



Cancer Expert Working Group on Cancer Prevention and Screening (CEWG)

Recommendations on Prevention and Screening for Nasopharyngeal Cancer For Health Professionals

Local epidemiology

Nasopharyngeal Cancer (NPC) was the 14th commonest cancer in Hong Kong in 2022. A total of 705 newly diagnosed cases (522 men and 183 female) were recorded, accounting for 2.0% of all new cancer cases.¹ The median age at diagnosis was 57 for male and 54 for female. The age-standardised incidence rates (ASIR)* were 9.3 for males and 2.6 for females per 100,000 population. NPC was the 12th leading cause of cancer death in Hong Kong in 2022, with 251 deaths recorded, accounting for 1.7% of all cancer deaths. The age-standardised mortality rates (ASMR)* of NPC was 1.6 per 100,000 population, the rates were 2.8 for males and 0.7 for females per 100,000 population.¹

2. The incidence and mortality rate of both sexes for NPC has been on a downward trend over the past 20 years.² Unlike most of the other common cancers, NPC is generally more common in middle-aged individuals. Locally, ASIR of NPC peaks at

* Rates are standardised to the Segi's World Standard Population (1960)

60 to 65 years for male and at 50 to 55 years for female.² In 2022, among 705 newly recorded NPC cases, about 20% were early stage disease (stage I and II).¹ The 5-year relative survival rate for NPC patients diagnosed during 2010-2018 was 68.7%. The earlier the stage at diagnosis, the higher the 5-year relative survival rate (92.7% at stage I vs 47.1% for stage IV).³

3. The geographical distribution of NPC is extremely uneven across the globe, with over 70% of the new cases were reported in East and Southeast Asia, including Indonesia, Singapore, Vietnam and southern China.⁴ Some parts of southern China have particularly high incidence rates for NPC, such as Zhongshan (ASIR 25.0 per 100,000) and Zhuhai (24.0 per 100,000) of Guangdong Province.⁵

Risk factors

4. Reactivation of Epstein-Barr virus (EBV) in the epithelial mucosal lining of the nasopharynx is strongly associated with NPC and it is a well-established risk factor for NPC.^{6,7,8}

5. Large-scale epidemiological studies have shown associations between NPC and other modifiable risk factors, including salted fish consumption, active and passive tobacco smoking and occupational exposure to wood dust and formaldehyde.^{9,10,11,12} A case-control study conducted in Guangxi reported that individuals consuming salted fish three times or more per month were around two times more likely to develop NPC.⁶ There was a dose-dependent relationship between frequency and duration of consumption and NPC risk. The association was stronger for intake of salted fish up to 10 years of age.¹³ A meta-analysis revealed that ever smokers had a 60% higher risk of NPC than never smokers, with risk increasing by 15% for every additional 10 pack-years of smoking, especially in heavy smokers.^{6,14,15} The World Health Organization's International Agency for Research on Cancer (IARC) has classified EBV, formaldehyde, Chinese-style salted fish and wood dust as carcinogenic agents with sufficient evidence in causing NPC in

humans.¹⁶

6. Non-modifiable risk factors for NPC include family history, gender and age. Individuals with a first-degree family history of NPC were found to have at least a 4-fold increase in risk of NPC compared to those without such family history.^{17,18} Men are two to three times more likely to develop NPC than women.¹ In contrast to most other cancers, NPC disproportionately affects middle-aged individuals, with the peak age of occurrence between 50 and 60 years.⁹

Primary prevention

7. There are primary preventive measures which can help reduce the risk of NPC, including:

- No smoking;
- Avoid eating Chinese-style salted fish; and
- Minimise occupational exposure of carcinogenic substances by adhering to occupational safety and health rules including the use of protective gear where appropriate.

Evidence for NPC screening

8. As the pathogenesis of NPC is closely related to EBV infection, most studies on screening for NPC were focused on EBV-based tests, including serum anti-EBV antibody and EBV DNA tests.⁵ There are three common anti-EBV antibody detection targets, namely anti-EBV capsid antigen (VCA-IgA), anti-EBV nuclear antigen (EBNA-1 IgA) and early antigen EA-IgA.¹⁹ Meanwhile, nasopharyngeal endoscopy (NP endoscopy) with histopathologic examination of suspected lesions remains the gold standard for diagnosis of NPC.

a) Screening with anti-EBV antibody

9. NPC screening by anti-EBV antibodies has been studied mainly in high-incidence areas of Mainland China and adopted strategy of combining multiple antibodies which resulted in better sensitivity and specificity but in general, did not achieve a high positive predictive value (PPV). In the first stage of a two-stage study conducted in Guangdong Province of China, six seromarkers were detected by immunosorbent assay (ELISA) and two traditional NPC seromarkers (VCA-IgA and EA-IgA) were detected by immunofluorescence assay in serum samples from 191 NPC patients and 337 controls., VCA-IgA combined with EBNA-IgA tested by ELISA was identified as the optimal combination. In the second stage, 5481 participants aged 30-59 and without clinical evidence of NPC were recruited for NPC screening. Their serum was tested simultaneously by various seromarkers and NP endoscopy was offered to those with positive seromarker result. Seven participants were found to have NPC, representing a detection rate of 1.3 case per 1000 screening.²⁰

10. In a cluster randomised trial conducted in southern China (Sihui City and Zhongshan City), 28,688 participants aged 30-59 were screened by combined VCA-IgA and EBNA1-IgA testing. Among them, 862 participants were identified at high risk by seromarkers and were offered NP endoscopy. 38 NPC cases were identified through screening, representing a detection rate of 1.3 case per 1000 screening was found. It yielded a 68.3% of early diagnosis (stage I and II) compared to 25.7% in the unscreened population. The sensitivity, specificity and positive predictive value (PPV) after 1 year of follow-up was 93%, 97% and 4.4% respectively.^{5,21} A lower NPC-specific mortality among the screening participants versus the control population (RR = 0.22, 95% CI 0.09-0.49) was observed after 6 years of follow-up.²²

11. The study was expanded and recruited 52 508 persons aged 30-69 for screening by combined VCA-IgA and EBNA1-IgA testing compared to no intervention in second phase. With 8 years of follow up, sensitivity, specificity and PPV was found to

be 75%, 95% and 5.1% respectively. A significant 30% reduction in NPC mortality was observed in the screening group compared with the control group. The benefit was most evident among individuals aged 50 or above.²³ Nevertheless, it was noted that PPV of screening for NPC by anti-EBV antibody was relatively low and this would create a significant proportion of participants with false positive results who had to receive unnecessary NP endoscopy and subsequent surveillance, increasing the cost and manpower needed for screening.

b) Screening with Plasma EBV DNA

12. Compared with serological screening, plasma EBV-DNA screening has higher sensitivity and specificity as well as PPV. Nevertheless, the cost of EBV-DNA testing is relatively high and it requires more advanced equipment and standardisation.

13. A study comparing the performance of EBV IgA and plasma EBV DNA load measured by polymerase chain reaction followed by next-generation sequencing (NGS) in Taiwan showed that screening by EBV DNA yielded significant higher sensitivity (93.2%) and specificity (98.1%) compared to that of EBV IgA (88.4% sensitivity and 94.9% specificity).²⁴

14. A trial has been conducted in Hong Kong from 2013 to 2016 to investigate the use of EBV DNA testing by real-time polymerase chain reaction in plasma samples for screening early NPC in asymptomatic people. Among the 20174 eligible participants (male aged 40-62 years) recruited from health education sessions, 309 had persistently (both baseline and after 4 weeks) detectable EBV DNA in plasma. Those with persistently detectable plasma EBV DNA would be provided with nasal endoscopy and magnetic resonance imaging. 34 of them were confirmed to have NPC representing a detection rate of 1.7 cases per 1000 screening. The sensitivity and specificity of the two-stage screening protocol for the detection of NPC were 97.1% (95% CI 95.5%-98.7%) and 98.6% (95 CI 98.6%-98.7%) respectively, while the PPV was 11.0% (95% CI 10.7%-

11.3%). The higher PPV renders plasma EBV DNA testing better than the EBV antibody testing which has a typical PPV of 3-4%. A significantly higher proportion of participants with NPC identified by screening had stage I or II disease (71%) when compared to the population in Hong Kong in 2013 (20%). In addition, these NPC patients had superior 3-year progression-free survival compared to a historical cohort of NPC patients (97% vs. 70%).²⁵

15. The second-round screening was conducted from 2017 to 2020 with 17 838 (88.6%) participants in the first-round screening rescreened. Among them, 423 (2.37%) had persistently positive plasma EBV DNA and 24 NPC cases were identified, representing a detection rate of 1.3 per 1000 screening and PPV of 5.6%. Similar to the first-round study, a significantly higher proportion of the patients had stage I/II cancer compared to the NPC patients diagnosed in Hong Kong in 2013 (67% vs. 20%; chi-square test, $P < 0.001$). They also had superior 3-year progression-free survival (100% vs. 78.8%).²⁶

16. Findings of local studies indicated that the use of cell-free EBV-DNA as a biomarker for NPC screening would be a better screening tool in terms of its higher sensitivity, specificity and PPV as compared to that of seromarkers. Nevertheless, PPV remains low at 11% for initial screening and 5.6% for second-round screening. Over 90% of participants with positive screening result were actually false positive cases and had to receive unnecessary NP endoscopy and subsequent surveillance.

17. The difference in the molecular profiles of plasma EBV DNA between NPC and non-NPC patients of the screening cohort in the above study, was further analyzed by sequencing-based analysis and the analysis revealed high concentrations of plasma EBV DNA and generally longer fragment lengths of plasma viral molecules in NPC patients than in non-NPC subjects. The modeled results of the next-generation sequencing (NGS)-based assay combining both count and size features of plasma EBV DNA achieved a higher PPV of 19.6%.²⁷ However, further research by RCTs should be done to validate the performance of such screening algorithm.

Cost effectiveness of NPC screening

18. In Hong Kong, no formal study on the cost-effectiveness of NPC screening has been conducted. Overseas cost-effectiveness study of NPC screening based on mathematical modeling suggested that once-lifetime, sex neutral EBV-based screening of middle-aged adults would be cost-effective in high-risk endemic regions of the world, using the incremental cost effectiveness ratios threshold of US\$50 000/quality-adjusted life year to define highly cost-effective interventions in high-income countries.^{5,28}

International recommendations and practice on NPC screening

19. In western countries where NPC is relatively rare, such as the United States, United Kingdom and Australia, there is no established national screening guideline for NPC screening. In Singapore, mass screening for general population at normal risk is not recommended. Individuals with a first-degree relative (parent, sibling) with NPC may be screened with EBV IgA serology and nasopharyngoscopy.²⁹

20. Mass NPC screening has been provided since 2007 to people aged 30-59 in some parts of China where the NPC incidence is particularly high, including Sihui City of Guangdong Province and Cangwu County of Guangxi Zhuang Autonomous Region, using EBV serology (VCA-IgA) with head and neck examination as screening test, which if screened positive, is followed by further nasopharyngoscopy and biopsy for diagnosis.^{30,31}

21. The virtual Nasopharyngeal Cancer Screening Conference was held in 2021 in which thirty-five experts from relevant disciplines reviewed and discussed the available data on the performance and cost-effectiveness of EBV-based screening for NPC. The Conference concluded that provided there are favourable cost-effectiveness analysis results, two rounds of screening in 5 years is recommended for sex-neutral or male-only

screening for middle-aged adults in high-risk endemic areas, and for middle-aged adults with a family history of NPC in intermediate-risk areas, using either EBV antibody or plasma EBV DNA testing.⁵

Conclusion

22. Various anti-EBV antibodies and their combinations (e.g., VCA-IgA, EA-IgA, EBNA1-IgA, EBV-IgA) have demonstrated good specificity and variable sensitivity as seromarkers for NPC. A statistically significant mortality reduction of around 30% from NPC was shown in the screened population vs a control population in a very high incidence region in Guangdong province.²³

23. Experience from Hong Kong and Taiwan showed that EBV DNA screening followed by confirmation by endoscopy and MRI yielded higher sensitivity, specificity and PPV than serology followed by endoscopy, albeit at a higher cost. NPC cases detected by EBV DNA screening had a significantly higher proportion with stage I or II disease and superior 3-year progression-free survival compared to a historical cohort of NPC patients.

24. Notwithstanding the above, the detection rate of NPC using serology or EBV DNA is comparatively low (around 1.3 per 1000 screening) even in high-risk endemic regions. The low PPV of serology or EBV DNA screening in the general population and their associated high false-positive rates may lead to over-investigation (e.g., subsequent nasal endoscopy and biopsy, MRI) and unnecessary medical surveillance in a majority of test-positive individuals.

25. There is also no formal study on the cost-effectiveness of NPC screening in the general population has been conducted in Hong Kong. At global and regional levels, mass screening for NPC has been implemented only in a few selected areas of Guangdong Province and Guangxi Zhuang Autonomous Region where incidence rate of NPC is much

higher than Hong Kong. No population-based NPC screening programme exists even for countries with similar incidence of NPC as Hong Kong, such as Singapore.

26. In summary, more justification from robust local cost-effectiveness data is required before recommending an NPC screening programme for the general population in Hong Kong. Individuals at increased risk of NPC such as middle-aged adults with a first degree relative having NPC are more likely to benefit from EBV DNA and anti-EBV serology screening (VCA-IgA with a detection threshold IgA titre of $\geq 1:160$ and EA-IgA with a detection threshold titre of $\geq 1:10$ measured via IFA), whose test performance has been documented well by local and regional researchers. Those individuals are recommended to seek advice from doctors regarding the pros and cons of screening before making an informed decision to do so. Promoting the awareness of symptoms of NPC and healthy lifestyle to the general public remains an important primary preventive measure to reduce the risk of NPC. The CEWG will keep in view the latest development and emerging evidence on NPC screening.

Revised recommendations by CEWG

27. Taking local epidemiology, emerging scientific evidence and overseas screening practices into consideration, the CEWG revised the recommendations on NPC prevention and screening for local population which were endorsed by the Cancer Coordinating Committee at its 20th meeting on 3 June 2025. The revised recommendations for the local population are given below:

Prevention	
1.	All individuals are recommended to adopt a healthy lifestyle, including no smoking and healthy eating (including the avoidance of Chinese-style salted fish especially during early childhood).
For asymptomatic population at average risk	
2.	There is insufficient evidence to recommend a population-based nasopharyngeal cancer (NPC) screening programme using Epstein-Barr virus (EBV) IgA serology or EBV DNA testing.

For asymptomatic persons at increased risk	
3.	Persons at increased risk, such as middle-aged adults with first degree relative having NPC are advised to seek advice from doctors before making an informed decision about screening by EBV IgA serology or EBV DNA testing.

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