. Under these assumptions, the prevalence of undiagnosed NPC for Asian American men was proportional to that of men from Hong Kong (see Supplemental Methods: Transition Probability Calibration, available in the online version of the article).2 For 50-year-old Asian American men, the calculated prevalence of undiagnosed NPC (men who unknowingly harbor cancer) was 36 per 100,000 (95% CI, 25-50 per 100,000).1 Using this prevalence of undiagnosed NPC, we calibrated our model to age-specific rates of newly diagnosed cases with data from the SEER program (Surveillance, Epidemiology, and End Results; Supplemental Methods and Figure S2, available in the online version of the article).3 We created 1000 sets of random transition probabilities and then performed search optimization starting with the best-fitting set (Rsolnp R package, version 1.16).19-21 Validation of the calculated prevalence of undiagnosed NPC among 50-year-old Asian American men was performed by visualization of the model calculated and known annual detection rates (Figure 1). For 50- to 54-year-old Asian American men, the annual detection rate according to SEER data was 7.6 per 100,000 (95% CI, 6.8-8.5 per 100,000), and the rate according to our model was 8.2 per 100,000 (95% CI, 7.6-8.6 per 100,000).

Survival outcomes for the healthy populations were taken from US life tables for Asian American men.22 With SEER data, the stage-specific mortality rates associated with NPC
Figure 1. The annual number of new cases of nasopharyngeal carcinoma among Asian American men, validated with SEER data. The number of new cases was specific to age and disease stage at the time of detection. Values are presented as box plots, with solid black lines representing medians; boxes representing interquartile ranges; and individual points representing values greater than 1.5 of the interquartile range from the nearest hinge.
were determined for men aged 30 to 70 years and diagnosed between 2004 and 2014 (Supplemental Methods: Mortality Rate Calculations, available in the online version of the article).

** Costs**

The costs of screening and additional workup were determined from means of the regional payment amounts listed in the Medicare Clinical Laboratory Fee Schedule Public Use File and the Medicare Physician Fee Schedule for 2017 (Supplemental Table S1, available in the online version of the article). Current Procedural Terminology code 87798, “infectious agent detection by nucleic acid (DNA or RNA), not otherwise specified,” was used to determine the cost for detection of plasma EBV DNA. Spending by Medicare informed the cost of care among the healthy population.25

The costs for treatment with radiation and chemoradiation were determined from a report on total Medicare spending for patients after a diagnosis of oropharyngeal cancer.26 We allowed the cost of care for these patients to return to that of the healthy population 5 years after an initial diagnosis, because (1) the costs at this time were not known and (2) the majority of cancer-associated costs, toxicities, and recurrences occur within the first 5 years of treatment.27-29 The cost for treatment with palliative chemotherapy for stage IVC disease was determined from a report on Medicare spending for patients undergoing chemotherapy alone for head and neck cancers.30

Incidental findings from additional workup due to a false-positive screening test could result in additional costs. The cost of care for management of an asymptomatic brain aneurysm was determined from a report of the mean total Medicare spending after surgical clipping or endovascular repair.31

All costs were adjusted to 2017 dollars with the Consumer Price Index.32

** Health State Utilities**

Those who screened positive initially underwent an intensive gold standard workup that was assumed to last about 1 month. The short-term effect of positive screening on utility is an area of controversy.33,34 We assigned this state a utility of 0.9, which was a conservative estimate favoring the usual care arm and was based on the responses of women with positive mammograms.34 Additionally, for patients who then tested positive after gold standard workup, we assigned a health utility decrement for 1 month prior to treatment initiation. This utility was based on patients with newly diagnosed head and neck cancers.35

The health state utilities of patients undergoing radiation were based on mapping responses from the Medical Outcomes Short Form–36 of patients with nasopharyngeal cancer who were treated with intensity-modulated radiation therapy in a randomized trial.36,37 The utilities of patients undergoing chemoradiation were based on health surveys from patients with locally advanced head and neck cancer treated on the control arm of RTOG 0522.38 The utility of being treated with palliative chemotherapy with stage IVC disease was based on surveys of patients with recurrent or metastatic head and neck cancer undergoing first-line therapy.39

** Sensitivity Analysis**

Deterministic 1-way sensitivity analyses assessed the effect on screening, given uncertainty of disease state, utility, and cost parameters.

Probabilistic sensitivity analysis encompassed 10,000 Monte Carlo simulations to determine the estimated mean effect from the joint uncertainty of the model parameters. To account for the uncertainty among transition probabilities, we performed calibration to sets of values representing the uncertainty in the initial stage distributions and expected rates of NPC detection. This resulted in 1000 sets of transition probabilities, which were then sampled during the probabilistic sensitivity analysis.

Additionally, there was correlation in the uncertainty distributions for our health state utilities based on commonsense preferences for those states. For example, the utility of the first year of treatment was inferior to that long after treatment, and the utility of metastatic disease was inferior to utilities for stage I-IVB disease. To establish joint uncertainty distributions among these utilities while preserving marginal distributions, we used an induced correlations method based on preference ordering (Supplemental Methods: Health State Utility Preferences, available in the online version of the article).40

** Secondary Analyses**

There are subpopulations of men living in the United States with a higher risk of developing NPC than 50-year-old Asian Americans. Two secondary analyses performed were for screening immigrants from endemic areas or those with a family history of NPC.41-43 We assumed that the prevalence of undetected NPC among immigrants from an endemic area would be similar to that found in the Hong Kong screening study. As for the familial risk of NPC, 1 study was conducted in a nonendemic area, Sweden.44 In that report, there was a relative risk of 4.28 (95% CI, 1.07-17.17) for developing NPC among people with first-degree relatives who also had NPC, and these numbers were used to inform the prevalence estimates.

We constructed the model with TreeAge Pro 2018 (TreeAge Software, Williamstown, Massachusetts), with calibration performed with R (version 3.4).

** Results**

**Base Case**

For Asian American men aged 50 years, the diagnoses of stage I, II, III-IVB, and IVC disease occurred among 6%, 29%, 54%, and 11% of those with NPC, respectively. Overall, usual care resulted in a discounted mean lifetime health care–related cost of $208,007, a life expectancy of 20.6930 years, and 20.6924 QALYs.

With one-time NPC screening, 1.4% of men screened positive, and 2.5% of those had NPC. The diagnoses of stage I, II, III-IVB, and IVC disease occurred among 43%, 24%,
screening cost $78,404 to $181,380 per QALY gained (95% CI, $5,632-$104,531). The prevalence of undiagnosed NPC among 50-year-old men with a first-degree relative who had NPC was estimated to be 155 per 100,000 (95% CI, 39-621 per 100,000), which corresponded to a screening cost of $22,912 per QALY gained (95% CI, $5,632-$104,531).

**Secondary Analyses**

The prevalence of undiagnosed NPC among 50-year-old male immigrants from an endemic area, Hong Kong, was 173 per 100,000 (95% CI, 121-241 per 100,000).

For this group, screening cost $20,400 per QALY gained (95% CI, $14,553-$29,708). The prevalence of undiagnosed NPC among 50-year-old men with a first-degree relative who had NPC was estimated to be 155 per 100,000 (95% CI, 39-621 per 100,000), which corresponded to a screening cost of $22,912 per QALY gained (95% CI, $5,632-$104,531).

**Discussion**

In this study, we performed an economic analysis of screening for NPC among 50-year-old Asian American men. We based the accuracy of testing on a study from a population where NPC is endemic, and we based costs on Medicare reimbursement rates. We found that onetime screening with plasma EBV DNA cost $113,341 per additional QALY gained. For men who were detected through screening, an additional 2.0 QALYs were expected as compared with usual care without screening. However, despite a screening test sensitivity of 97.1% and specificity of 98.6%, we found that the cost of screening varied from $78,404 to $181,380 per QALY gained (Figure 2). Within the estimated range of test sensitivity and specificity, screening cost $109,559 to $133,265 per QALY gained and $107,803 to $119,689 per QALY gained, respectively. Two-way sensitivity analysis testing the uncertainty in sensitivity and specificity found that testing continued to cost >$100,000 per QALY gained across tested combinations (Supplemental Table S4, available in the online version of the article). The threshold at which screening became cost-effective occurred when the test specificity was ≥0.990, the estimated prevalence of undiagnosed NPC was ≥40 per 100,000, and the screening test cost ≤$39. There was no threshold for cost-effectiveness for test sensitivity or compliance (Supplemental Table S5, available in the online version of the article).

In probabilistic sensitivity analysis, screening Asian American men was cost-effective at $100,000 per QALY gained in 35% of samples (Figure 3). If a positive screening test did not result in a decrement to a patient’s health utility, screening would be cost-effective in 50% of samples. If the screening test cost was at the current Medicare national limit amount of $48.14, screening would be cost-effective in 30% of samples. Given the importance of the screening test cost, we also tested the effect of a screening test of $39 (the threshold cost), which would be cost-effective in 39% of samples.

**Sensitivity Analysis**

Deterministic 1-way sensitivity analyses showed that within the range of estimated prevalence of undetected NPC, screening cost $78,404 to $181,380 per QALY gained (Figure 2). Within the estimated range of test sensitivity and specificity, screening cost $109,559 to $133,265 per QALY gained and $107,803 to $119,689 per QALY gained, respectively. Two-way sensitivity analysis testing the uncertainty in sensitivity and specificity found that screening continued to cost >$100,000 per QALY gained across tested combinations (Supplemental Table S4, available in the online version of the article). The

**Figure 2.** Cost-effectiveness dependence on the prevalence of undiagnosed nasopharyngeal carcinoma (NPC) at age 50 years among Asian American men. In the base case analysis, screening cost $113,341 per quality-adjusted life-year (QALY) gained. ICER, incremental cost-effectiveness ratio.
outlines the benchmarks in test accuracy and cancer prevalence that would need to be met for screening of NPC to be considered reasonable in the United States.

The accuracy and clinical outcomes from screening for NPC in nonendemic areas are unknown. However, it was previously suggested that there may be high-risk populations within nonendemic areas for whom screening could be cost-effective.46 The current study focused on Asian American men at an age when NPC rates peak, but there are also smaller subpopulations that are at even higher risk.41-44 We found that screening 50-year-old men who either were immigrants from Hong Kong or had a first-degree family member with NPC may be cost-effective. However, caution should be taken, and epidemiologic studies would be needed to directly measure the prevalence of undiagnosed NPC among these groups before routine screening could be considered efficacious and cost-effective in the United States.

The primary benefit to screening that drove our results was the reduction in the portion of patients with locally advanced or metastatic disease. The study reported by Chan et al discovered 34 cases of NPC, of which 71% had stage I-II disease.7 Despite the high level of uncertainty regarding stage distribution, this number was well within the range of 57% to 91% observed in prior screening studies with EBV antibody testing.8,9,47,48 Similarly, our model found that screening resulted in earlier detection, which then resulted in lower costs, more successful treatment, and consequent prolonged life and better quality of life.

The model has a number of limitations, including that the estimated test sensitivity and specificity were based on conducting 2 tests for plasma EBV DNA in an endemic region.2 The test accuracy affects the number of false positives, which may arise when EBV DNA is present in a patient’s serum due to EBV reactivation or a new infection.49 The 2 tests were separated by 1 month to reduce the number of patients experiencing a transient EBV infection, but it is not known what the true sensitivity and specificity of this type of screening would be in the United States. If EBV infections were more frequent or their courses more prolonged in the United States, the screening test accuracy would decrease. In our 2-way sensitivity analysis of sensitivity and specificity, screening cost $104,286 to $141,384 per QALY gained. However, a screening study conducted in the United States is necessary to clarify how well plasma EBV DNA can differentiate patients with cancer from those with a transient infection. Furthermore, EBV DNA polymerase chain reaction testing is challenging and may not be reproducible among laboratories. However, this challenge was recognized and overcome by investigators of the recent NRG HN001 trial, who created a harmonization process resulting in good correlation, sufficient for qualitative testing of serum EBV DNA, and so additional clinical studies with similar techniques are feasible.50

Another limitation is that complications from false-positive screening tests need to be better established in the United States. In the current study, a false-positive test required MRI and endoscopy, which could result in further health care interactions and costs. Model estimates were based on studies of MRI examinations of healthy volunteers, which may not be generalizable to the screened population. Additionally, assumptions were made that the total health care–related expenditures for chemoradiation were similar to those for oropharynx cancer. In practice, adjuvant chemotherapy is often employed following chemoradiation for locally advanced NPC, so costs of treatment may have been

![Figure 3. (A) Incremental cost-effectiveness plot. (B) Cost-effectiveness acceptability curve for the conditions that a positive screening test did not adversely affect a patient’s health utility and the screening test cost the Medicare national limit. QALY, quality-adjusted life-year.](image-url)
underestimated for stage II-IVB disease. Ultimately, this may have biased toward the null that screening is not cost-effective, and we would advocate for continued cost studies to reduce uncertainty and improve our understanding of the potential effect of screening. Furthermore, as treatments for NPC continue to develop in the form of advances with radiation techniques, including with proton therapy, as well as with systemic therapies, the effectiveness and costs of disease management will continue to evolve and could affect whether screening is cost-effective.

Notably, empirical screening studies are often prone to lead time bias because they potentially ignore the time of progression when a patient has asymptomatic cancer prior to diagnosis. In our study, we modeled the underlying disease, which accounted for this time delay, and mortality risks were not taken from an empirical screening study that could be susceptible to this type of bias. Similarly, because we have complete information about the population with undiagnosed cancer within the model, the typical length time bias that is a natural development of heterogeneity in tumors does not apply.

Screening for NPC with plasma EBV DNA for 50-year-old Asian American men in the United States is unlikely to be cost-effective despite high levels of test sensitivity and specificity and an inexpensive screening test. There may be subpopulations at higher risk for NPC for whom screening would be reasonable. However, the rate of false-positive results would be high, and additional clinical studies in any population will be required before implementation.

Author Contributions

Jeremy P. Harris, conceptualization, data curation, formal analysis, funding acquisition, investigation, methodology, project administration, resources, software, supervision, validation, visualization, writing—original draft, and writing—review and editing, final approval of the version to be published; agreement to be accountable for all aspects of the work; Anirudh Saraswathula, data curation, formal analysis, funding acquisition, investigation, methodology, validation, visualization, writing—original draft, and writing—review and editing, final approval of the version to be published; Yushen Qian, methodology, writing—original draft, and writing—review and editing, final approval of the version to be published; Anthony T. C. Chan, design, writing—review and editing, final approval of the version to be published; agreement to be accountable for all aspects of the work; Douglas K. Owens, methodology, supervision, and writing—review and editing, final approval of the version to be published; agreement to be accountable for all aspects of the work; Jeremy D. Goldhaber-Fiebert, methodology, supervision, and writing—review and editing, final approval of the version to be published; agreement to be accountable for all aspects of the work; Erqi Pollom, methodology, supervision, and writing—review and editing, final approval of the version to be published; agreement to be accountable for all aspects of the work.

Disclosures

Competing interests: K. C. Allen Chan has received grants and personal fees from Grail and has financial activities at Grail. In addition, Dr Chan has a portfolio of >50 families of patents on molecular diagnostics; portfolios of patents have been licensed to Grail, Illumina, Sequenom, and DRA.

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Supplemental Material

Additional supporting information is available in the online version of the article.

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